

## EQUIPOISE AND THE ETHICS OF CLINICAL RESEARCH

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### Abstract

The ethics of clinical research requires equipoise — a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial. Should the investigator discover that one treatment is of superior therapeutic merit, he or she is ethically obliged to offer that treatment. The current understanding of this requirement, which entails that the investigator have no “treatment preference” throughout the course of the trial, presents nearly insuperable obstacles to the ethical commencement or completion of a controlled trial and may also contribute to the termination of trials because of the failure to enroll enough patients.

I suggest an alternative concept of equipoise, which would be based on present or imminent controversy in the clinical community over the preferred treatment. According to this concept of “clinical equipoise,”<sup>1</sup> the requirement is satisfied if there is genuine uncertainty within the expert medical community — not necessarily on the part of the individual investigator — about the preferred treatment.

There is widespread agreement that ethics requires that each clinical trial begin with an honest null hypothesis.<sup>2</sup> In the simplest model, testing a new treatment B on a defined patient population P for which the current accepted treatment is A, it is necessary that the clinical investigator be in a state of genuine uncertainty regarding the comparative merits of treatments A and B for population P. If a physician knows that these treatments are not equivalent, ethics requires that the superior treatment be recommended. Following Fried, I call this state of uncertainty about the relative merits of A and B “equipoise.”<sup>3</sup>

Equipoise is an ethically necessary condition in all cases of clinical research. In trials with several arms, equipoise must exist between all arms of the trial; otherwise the trial design should be modified to exclude the inferior treatment. If equipoise is disturbed during the course of a trial, the trial may need to be terminated and all subjects previously enrolled (as well as other patients within the relevant popula-

tion) may have to be offered the superior treatment. It has been rigorously argued that a trial with a placebo is ethical only in investigating conditions for which there is no known treatment<sup>2</sup>; this argument reflects a special application of the requirement for equipoise. Although equipoise has commonly been discussed in the special context of the ethics of randomized clinical trials,<sup>4,5</sup> it is important to recognize it as an ethical condition of all controlled clinical trials, whether or not they are randomized, placebo-controlled, or blinded.

The recent increase in attention to the ethics of research with human subjects has highlighted problems associated with equipoise. Yet, as I shall attempt to show, contemporary literature, if anything, minimizes those difficulties. Moreover, there is evidence that concern on the part of investigators about failure to satisfy the requirements for equipoise can doom a trial as a result of the consequent failure to enroll a sufficient number of subjects.

The solutions that have been offered to date fail to resolve these problems in a way that would permit clinical trials to proceed. This paper argues that these problems are predicated on a faulty concept of equipoise itself. An alternative understanding of equipoise as an ethical requirement of clinical trials is proposed, and its implications are explored.

Many of the problems raised by the requirement for equipoise are familiar. Shaw and Chalmers have written that a clinician who “knows, or has good reason to believe,” that one arm of the trial is superior may not ethically participate.<sup>6</sup> But the reasoning or preliminary results that prompt the trial (and that may themselves be ethically mandatory)<sup>7</sup> may jolt the investigator (if not his or her colleagues) out of equipoise before the trial begins. Even if the investigator is undecided between A and B in terms of gross measures such as mortality and morbidity, equipoise may be disturbed because evident differences in the quality of life (as in the case of two surgical approaches) tip the balance.<sup>3,5,8</sup> In either case, in saying “we do not know” whether A or B is better, the investigator may create a false impression in prospective subjects, who hear him or her as saying “no evidence leans either way,” when the investigator means “no controlled study has yet had results that reach statistical significance.”

Late in the study — when P values are between 0.05 and 0.06 — the moral issue of equipoise is most readily apparent,<sup>9,10</sup> but the same problem arises when the earliest comparative results are analyzed.<sup>11</sup> Within the closed statistical universe of the clinical trial, each result that demonstrates a difference between the arms of the trial contributes exactly as much to the statistical conclusion that a difference exists as does any other. The contribution of the last pair of cases in the trial is no greater than that of the

first. If, therefore, equipoise is a condition that reflects equivalent evidence for alternative hypotheses, it is jeopardized by the first pair of cases as much as by the last. The investigator who is concerned about the ethics of recruitment after the penultimate pair must logically be concerned after the first pair as well.

Finally, these issues are more than a philosopher's nightmare. Considerable interest has been generated by a paper in which Taylor et al.<sup>12</sup> describe the termination of a trial of alternative treatments for breast cancer. The trial foundered on the problem of patient recruitment, and the investigators trace much of the difficulty in enrolling patients to the fact that the investigators were not in a state of equipoise regarding the arms of the trial. With the increase in concern about the ethics of research and with the increasing presence of this topic in the curricula of medical and graduate schools, instances of the type that Taylor and her colleagues describe are likely to become more common. The requirement for equipoise thus poses a practical threat to clinical research.

### Responses to the Problems of Equipoise

The problems described above apply to a broad class of clinical trials, at all stages of their development. Their resolution will need to be similarly comprehensive. However, the solutions that have so far been proposed address a portion of the difficulties, at best, and cannot be considered fully satisfactory.

Chalmers' approach to problems at the onset of a trial is to recommend that randomization begin with the very first subject." If there are no preliminary, uncontrolled data in support of the experimental treatment B, equipoise regarding treatments A and B for the patient population P is not disturbed. There are several difficulties with this approach. Practically speaking, it is often necessary to establish details of administration, dosage, and so on, before a controlled trial begins, by means of uncontrolled trials in human subjects. In addition, as I have argued above, equipoise from the investigator's point of view is likely to be disturbed when the hypothesis is being formulated and a protocol is being prepared. It is then, before any subjects have been enrolled, that the information that the investigator has assembled makes the experimental treatment appear to be a reasonable gamble. Apart from these problems, initial randomization will not, as Chalmers recognizes, address disturbances of equipoise that occur in the course of a trial.

Data-monitoring committees have been proposed as a solution to problems arising in the course of the trial.<sup>13</sup> Such committees, operating independently of the investigators, are the only bodies with

information concerning the trial's ongoing results. Since this knowledge is not available to the investigators, their equipoise is not disturbed. Although committees are useful in keeping the conduct of a trial free of bias, they cannot resolve the investigators' ethical difficulties. A clinician is not merely obliged to treat a patient on the basis of the information that he or she currently has, but is also required to discover information that would be relevant to treatment decisions. If interim results would disturb equipoise, the investigators are obliged to gather and use that information. Their agreement to remain in ignorance of preliminary results would, by definition, be an unethical agreement, just as a failure to call up the laboratory to find out a patient's test results is unethical. Moreover, the use of a monitoring committee does not solve problems of equipoise that arise before and at the beginning of a trial.

Recognizing the broad problems with equipoise, three authors have proposed radical solutions. All three think that there is an irresolvable conflict between the requirement that a patient be offered the best treatment known (the principle underlying the requirement for equipoise) and the conduct of clinical trials; they therefore suggest that the "best treatment" requirement be weakened.

Schafer has argued that the concept of equipoise, and the associated notion of the best medical treatment, depends on the judgment of patients rather than of clinical investigators.<sup>14</sup> Although the equipoise of an investigator may be disturbed if he or she favors B over A, the ultimate choice of treatment is the patient's. Because the patient's values may restore equipoise. Schafer argues, it is ethical for the investigator to proceed with a trial when the patient consents. Schafer's strategy is directed toward trials that test treatments with known and divergent side effects and will probably not be useful in trials conducted to test efficacy or unknown side effects. This approach, moreover, confuses the ethics of competent medical practice with those of consent. If we assume that the investigator is a competent clinician, by saying that the investigator is out of equipoise, we have by Schafer's account said that in the investigator's professional judgment one treatment is therapeutically inferior — for that patient, in that condition, given the quality of life that can be achieved. Even if a patient would consent to an inferior treatment, it seems to me a violation of competent medical practice, and hence of ethics, to make the offer. Of course, complex issues may arise when a patient refuses what the physician considers the best treatment and demands instead an inferior treatment. Without settling that problem, however, we can reject Schafer's position. For Schafer claims that in order to continue to conduct clinical trials, it is ethical for

the physician to offer (not merely accede to) inferior treatment.

Meier suggests that “most of us would be quite willing to forgo a modest expected gain in the general interest of learning something of value.”<sup>15</sup> He argues that we accept risks in everyday life to achieve a variety of benefits, including convenience and economy. In the same way, Meier states, it is acceptable to enroll subjects in clinical trials even though they may not receive the best treatment throughout the course of the trial. Schafer suggests an essentially similar approach.<sup>5,14</sup> According to this view, continued progress in medical knowledge through clinical trials requires an explicit abandonment of the doctor’s fully patient-centered ethic.

These proposals seem to be frank counsels of desperation. They resolve the ethical problems of equipoise by abandoning the need for equipoise. In any event, would their approach allow clinical trials to be conducted? I think this may fairly be doubted. Although many people are presumably altruistic enough to forgo the best medical treatment in the interest of the progress of science, many are not. The numbers and proportions required to sustain the statistical validity of trial results suggest that in the absence of overwhelming altruism, the enrollment of satisfactory numbers of patients will not be possible. In particular, very ill patients, toward whom many of the most important clinical trials are directed, may be disinclined to be altruistic. Finally, as the study by Taylor et al.<sup>12</sup> remind us, the problems of equipoise trouble investigators as well as patients. Even if patients are prepared to dispense with the best treatment, their physicians, for reasons of ethics and professionalism, may well not be willing to do so.

Marquis has suggested a third approach. “Perhaps what is needed is an ethics that will justify the conscription of subjects for medical research,” he has written. “Nothing less seems to justify present practice.”<sup>14</sup> Yet, although conscription might enable us to continue present practice, it would scarcely justify it. Moreover, the conscription of physician investigators, as well as subjects, would be necessary, because, as has been repeatedly argued, the problems of equipoise are as disturbing to clinicians as they are to subjects. Is any less radical and more plausible approach possible?

### **Theoretical Equipoise versus Clinical Equipoise**

The problems of equipoise examined above arise from a particular understanding of that concept, which I will term “theoretical equipoise.” It is an understanding that is both conceptually odd and ethically irrelevant. Theoretical equipoise exists when, overall, the evidence on behalf of two alterna-

tive treatment regimens is exactly balanced. This evidence may be derived from a variety of sources, including data from the literature, uncontrolled experience, considerations of basic science and fundamental physiologic processes, and perhaps a “gut feeling” or “instinct” resulting from (or superimposed on) other considerations. The problems examined above arise from the principle that if theoretical equipoise is disturbed, the physician has, in Schafer’s words, a “treatment preference” — let us say, favoring experimental treatment B. A trial testing A against B requires that some patients be enrolled in violation of this treatment preference.

Theoretical equipoise is overwhelmingly fragile; that is, it is disturbed by a slight accretion of evidence favoring one arm of the trial. In Chalmers’ view, equipoise is disturbed when the odds that A will be more successful than B are anything other than 50 percent. It is therefore necessary to randomize treatment assignments beginning with the very first patient, lest equipoise be disturbed. We may say that theoretical equipoise is balanced on a knife’s edge.

Theoretical equipoise is most appropriate to one-dimensional hypotheses and causes us to think in those terms. The null hypothesis must be sufficiently simple and “clean” to be finely balanced: Will A or B be superior in reducing mortality or shrinking tumors or lowering fevers in population P? Clinical choice is commonly more complex. The choice of A or B depends on some combination of effectiveness, consistency, minimal or relievable side effects, and other factors. On close examination, for example, it sometimes appears that even trials that purport to test a single hypothesis in fact involve a more complicated, portmanteau measure — e.g., the “therapeutic index” of A versus B. The formulation of the conditions of theoretical equipoise for such complex, multidimensional clinical hypotheses is tantamount to the formulation of a rigorous calculus of apples and oranges.

Theoretical equipoise is also highly sensitive to the vagaries of the investigator’s attention and perception. Because of its fragility, theoretical equipoise is disturbed as soon as the investigator perceives a difference between the alternatives — whether or not any genuine difference exists. Prescott writes, for example, “It will be common at some stage in most trials for the survival curves to show visually different survivals,” short of significance but “sufficient to raise ethical difficulties for the participants.”<sup>16</sup> A visual difference, however, is purely an artifact of the research methods employed: when and by what means data are assembled and analyzed and what scale is adopted for the graphic presentation of data. Similarly, it is common for researchers to employ interval scales for phenomena that are recognized to

be continuous by nature — e.g., five-point scales of pain or stages of tumor progression. These interval scales, which represent an arbitrary distortion of the available evidence to simplify research, may magnify the differences actually found, with a resulting disturbance of theoretical equipoise.

Finally, as described by several authors, theoretical equipoise is personal and idiosyncratic. It is disturbed when the clinician has, in Schafer's words, what "might even be labeled a bias or a hunch," a preference of a "merely intuitive nature."<sup>14</sup> The investigator who ignores such a hunch, by failing to advise the patient that because of it the investigator prefers B to A or by recommending A (or a chance of random assignment to A) to the patient, has violated the requirement for equipoise and its companion requirement to recommend the best medical treatment.

The problems with this concept of equipoise should be evident. To understand the alternative, preferable interpretation of equipoise, we need to recall the basic reason for conducting clinical trials: there is a current or imminent conflict in the clinical community over what treatment is preferred for patients in a defined population P. The standard treatment is A, but some evidence suggests that B will be superior (because of its effectiveness or its reduction of undesirable side effects, or for some other reason). (In the rare case when the first evidence of a novel therapy's superiority would be entirely convincing to the clinical community, equipoise is already disturbed.) Or there is a split in the clinical community, with some clinicians favoring A and others favoring B. Each side recognizes that the opposing side has evidence to support its position, yet each still thinks that overall its own view is correct. There exists (or, in the case of a novel therapy, there may soon exist) an honest, professional disagreement among expert clinicians about the preferred treatment. A clinical trial is instituted with the aim of resolving this dispute.

At this point, a state of "clinical equipoise" exists. There is no consensus within the expert clinical community about the comparative merits of the alternatives to be tested. We may state the formal conditions under which such a trial would be ethical as follows: at the start of the trial, there must be a state of clinical equipoise regarding the merits of the regimens to be tested, and the trial must be designed in such a way as to make it reasonable to expect that, if it is successfully concluded, clinical equipoise will be disturbed. In other words, the results of a successful clinical trial should be convincing enough to resolve the dispute among clinicians.

A state of clinical equipoise is consistent with a decided treatment preference on the part of the investigators. They must simply recognize that their

less-favored treatment is preferred by colleagues whom they consider to be responsible and competent. Even if the interim results favor the preference of the investigators, treatment B, clinical equipoise persists as long as those results are too weak to influence the judgment of the community of clinicians, because of limited sample size, unresolved possibilities of side effects, or other factors. (This judgment can necessarily be made only by those who know the interim results — whether a data-monitoring committee or the investigators.)

At the point when the accumulated evidence in favor of B is so strong that the committee or investigators believe no open-minded clinician informed of the results would still favor A, clinical equipoise has been disturbed. This may occur well short of the original schedule for the termination of the trial, for unexpected reasons. (Therapeutic effects or side effects may be much stronger than anticipated, for example, or a definable subgroup within population P may be recognized for which the results demonstrably disturb clinical equipoise.) Because of the arbitrary character of human judgment and persuasion, some ethical problems regarding the termination of a trial will remain. Clinical equipoise will confine these problems to unusual or extreme cases, however, and will allow us to cast persistent problems in the proper terms. For example, in the face of a strong established trend, must we continue the trial because of others' blind fealty to an arbitrary statistical bench mark?

Clearly, clinical equipoise is a far weaker — and more common — condition than theoretical equipoise. Is it ethical to conduct a trial on the basis of clinical equipoise, when theoretical equipoise is disturbed? Or, as Schafer and others have argued, is doing so a violation of the physician's obligation to provide patients with the best medical treatment?<sup>4,5,14</sup> Let us assume that the investigators have a decided preference for B but wish to conduct a trial on the grounds that clinical (not theoretical) equipoise exists. The ethics committee asks the investigators whether, if they or members of their families were within population P, they would not want to be treated with their preference, B? An affirmative answer is often thought to be fatal to the prospects for such a trial, yet the investigators answer in the affirmative. Would a trial satisfying this weaker form of equipoise be ethical?

I believe that it clearly is ethical. As Fried has emphasized,<sup>3</sup> competent (hence, ethical) medicine is social rather than individual in nature. Progress in medicine relies on progressive consensus within the medical and research communities. The ethics of medical practice grants no ethical or normative meaning to a treatment preference, however powerful, that is based on a hunch or on anything less than

evidence publicly presented and convincing to the clinical community. Persons are licensed as physicians after they demonstrate the acquisition of this professionally validated knowledge, not after they reveal a superior capacity for guessing. Normative judgments of their behavior — e.g., malpractice actions — rely on a comparison with what is done by the community of medical practitioners. Failure to follow a “treatment preference” not shared by this community and not based on information that would convince it could not be the basis for an allegation of legal or ethical malpractice. As Fried states: “[T]he conception of what is good medicine is the product of a professional consensus.” By definition, in a state of clinical equipoise, “good medicine” finds the choice between A and B indifferent.

In contrast to theoretical equipoise, clinical equipoise is robust. The ethical difficulties at the beginning and end of a trial are therefore largely alleviated. There remain difficulties about consent, but these too may be diminished. Instead of emphasizing the lack of evidence favoring one arm over another that is required by theoretical equipoise, clinical equipoise places the emphasis in informing the patient on the honest disagreement among expert clinicians. The fact that the investigator has a “treatment preference,” if he or she does, could be disclosed; indeed, if the preference is a decided one, and based on something more than a hunch, it could be ethically mandatory to disclose it. At the same time, it would be emphasized that this preference is not shared by others. It is likely to be a matter of chance that the patient is being seen by a clinician with a preference for B over A, rather than by an equally competent clinician with the opposite preference.

Clinical equipoise does not depend on concealing relevant information from researchers and subjects, as does the use of independent data-monitoring committees. Rather, it allows investigators, in informing subjects, to distinguish appropriately among validated knowledge accepted by the clinical community, data on treatments that are promising but are not (or, for novel therapies, would not be) generally convincing, and mere hunches. Should informed patients decline to participate because they have chosen a specific clinician and trust his or her judgment — over and above the consensus in the professional community — that is no more than the patients’ right. We do not conscript patients to serve as subjects in clinical trials.

### **The Implications of Clinical Equipoise**

The theory of clinical equipoise has been formulated as an alternative to some current views on the ethics of human research. At the same time, it corresponds closely to a preanalytic concept held by many

in the research and regulatory communities. Clinical equipoise serves, then, as a rational formulation of the approach of many toward research ethics; it does not so much change things as explain why they are the way they are.

Nevertheless, the precision afforded by the theory of clinical equipoise does help to clarify or reformulate some aspects of research ethics: I will mention only two.

First, there is a recurrent debate about the ethical propriety of conducting clinical trials of discredited treatments, such as Laetrile.<sup>7</sup> Often, substantial political pressure to conduct such tests is brought to bear by adherents of quack therapies. The theory of clinical equipoise suggests that when there is no support for a treatment regimen within the expert clinical community, the first ethical requirement of a trial — clinical equipoise — is lacking it would therefore be unethical to conduct such a trial.

Second, Feinstein has criticized the tendency of clinical investigators to narrow excessively the conditions and hypotheses of a trial in order to ensure the validity of its results.<sup>8</sup> This “fastidious” approach purchases scientific manageability at the expense of an inability to apply the results to the “messy” conditions of clinical practice. The theory of clinical equipoise adds some strength to this criticism. Overly “fastidious” trials, designed to resolve some theoretical question, fail to satisfy the second ethical requirement of clinical research, since the special conditions of the trial will render it useless for influencing clinical decisions, even if it is successfully completed.

The most important result of the concept of clinical equipoise, however, might be to relieve the current crisis of confidence in the ethics of clinical trials. Equipoise, properly understood, remains an ethical condition for clinical trials. It is consistent with much current practice. Clinicians and philosophers alike have been premature in calling for desperate measures to resolve problems of equipoise.

### **Acknowledgement**

I am indebted to Robert J. Levine, MD, and to Harold Merskey, DM, for their valuable suggestions.

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