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### The Irrelevance of Equipose

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## The Irrelevance of Equipoise

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*It is commonly believed in research ethics that some form of equipoise is a necessary condition for justifying randomized clinical trials, that without it clinicians are violating the moral duty to do what is best for the patient. Recent criticisms have shown how complex the concept of equipoise is, but often retain the commitment to some form of equipoise for randomization to be justified. This article rejects that claim. It first asks for what one should be equally poised (scientific or clinical equipoise), then asks who should be equally poised (scientist, clinician, or subject), and finally asks why any of these players need be equally poised between treatment options. The article argues that only the subject's evaluation of the options is morally relevant and that even the subject need not be equally poised or indifferent between the options in order to volunteer for randomization. All that is needed is adequately informed, free, and unexploited consent. It concludes equipoise is irrelevant.*

**Keywords:** *consent to randomization, equipoise, idiosyncratic preferences, individual versus clinical equipoise*

### I. INTRODUCTION

Previously, I have argued that equipoise of the clinical or research community was not decisive in justifying randomized clinical trials (Veatch, 2002). I argued that what was morally critical was the willingness of some group of potential research subjects to agree to be randomized after having enough information about the alternatives. I further suggested that if the adequately informed potential subject (rather than the clinician, researcher, or research

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community) is relatively indifferent between two treatment options, there is good reason to expect that that person might consent to being randomized. The underlying premise of this rejection of clinician or researcher equipoise is that evaluation of treatment alternatives is inevitably a subjective process and that it is not necessarily irrational for some people to find themselves poised, that is suspended, more or less equally balanced, between two options even if the communities or researchers, clinicians, or lay people have developed a decided preference for one of the options. Likewise, it is not necessarily irrational for some people to have a decided preference for one of the options even though the various communities of observers are more or less in equipoise between choices.

Consider a randomized trial of two multi-drug chemotherapies for a certain cancer. If the clinical community is legitimately uncertain which has the better five-year survival rate, the community of researchers may be in equipoise regarding the scientific question of which has the higher survival rate. Even in this case, however, some particular potential subjects could have decided preferences for one package of side effects over the other—preferring alopecia (hair loss) over nausea or the other way around, for example. It would not be irrational for a potential subject to favor one of the regimens even though the community of investigators saw them equally balanced. The bald-headed man who hates nausea might have a decided preference for the alopecia risk while a bulimic young woman who fears hair loss might prefer the other even though clinicians and investigators had no decided preference for one package or the other.

In that previous work I mistakenly implied that it was necessary for potential subjects to be more or less balanced between choices (arms of a potential randomized trial) in order for them to agree to be randomized. In this article, I want to clarify the connection (or lack thereof) between willingness to be randomized and being in equipoise. Specifically, I wish to argue for the logical irrelevance of any person or any group being in equipoise. In short, I wish to make the case for the irrelevance of equipoise. I shall do so by asking three questions:

1. For what should one be equally poised?
2. Who should be equally poised? and
3. Why should individual subjects need to be equally poised between options to volunteer to be randomized?

## II. FOR WHAT SHOULD ONE BE EQUALLY POISED?

The history of the literature on equipoise suggests that a necessary condition for justifying a randomization is that some person or some group be equally balanced or equally poised between two or more choices. The original

problem addressed by Charles Fried (1974) and later by Benjamin Freedman (1987) was how a practicing clinician caring for a patient could reconcile his or her primary Hippocratic duty to do what will benefit the patient with offering that patient a random assignment to two or more treatment groups.

The initial moral insight is that flipping a coin random choice is consistent with doing what will most benefit the patient when there is no reason to prefer one option over others. All options are equally likely, based on what is known at the time, to maximize patient benefit. One might at first assume that the clinician would then be justified in offering randomization only when that clinician was equally attracted to two or more options in the randomization. However, when one realizes that an individual clinician is at most momentarily exactly equally divided between two or more options, one might find this potential justification of randomization of more theoretical than practical importance.

### Why Individual Clinician Equipoise is Irrelevant

The significant contribution of Freedman was to point out that the equipoise of the individual clinician is not really decisive. Some practitioner may be indifferent between options even though a consensus among relevant experts or peers has developed a preference. Alternatively, some practitioner may have a preference even though the consensus of relevant experts or peers favors no one choice. Freedman's suggestion was that when the relevant community has not yet reached a consensus in favor of one option, there is no basis for favoring that option and therefore a randomization can be justified even in the face of the opinion of some clinician that favors one of the options.

More recently, Djulbegovic and Clarke (2001, p. 1206) have referred to this rationale for randomized trials as the uncertainty principle, holding that a patient should be enrolled in a randomized controlled trial only if there is substantial uncertainty about which of the trial treatments would benefit the patient more. Weijer and colleagues (2000, p. 756), while rejecting the language of the uncertainty principle claiming it implies that the individual clinician must be uncertain, nevertheless accept clinical equipoise, claiming that it recognizes explicitly that it is not the individual physician but the community of physicians that establishes standards of practice.

### Why Community Equipoise Is Irrelevant

In the decades since this original justification for randomized clinical trials emerged, a significant number of problems have been discovered. Ashcroft (1999) has suggested that, in fact, we have no viable conception of equipoise. One of these problems is over exactly what it is about which people ought to be equally poised.

## SCIENTIFIC VERSUS CLINICAL EQUIPOISE

The literature sometimes has addressed this problem by distinguishing between scientific and clinical equipoise (Gifford, 2000). One might be in equipoise scientifically. In that case there is some research question about which the relevant person or group does not yet have enough information to form an opinion. Scientific hypotheses must be tested against evidence, usually evidence that accumulates from carefully controlled experiments. For example, pharmacologists may legitimately be uncertain which of two combinations of chemotherapeutic agents more effectively reduces tumor size for a particular cancer at a particular stage. When scientists do not know which of two interventions produces the treatment effect with greater magnitude or frequency, the relevant scientific community can be said to be uncertain. When there is no basis for believing one or the other has a higher likelihood of producing the effect, the community can be said to be in scientific equipoise.

Some have suggested that there must be a legitimate scientific question in dispute before a randomized clinical trial is justified. Careful commentators would acknowledge that a scientific question may be in legitimate dispute even though some individual scientists reading the existing data may have concluded that one or another intervention produces the treatment effect more reliably. Some equipoise theorists have this scientific equipoise in mind when they argue that equipoise is the necessary condition for justifying randomization. In this case, the relevant community would appear to be the community of scientists with expertise on the scientific question in dispute. Practicing clinicians, even the community of clinicians, would not possess the relevant expertise and their community equipoise would not be definitive.

On the other hand, it must be clear that scientific uncertainty by itself cannot provide adequate rationale for randomization. Consider two treatments for persistent cardiac arrhythmias, one involving a safe, simple, and inexpensive oral medication and another involving radical open-heart surgery. Surely, genuine uncertainty which of the two treatments is more effective at suppressing the arrhythmias cannot provide a justification for randomization. To the contrary, if there was real uncertainty, no rational person would agree to be randomized to radical surgery. Only if the radical surgery were believed to be substantially superior to the safe and simple oral medication would one contemplate being randomized. We could say at this point there was clinical equipoise alongside a belief that one treatment was superior in controlling arrhythmias. The belief in the superiority of the surgery would have to counterbalance the risks, pain, and inconvenience of the surgery by just the right amount for the surgery to be an option.

To anticipate the argument later in the article, the balancing of the belief in the superiority of surgery with the risks, pain, and inconvenience is

necessarily a subjective process. There is no reason why all people would balance the surgery and medical treatment in the same way and therefore no reason why potential subjects would find the balance point at the same place that scientists, researchers, or clinicians would. Moreover, there is no reason why all subjects would find the options equally attractive at the same time. Some minority of subjects could find the two options equally attractive while almost all clinicians would have developed a preference for one of the options. (It goes without saying that the same could be said regarding the community of scientists. There is no particular reason why the community of scientists should have a definitive opinion on the question of when the surgery and medical treatment were equally balanced.)

Scientists are concerned about testing hypotheses and establishing support for claims about facts (facts such as which of two interventions produces the higher probability of restoring normal heart rhythms). Clinicians are not immediately concerned about that question. Rather they are concerned about which intervention is best for their patients. They are concerned about not only intended treatment effect, but also potential side effects, burdens on patient life-style, costs, and psychological impacts. To put the issue in Hippocratic terms, they would reasonably want to know which treatment intervention is best for the patient. When, and only when, one risk-benefit package appears to be superior to another would they develop a clinical preference for an option. Prior to that time, they may be in a state of indecision. They may be close enough to being suspended midway between two options that they can be said to be equally poised (or in equipoise). When the clinical community has developed no decisive preference for one option, there can be said to be clinical community equipoise. Clinical community equipoise and scientific community equipoise are logically separate. Normally they would not arise at the same point.

Thus, when equipoise theorists discuss equipoise they may be referring to equipoise regarding a scientific hypothesis or they may be referring to equipoise regarding some clinical choice. They two are not the same. Scientific equipoise is neither necessary nor sufficient to justify a randomization. Clinical equipoise shows more promise, but it too can be shown to be neither necessary nor sufficient at least if it is the clinician or clinical community that is positioned in a suspended state between two options.

#### EXACT VERSUS RELATIVE EQUIPOISE

It is reasonable for funders of research to be interested in what we have called scientific equipoise. It usually makes no sense to fund research to test a hypothesis about which the answer is already known with a high degree of certainty. Thus, scientific equipoise is not irrelevant for all matters of scientific decision. However, it is not necessary for the scientific community to be in equipoise about the scientific question in order to justify funding research.

At this point in the analysis it is critical to recognize a range of positions along a continuum of certainty. Perfect equipoise is fleeting at best. The state of being absolutely equally torn between two options is momentary. New pieces of evidence are constantly emerging so that often the scientific community might be said to be relatively uncertain while still seeing the evidence as providing slightly more support for one option than another. I have referred to this as relative equipoise or relative uncertainty.

Even more interesting is the possibility that there exists at a given point evidence that is quite strong in support of one conclusion over another. Scientists will not claim that they can accept or reject a hypothesis until substantial evidence is provided. In statistical terms, hypotheses are not rejected until some stopping boundary is reached. For example, some studies require that some p-value such as  $p=0.05$  or  $0.01$  is achieved before an answer is said to be established. It is essential to recognize that there is a substantial range along the continuum in which one cannot claim that a conclusion has been proved, but one cannot be said to be in exact equipoise either. Even relative equipoise may long since have been abandoned. At a p-value of  $0.06$  the only reasonable scientific statement is that the scientific question is not yet resolved, yet, if one started the research completely uncertain whether the hypothesis could be supported or not, one's epistemic position would have changed considerably by the time a data analysis showed a difference at a level of  $p = 0.06$ .

It would, of course, be wrong for the scientist to conclude that the hypothesis can be rejected (at an adequate level of significance), but the clinician or patient given the new information should be pushed substantially in the direction of the data trend.<sup>1</sup> One who was indifferent before seeing the interim analysis should no longer be so. A clinician, having to make a forced choice between two treatments, who was entirely indifferent before the start of the trial would be wise in choosing the apparently winning arm *if forced to choose at the moment that the interim analysis was conducted*.

### III. WHO SHOULD BE EQUALLY POISED?

This raises the question of who should be equally poised for equipoise to exist. In the situation just described, a scientist may no longer be equally poised, but would not have enough information to reach a firm conclusion about the hypothesis being tested. On the other hand, while the clinician could not be said to have definitive information, he or she would surely have a basis for changing a clinical communication. The clinician who could perceive no basis for recommending one course over another before the trial began would now be able to give a reason why, if forced to choose, he or she would go with one of the options. The recommendation would, of course, have to come with the qualification that the question is

not settled definitively, but, if there were absolutely no basis for picking between two options before the trial started, there would be a tentative basis for choosing when an interim analysis returns a  $p$ -value of 0.06.

The clinician should also qualify any recommendation by indicating the recommendation was based on his or her personal, perhaps idiosyncratic values. Assuming that the end-stage cancer patient held those same values and did not have the option of waiting for the completion of the study, there is a rational basis for shifting one's evaluation in favor of the apparently winning arm.

This, of course, poses very serious moral and procedural issues for conducting clinical trials. I have long argued that there exists a rational basis for using this preliminary information in a case in which one cannot wait for final results (Veatch, 1979; 1987). I am now suggesting that the rules of informed consent require providing that information to clinician and patient if a decision is to be informed with all the information that would be material or rational to take into consideration in making a forced clinical choice. This, of course, poses a threat to completing the trial.

We have already seen that the equipoise of individual scientists or clinicians is unnecessary to justify randomized clinical trials. It is now apparent that equipoise by the two communities is not sufficient either. The community of scientists may be equally poised between accepting and rejecting a hypothesis without providing justification for randomization. Likewise, that community may be out of equipoise without making a randomization unethical.

It may be less clear why the equipoise of the community of clinicians is neither necessary nor sufficient. The key to reaching that conclusion is the recognition of the subjectivity of clinical judgments. Clinical equipoise is the state at which the individual clinician or more typically the clinical community as a whole is equally torn between two treatment options when comparing their risk-benefit profiles. We have already seen that clinicians may be in this state even though scientists are no longer in scientific equipoise. Clinicians may be equally suspended between two treatment options when, considering the judgments of the community of clinicians, no clear preference exists for one risk-benefit package over another. They may be said to be equally suspended even though scientists see one of the options as producing a clearly larger treatment effect. They may be said to be equally suspended even though some clinicians prefer one of the risk-benefit packages over the other. As long as neither risk-benefit package generates a clear consensus of support, the clinical community can be said to be in clinical equipoise.

Looking at why some clinicians may prefer one treatment over the other in the face of equipoise in the clinical community will help reveal the fundamental problem. Some clinicians may have a preference for one treatment over the other out of ignorance. He or she may not know of a recent study showing that the preferred option has some newly discovered negative

(or that the alternative has some recently discovered positive). In that case we can write off the outlier clinician as inadequately informed. But what if the outlier clinician prefers one treatment option over the other because he or she has a strong idiosyncratic, but rational preference for its benefit-harm package over the other?

The concept of idiosyncratic, but rational, preference is critical here. A treatment option offers a package of effects. By convention some are called benefits and others harms. We already see the depth of the problem if we pause to realize that science cannot establish that an effect is a benefit or a harm. Only individual preference functions can impose that value judgment. Consider, for example, a drug that produces a side effect of making patients drowsy. For some that could be considered a seriously negative side effect, but for others it may be a side effect that is evaluated positively. How negative or how positive will depend on the situation of the evaluator.

Hence, some clinicians with idiosyncratic preference functions may prefer one treatment over the other because they place unusually high utility on some of the effects they consider benefits or unusually strong disutility on some of the effects they consider harms.

Such idiosyncratic preferences need not be irrational. They may be said to be rational if they take into account reasonable amounts of available information and incorporate value judgments that are not irrational. They may rest on the unusual position or tastes of the one making the evaluation. They may rest on special needs or interests. Nevertheless, they are not irrational in the sense that they incorporate prudent amounts of information and value judgments that are not irrational. Drowsiness may be a disaster for one who regularly operates dangerous machinery, but a blessing for one who is an insomniac who only takes the medication before bedtime.

Some preferences may be so bizarre that they can be said to be irrational. Objective list theories of the good would hold that some claims about what is desirable are simply wrong (Parfit, 1984; Gert; 1990; DeGrazia, 1995). Regardless, of whether one holds to an objective list theory of the good or some other theory, it can be said that some idiosyncratic preferences are not irrational. They can be said to be rational to the extent that they are based on accurate accounts of the nonevaluative facts, are held by persons who are adequately dispassionate and perceptive, and are not blatantly wrong evaluations.

If a clinician has strong idiosyncratic, but rational preferences it is quite possible that he or she will evaluate treatment options differently from his or her colleagues. There is no logical reason why all clinicians have to evaluate all benefit-risk packages in exactly the same way. In fact it is a blatantly obvious fact that competent, reasonable clinicians do not evaluate benefit-risk packages in exactly the same way. Therefore no logical reasons exist why some deviant clinician is necessarily acting irrationally if he or she does

not stand in clinical equipoise at the same time that the clinical community in general does (Veatch, 2000).

We can thus conclude that it is not irrational for a clinician honestly and sincerely to prefer one treatment over another and therefore recommend it to his or her patient even though the community of his or her clinical colleagues is in equipoise (or at least relatively so). For all the same reasons, an individual clinician may be in equipoise even though the clinical community in general has been forced by the development of new information to leave the state of equipoise and develop a preference for one treatment or the other. Surely, it cannot be immoral for a clinician to advise his patient against volunteering for randomization based on the clinician's idiosyncratic, but rational preferences. As long as the clinician simultaneously informs the potential subject that his or her colleagues do not see it the same way and the subject recognizes the irrelevancy of the clinician's value judgments, presenting the clinician's own perspective must be acceptable.<sup>2</sup>

If individual clinicians reach rational idiosyncratic judgments about the benefit-harm packages of alternative treatments, then surely they have a right to take this into account when deciding whether they want to participate in clinical trials. Consider a randomized clinical trial in which an individual clinician has concluded that the experimental treatment is superior to the standard treatment even though the clinical community in general remains in equipoise. That clinician must retain the right not to participate in the trial. If the experimental agent is already on the market and thus available, the Hippocratic duty of the clinician must be to offer that experimental agent to the patient on a nonrandomized basis together with his or her assessment of why it is superior as well as an honest statement that his or her colleagues do not agree. Presumably, if the patient wanted the experimental agent, that is, if the patient's value-judgment lined up with the clinician's, then the clinician should prescribe the available experimental agent. If, on the other hand, the patient preferred the standard treatment, based on idiosyncratic preferences, presumably the clinician would be forced to prescribe that treatment (or recommend transfer to another clinician with similar preference functions).

What should happen if the patient agrees with the clinical consensus, that is, the patient is indifferent between the two benefit-risk packages? Presumably, a clinician could agree to randomize if he or she could do without violating conscience. Alternatively, he or she could tell the patient about the clinician's discomfort with participation the trial and recommend that the patient transfer to a colleague more comfortable with the randomization. Surely, however, there can be nothing immoral about randomizing a willing patient who is more or less in equipoise just because the individual clinician has an idiosyncratic preference among treatments.

This suggests that equipoise by clinicians is not necessary to provide a moral justification of randomization. Here several of the most insightful

authors criticizing equipoise seem to fall short. In a number of cases, these authors point out the conceptual problems with equipoise and even acknowledge the possibility that a potential subject may be out of equipoise when the scientific or clinical communities are equally poised. They, in some cases, however, still insist that it would be unacceptable to randomize a patient when community equipoise is absent. (See, for example, Gifford, (2007), "It's true that we wouldn't do the trial if we weren't in equipoise...."; and Evans & London, 2006, "If...the data are sufficient to bring about a reasonable consensus among expert clinicians about the superiority of either A or B as a treatment for P, then it would no longer be permissible for P to participate in the trial because equipoise would have been disturbed.")

But there are surely important scientific reasons why randomization should take place: to reach a stopping boundary or to disprove a widespread folk belief in an alternative therapy, for example. I suggest that in these cases the absence of community equipoise is not a reason to prohibit offering randomization to subjects provided the subjects realize that there exists a consensus among various communities of experts in favor of one of the treatments. Some potential subjects may have idiosyncratic, but rational, preference functions that leave them equally poised even in the face of such community consensus.

Moreover, some potential subjects may have good enough reasons for wanting the trial completed even though they have a preference for one of the treatments that they volunteer to be randomized. The mere presence of a substantial value consensus in some community in favor of one of the treatments in no way warrants moral disapproval of consent to randomization of adequately informed and free volunteers some of whom may, in fact, have no preference between the available options. This will turn out to be crucial in answering the question of how trials can be completed ethically once equipoise is disturbed among the scientific or clinical communities.

It also reveals that such equipoise is not sufficient either. Clinicians may be in equipoise when their patients are not. This clarifies the lack of relevance of clinical community equipoise in justifying a randomization. The mere fact that a particular clinician or even a community of clinicians is in equipoise does not imply that a potential subject should be. Equipoise in the clinical community is neither necessary nor sufficient. It is no more necessary or sufficient than is equipoise in the scientific community.

As I have suggested, in some situations, this conclusion can be critical for completing clinical trials. Several of us have now suggested that exact equipoise is fleeting. As evidence begins to accumulate the clinical communities may develop slight preferences for one arm or the other. They may develop these slight preferences long before a stopping boundary is reached and long before the clinicians themselves feel completely confident in their conclusions.

Hippocratic physicians are duty-bound to explain to patients who are candidates for randomization that emerging evidence provides a tentative

basis for them to recommend one treatment option over the other. Patients who (irrationally) believe that it is reasonable to follow such clinician recommendations will be forced to refuse randomization even if the clinician feels morally justified in offering it.

Under such circumstances a trial may never be completed to the point of reaching a stopping boundary. If, however, it is moral for a clinician to offer randomization even though he or she has developed a preference for one of the treatment options, then the trial might progress to completion. It could do so if the potential subject had idiosyncratic preferences that leave that subject relatively indifferent or if the subject were willing to take the risk of receiving the less attractive arm for the good of science. Both individual clinicians and the clinical community as a whole will typically be out of equipoise before stopping boundaries are reached. The only way to complete a clinical trial is for clinicians to proceed to offer randomizations while simultaneously informing subjects of their assessment of the situation. Potential subjects may very plausibly still agree to be randomized because they have idiosyncratic preference functions that leave them more or less equally poised between treatment options. But that raises the question of whether such potential subjects must be so positioned in order for their consent to be morally justified.

#### IV. WHY SHOULD INDIVIDUAL SUBJECTS NEED TO BE EQUALLY POISED?

It should by now be apparent that what is critical is the perspective of the potential subject. Neither the equipoise of the individual clinician nor that of the clinical community is definitive; neither is the equipoise of the individual scientist or the scientific community. Both scientists and clinicians may have good reasons to randomize subjects when they are not in equipoise and those reasons do not necessarily violate the rights or interests of the subject. Scientific equipoise and clinical equipoise are different but neither is definitive in justifying randomized clinical trials.

The significant contribution of Miller and Brody to this discussion has been to make clear that equipoise in the clinical and scientific communities is not a necessary condition for morally justified randomization (Miller & Brody, 2003; Miller & Brody, 2007). Since there are important reasons, particularly related to completing trials, why randomizations might serve scientific purposes, their analysis is critical. Jansen's recent criticism of their analysis (Jansen, 2005) expresses concern that in the absence of equipoise subjects may receive substandard care. In offering this criticism she fails to appreciate the moral requirement imposed by Miller and Brody that subjects be adequately informed, give their consent, and not be exploited.

More importantly, she fails to acknowledge how routinely clinicians interact with patients for purposes other than the promotion of the patient's medical well-being. Clinicians procure healthy kidneys for transplant, refuse to prescribe antibiotics so society can preserve their effectiveness for more critical patients, cooperate in cost containment efforts, and participate in public health efforts that are not necessarily in the interests of their patients. They terminate normal pregnancies, provide cosmetic surgery, and perhaps even prescribe drugs for the purpose of assisting in suicide, none of which promote the patient's medical well-being. Some of these behaviors are surely legitimate even though the goal is not to promote the patient's medical well-being.

What concerns me is not that Miller and Brody support clinician participation in randomized trials in the absence of equipoise in the clinical community. What concerns me with their analysis is their failure to emphasize the subjective nature of equipoise that leads to the realization that different players in the conversation may be in equipoise at different times and that rational subjects may have reasons to volunteer for randomizations among which is the fact that the subject is in equipoise even if the clinical community is not.

What is critical is the perspective of the patient. Obviously, patients need to be adequately informed and, as Miller and Brody argue, should not be exploited. It may not be as obvious to clinical trialists, but being adequately informed must include any information about trends in the data that have emerged since the trial began. This information may come from outside sources (other trials or theoretical developments) or from interim looks at data of the trial for which the subject is a candidate. It is rational for patients and their clinicians to take this information into account in making forced choices even if it is irrational for scientists to conclude that the scientific question has been answered at that point.

Once the individual potential subject is adequately informed about the treatment options (including the fact that the scientific and clinical communities may not be at exact or even relative equipoise), then it is the responsibility of that person to decide where he or she stands on the choice. As long as the potential subject is not coerced into consenting or otherwise exploited, the equipoise of any of the other players does not matter. Since evaluation of treatment benefit-risk packages is inherently subjective and idiosyncratic, the evaluation of the patient may or may not agree with that of either the individual clinician or the community of clinicians. Moreover, the patient may or may not agree that the scientific questions are worth pursuing.

If the individual patient were to compare the benefit-risk packages of two treatment options and find them exactly equal, what could the poor patient do but ask for a coin flip. Such a patient could be said to be in exact equipoise. Randomization is beyond controversy in this case (regardless of the equipoise of other parties including scientists and clinicians). What is surprising is that it is beyond controversy even if the scientific and clinical

communities are no longer even in relative equipoise. It is not equipoise of these communities that is relevant. Even the equipoise of the community of patients is not relevant (Gifford, 1995). The indifference of the individual patient is one condition under which randomization would be justified. Patients who are completely indifferent to treatment options have plausible reason to consent to entering a randomized trial even if clinicians and scientists are no longer in equipoise. This led me mistakenly to imply in an earlier paper (Veatch, 2002) that patient equipoise was a necessary condition. It clearly is not. It is merely a condition under which reasonable patients would plausibly be inclined to consent to being randomized. In fact, if a patient/subject is at exact equipoise it is hard to imagine what he or she would do except use some random method of choosing. Surely, barring exploitation there is nothing wrong with making that random choice systematic.

There is a critical problem with equipoise theory. A space exists along the continuum between the point at which various communities are no longer in equipoise and the point at which the scientific community concludes an answer has been determined for their scientific question. Equipoise is the state of being suspended equally between two options. Relative equipoise is the zone within which there is legitimate disagreement about whether one treatment is superior to another from the point of view of the relevant scientists or clinicians. There is considerable space between the point at which one is no longer in relative equipoise (the point at which a consensus emerges supporting one treatment over another) and the point at which there is adequate evidence based on stopping boundaries or p-values that a scientific conclusion can be reached.

Think of a study using a p-value of 0.05 as a stopping boundary while an interim analysis produces a p-value between 0.05 and 0.06. Reasonable people should not be in even relative equipoise, but they are not certain of a conclusion either. The morally problematic zone is the range between the area in which the clinical community can be said to be in relative equipoise and the point at which scientists can comfortably reach a conclusion to the research hypothesis. In that zone, there is neither equipoise nor proof of the conclusion. Trial designers are in a bind if they hold that equipoise is the moral justification of randomization. If there is a gap between the point when one is no longer in the zone of relative indifference and the point at which one can reach a conclusion, then, according to equipoise theory, it is no longer morally justified to randomize, but not enough data have been accumulated to reach a scientific conclusion.

That is where this argument for the irrelevance of equipoise becomes critical to the completing of scientific investigations. If individual potential subjects after being adequately informed can be completely indifferent between two benefit-harm packages while the community of clinicians or the community of scientists is no longer indifferent, then surely those individuals can justifiably still be randomized.

Consider a study that began with the clinical and scientific communities in equipoise that, after an interim analysis, reveals one arm superior, but only at a p-value of 0.10. That means that there is only one chance in ten of a difference as large as the observed one occurring if, in fact, there is no real difference in the two treatments. Those indifferent at the beginning should no longer be so if they are required to make a forced choice therapeutic decision. On the other hand, there is clearly not enough evidence to reach a scientific conclusion worthy of resolving the issue in dispute. Since individual zones of indifference are subjective, some subjects who originally had a preference for the now-apparently-losing arm could be pushed into their personal zones of indifference just when the clinical or scientific communities are pushed out of theirs. By capturing the importance of these subjective, idiosyncratic zones of indifference investigators will be able to have a moral justification for completing their trials after the relevant communities are no longer in equipoise but not enough evidence is available to reach a robust conclusion.

In fact, even if the potential subject is only relatively indifferent between treatment options, he or she may be willing to be randomized. Depending on the importance that subject places on the scientific project and the weight he or she places on being assigned the less attractive arm, he or she may be willing to forgo the advantage of getting his or her personally preferred treatment option.

The same analysis can be pushed to its final step. Even if the potential subject has a strong preference for one treatment package over another, he or she might *still* be willing to be randomized for the good of science. Depending on the personal consequences of getting randomized to the arm that is less attractive, some people may sacrifice personal gain for the good of science. Others may be sufficiently personally invested in answering the scientific question that they volunteer to be randomized knowing they might be assigned the less attractive arm.

For example, in a paper criticizing the claim of equipoise in the Enhanced Suppression of the Platelet IIb/IIIb Receptor with Integrilin Trial (ESPRIT), Howard Mann and colleagues (2005) concluded that a trial comparing an experimental agent with a placebo was not justified because sufficient evidence existed that the currently used treatment provided benefit. While I concur that many clinicians and many potential subjects would find a lack of equipoise sufficient to reject an offer of randomization, I would accept the possibility that some adequately informed subjects might be willing to be randomized in this trial either because they had definitive objections to the standard treatment or because of a willingness to sacrifice those benefits for the good of science. If no adequately informed subjects volunteered, that would defeat the proposed study without imposing a normative judgment on the potential subjects.

This in turn raises a subsidiary question of what, if anything, scientists or clinicians can do ethically to encourage potential subjects to agree to be randomized. Some with more libertarian leanings believe that financial and other incentives to drive potential subjects into a willingness to be randomized are legitimate (Pedroni, 1998). That is, after all, the basis for recruiting normal volunteers for much research unconnected with therapeutic intent.

Even those who find financial incentives problematic may be open to moral incentives (such as pointing out how important a contribution to science could be). There is still another option, however. Once we realize that equipoise is a personal matter that must rest on idiosyncratic preferences of individual persons, it is possible that some outliers in the community will be honestly indifferent among treatment options when the majority of the community can no longer be said to be in equipoise. These are people who sacrifice nothing if they volunteer to be randomized. Similarly, those who are atypical enough that they have only minor preferences even though the community generally has a stronger (but not definitive) reason to prefer one of the options, could be asked to volunteer without making substantial sacrifice. If we can recruit these subjects, we will be able to complete the studies even though scientists, clinicians, and most lay people are no longer in equipoise.

The randomization of subjects with idiosyncratic preference functions may pose some scientific questions. The subjects who volunteer may be sociologically atypical. Similar issues arise if we rely on persons who have a decided preference but volunteer for the good of science. We cannot assume these are typical subjects. Therefore, questions may arise about the validity of the study if some of the subjects are drawn from pools with atypical preference functions or atypical degrees of altruism. Whether this poses a serious problem will vary from study to study. In some cases, it could be a serious problem. In other cases, it may not be. No sample of subjects perfectly reflects the underlying population.

Basic research ethics has long recognized the need to permit subjects to refuse to volunteer for randomization even in cases in which the clinical and scientific communities are firmly in equipoise and therefore might fail to perceive a rational reason for refusing randomization. Even in these cases, we acknowledge the right of persons to refuse to consent. This means that those who are atypically conservative about innovation—those who retain a preference for standard over experimental treatments, for example—have the right to exclude themselves unilaterally from the sample. Since those who are atypically aggressive and want the experimental treatment do not similarly refuse consent to randomization (assuming that is the only way they can get access to an experimental treatment), this means that all research samples are skewed with the more conservative tail of the distribution excluding itself while the more interventionistic tail is included.

Thus, all samples are unique subsets from the larger population. In fact, if it is the conservatives who originally had a preference for standard treatment who gradually are driven into their zones of indifference by the emerging data, then we may be able to re-capture some of this group we had originally lost.

In the end, it is not anyone's equipoise that is morally critical; it is whether the potential subjects consent to be randomized without being unduly coerced, manipulated, or exploited. In every study scientists will move in and out of their zones of indifference and at some points will not be in scientific equipoise. At some points even the scientific community as a whole will not be. Whether they are in scientific equipoise is not decisive. Likewise, in every study clinicians will move in and out of their zones of indifference and at some points will not be in clinical equipoise. At some points even the clinical community as a whole will not be. Whether they are in clinical equipoise is not decisive. Most critically, potential subjects will bring subjective, idiosyncratic preference functions to bear and, based in part on those functions, may see it appropriate to consent to being randomized after being adequately informed. Whether they are in personal equipoise is not decisive. In the end, equipoise is irrelevant.

## NOTES

1. Alternatively, one might say that sufficient evidence does exist to reject the null hypothesis at the 0.06 level, but we will not accept a conclusion as sufficiently demonstrated until one reaches some higher level of significance, say 0.05. The difference between rejecting a hypothesis at the 0.06 level and at the 0.05 level is marginal.

2. In fact, the Hippocratic Oath explicitly enjoins the clinician to make judgments to benefit the patient according to the physician's ability and judgment. The presentation of a widespread consensus to supporting some contrary conclusion is not required and is actually excluded if one assumes that the Hippocratic physician would determine that presenting the contrary account would confuse or upset the patient. We have, fortunately, outgrown the immoral paternalism of the Hippocratic Oath, but it is hard to imagine why the clinician would be prohibited from offering randomization just because he or she is out of equipoise.

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