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A Critique of Clinical Equipoise

Therapeutic Misconception in the Ethics of Clinical Trials

by FRANKLIN G. MILLER AND HOWARD BRODY

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A predominant ethical view holds that physician-investigators should conduct their research with therapeutic intent. And since a physician offering a therapy wouldn't prescribe second-rate treatments, the experimental intervention and the best proven therapy should appear equally effective. "Clinical equipoise" is necessary. But this perspective is flawed. The ethics of research and of therapy are fundamentally different, and clinical equipoise should be abandoned.

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**T**he Hypericum Depression Trial Study Group published in 2002 the results of a randomized trial comparing hypericum (St. John's Wort), sertraline (Zoloft), and placebo in the treatment of major depression.<sup>1</sup> In the study, funded by the National Institutes of Health, 340 subjects from twelve participating centers were randomized to three trial arms for an eight-week period, with careful monitoring to assure that patients who worsened significantly or who became suicidal were removed from the study and received adequate treatment. Neither hypericum

nor sertraline was found to be superior to placebo on the primary outcome measures. The authors noted, "From a methodological point of view, this study can be considered an example of the importance of including inactive and active comparators in trials testing the possible antidepressant effects of medications. In fact, without a placebo, hypericum could easily have been considered as effective as sertraline."<sup>2</sup>

What can we conclude about the ethics of this trial? One dominant viewpoint in research ethics would have prohibited the study. On this viewpoint, a randomized trial is ethical only in circumstances of "clinical equipoise"—a genuine uncertainty within the medical community as to whether (in this case) any of the three treatment arms are superior to the

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other two. No such uncertainty exists. Approximately twenty-five clinically available antidepressants, including sertraline, have been shown to be superior to placebo.<sup>3</sup> Moreover, the majority opinion within psychiatry probably holds that sertraline is definitely superior to hypericum for major depression, even if hypericum has potential for the treatment of mild to moderate depression. But another widespread viewpoint would hold that the trial was ethically sound. Depressed individuals widely use hypericum, a “natural” agent, despite the lack of proven efficacy. Accordingly, a rigorous evaluation offered scientific, clinical, and social value. According to the report of trial results, the study was approved by institutional review boards (IRBs) at twelve sites and subjects provided written informed consent.

But if clinical equipoise is a basic requirement for ethical research, how could all these review boards be blind to the unethical nature of this trial? And how could two such radically divergent viewpoints exist, without research ethics being widely regarded as in a state of crisis?

### **Therapeutic Misconceptions**

The prevailing ethical perspective on clinical trials holds that physician-investigators can discharge their “therapeutic obligation” to patients in the context of randomized clinical trials (RCTs) as long as treatments being tested scientifically satisfy clinical equipoise. We contend that this ethical perspective is fundamentally flawed. An ethical framework that provides normative guidance about a practice should accurately characterize the practice. The prevailing ethical perspective fails this test: All sound ethical thinking about clinical research, and the regulatory framework for review of protocols for clinical investigation, depends on a basic distinction between research and therapy. But the claims in the prevailing ethical perspective on clinical trials conflate research and therapy. These

claims are that the ethics of the physician-patient relationship must govern RCTs, that physicians who conduct these trials have a “therapeutic obligation” to patients enrolled in them, and that RCTs must be compatible with some form of equipoise.

Certainly, investigators and ethicists recognize that clinical trials are scientific experiments, which differ from standard medical care. They also recognize that they are subject to regulatory requirements which do not apply to routine medical practice. However, the prevailing ethical framework views clinical trials through a therapeutic lens. The mainstream ethical approach to clinical trials attempts to have it both ways: to view the clinical trial as a scientific experiment, aimed at producing knowledge that can help improve the care of future patients, and as treatment conducted by physicians who retain fidelity to the principles of therapeutic beneficence and therapeutic non-maleficence that govern the ethics of clinical medicine. The doctrine of clinical equipoise has emerged as the bridge between medical care and scientific experimentation, allegedly making it possible to conduct RCTs without sacrificing the therapeutic obligation of physicians to provide treatment according to a scientifically validated standard of care. This constitutes a “therapeutic misconception” concerning the ethics of clinical trials, analogous to the tendency of patient volunteers to confuse treatment in the context of RCTs with routine medical care.<sup>4</sup> As Paul Appelbaum has recently observed, “In fact, this confusion between the ethics of research and of ordinary clinical care appears rampant in the world of clinical trials.”<sup>5</sup>

The therapeutic misconception in the ethics of clinical trials is reflected in the language commonly used within the clinical research enterprise. Clinical trials are often described as “therapeutic research,” and investigators are regarded as having a “therapeutic intent.” Research participants who are being studied because they

have a medical condition under investigation are referred to as “patients,” and investigators as “physicians” or “doctors,” without qualification.

To demonstrate our contention about the mainstream approach to the ethics of clinical trials, we will offer an intellectual reconstruction of some of the history of research ethics since the 1970s. This history is characterized by incoherence resulting from commitment to two incompatible positions, each approaching research ethics in a fundamentally different way. The therapeutic misconception about the ethics of clinical trials has emerged from the “similarity position,” which argues that ultimately, the ethics of clinical trials rest on the same moral considerations that underlie the ethics of therapeutic medicine. The “difference position” argues that the ethics of clinical trials must start with the realization that medical research and medical treatment are two distinct forms of activity, governed by different ethical principles.

The reigning ethical paradigm for clinical trials has coexisted with clinical trials practice that departs from its guidance. Clinical equipoise, the cornerstone of the similarity position, rules out placebo-controlled trials whenever there is a proven effective treatment for the disorder under investigation.<sup>6</sup> However, IRBs have routinely approved such placebo-controlled trials. These two anomalies—unappreciated theoretical incoherence and conflict between the theoretical paradigm and the practice of ethical review of clinical trials—call for critical examination of the similarity position and the doctrine of clinical equipoise.

### **The Distinction between Research and Therapy**

In 1979, Robert Levine summarized “the most important achievements of the National Commission” for the Protection of Human Subjects of Biomedical and Behavioral Research in

“correcting the conceptual and semantic errors that had undermined virtually all previous attempts to develop rational public policy on research involving human subjects.”<sup>7</sup> Two portions of Levine’s summary capture the essential ingredients of the difference position: recognizing the distinction between research and therapy and, accordingly, abandoning the distinction between therapeutic and nontherapeutic research.

Clinical research shares with medical care the fact that both are performed by physicians in clinical settings, and both often use similar diagnostic and treatment interventions. When the commission began its work, physicians commonly regarded clinical research and medical therapy as inextricably connected. One authority quoted by Levine claimed that “Every time a physician administers a drug to a patient, he is in a sense performing an experiment.” But the commission recognized the importance of determining the boundaries between routine medical practice and research. For Levine, the commission’s conceptual breakthrough came with the realization that the physicians of the day were thinking about clinical research in the wrong way, and that the boundary between research and therapy was clear rather than fuzzy. The commission came to hold that clinical research is fundamentally different from medical practice.<sup>8</sup>

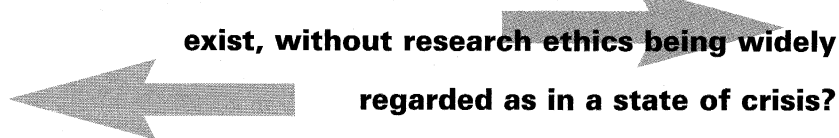
Clinical medicine aims at providing optimal medical care for individual patients. Ethically, it is governed by the principles of therapeutic beneficence and therapeutic non-maleficence. Therapeutic beneficence directs physicians to practice medicine with primary fidelity to promoting the health of particular patients. According to therapeutic nonmaleficence, the risks of medical care to which a patient is exposed are to be justified by the prospect of compensating medical benefits for that patient. The physician uses scientific knowledge to care for the patient and engages in therapeutic experimenta-

tion with the aim only of finding optimal treatment. It is not part of the role of the physician in providing medical care to develop scientific knowledge that can help future patients.

Clinical research, in contrast, is not a therapeutic activity devoted to the personal care of patients. It is designed for answering a scientific question, with the aim of producing “generalizable knowledge.” The investigator seeks to learn about disease and its treatment in *groups* of patients, with the ultimate aim of improving medical care. Scientific interest in any particular patient concerns what can be learned that is applicable to other patients. In view of the nature and pur-

In clinical research, by contrast, the interests of investigators and patient volunteers are likely to diverge, even when the investigator acts with complete integrity. Patient volunteers, especially in clinical trials, typically seek therapeutic benefit, though they also may be motivated by altruism.<sup>10</sup> Investigators are interested primarily in developing scientific knowledge about groups of patients. Regardless of investigators’ motivations, patient volunteers are at risk of having their well-being compromised in the course of scientific investigation. Clinical research involves an inherent tension between pursuing rigorous science and protecting research participants from harm.<sup>11</sup>

**How could two such radically divergent viewpoints exist, without research ethics being widely regarded as in a state of crisis?**



pose of clinical research, the principles of beneficence and nonmaleficence applicable to clinical research lack the therapeutic meaning that guides their application to medical care. Clinical research is dedicated primarily to promoting the medical good of future patients by means of scientific knowledge derived from experimentation with current research participants—a frankly utilitarian purpose.

A major reason for distinguishing research from therapy is to underscore that clinical research has an inherent potential for exploiting research participants.<sup>9</sup> Exploitation also may occur in clinical medicine—venal physicians sometimes perform medically unnecessary procedures for the sake of profit, for example. Yet when physicians of integrity practice medicine, physicians’ and patients’ interests converge. The patient desires to regain or maintain health or to relieve suffering; the physician is dedicated to providing the medical help that the patient needs.

Historically, the ethical distinction between research and therapy emerged out of concern about exploitive abuses of patients in clinical research. Reflection on this dark history gave rise to a major development in the ethics of clinical research: the requirement for independent, prospective review and approval of research protocols.<sup>12</sup> Prior independent review was considered necessary for clinical research because of the divergence between the interests of the investigator and the research participant. Self-regulation by physician-investigators could not be trusted in the research context to the same extent that self-regulation by physicians was appropriate in the therapeutic context. The basic rationale for prospective, independent research review depends on the distinction between research and therapy.

The point of distinguishing research and therapy is not to make an invidious comparison, implying that clinical trials are more risky or ethically problematic than routine clinical practice. Indeed, there is some ev-

idence that patients receive more favorable medical outcomes in many clinical trials,<sup>13</sup> and clinical medicine is certainly rife with ethical problems. Further, since research is more carefully regulated than medical practice, it is quite likely that fewer ethical violations occur in research. To say that two activities are ethically different is not to say that either is inherently better than the other.

### **Abandoning the Distinction**

The distinction between research and therapy is most likely to be obfuscated in the context of clinical trials, which test the safety or efficacy of investigational and standard treatments. Since patients may derive medical benefit from trial participation, especially in phase III RCTs (the

expect to find considerable variation in the treatment administered to those 340 patients after eight weeks or so. From the vantage point of therapy, this is what it means to provide care to patients.

From the vantage point of research, such variation would wreak havoc on experimental design and the validity and generalizability of findings. So when patients are randomized to one or another experimental drug, and are treated according to relatively inflexible protocols, the activity is very different from therapeutic medicine.

In many other ways, too, routine aspects of research deviate from what would be required by the duties of therapeutic beneficence and non-maleficence. Volunteer patients and physician investigators are often igno-

For these reasons, Levine argued that the second major contribution of the commission was to abandon the “illogical” distinction between therapeutic and nontherapeutic research, which previous policymakers thought was essential to the proper regulation of research and the protection of human subjects.<sup>15</sup> Because research and therapy are distinct activities, and the ethics of therapeutic medicine therefore cannot be automatically extended to guide research, it is mistaken to label research as “therapeutic” or “nontherapeutic,” as if that made any fundamental ethical difference. Many research trials consist of a complex mix of therapeutic and nontherapeutic elements—the placebo-controlled trial being only one obvious example—such that labeling the trial as a whole as “therapeutic” or “nontherapeutic” is misleading. In addition, the therapeutic-nontherapeutic distinction diverts attention from key ethical issues. Consider a nontherapeutic trial in which one interviews subjects and takes saliva samples, and a therapeutic trial in which one is testing a new cancer drug that has some promise for creating remission, but also has potentially life-threatening toxicity. Is the latter trial less in need of stringent regulatory oversight because it is “therapeutic”? Or does the therapeutic-nontherapeutic distinction distract the observer from those aspects of the trials that assume far greater moral weight, such as the level of risks and the potential vulnerability of subjects?

Once one understands the distinction between research and therapy, one realizes that “therapeutic” research is still research, and that the ethical rules appropriate to it are those appropriate for clinical research generally. Even though the patient may derive benefit from treatment being evaluated, the basic goal of the activity is not personal therapy, but rather the acquisition of generally applicable scientific knowledge. The basic goal and nature of the activity determines the ethical standards that ought to apply.

**A major reason for distinguishing research from therapy is to underscore that clinical research has an inherent potential for exploiting research participants. In clinical research, by contrast, the interests of investigators and patient volunteers are likely to diverge, even when the investigator acts with complete integrity.**

final stage of testing, which many investigational drugs never even reach), clinical trials are often characterized as “therapeutic research.”

Nonetheless, the process of treatment in RCTs differs radically from routine clinical practice.<sup>14</sup> Consider the contrast between the hypericum-sertraline trial and routine medical care for depression. If a physician treated 340 patients for major depression, she would not decide which drug to administer by flipping a coin. If the physician elected to use sertraline, she would judge each case individually to determine dose, when to change the dose, and whether to prescribe a second antidepressant or recommend other treatment. We would

rant of assignment to the experimental or control treatment, which may be a placebo. Trials often include interventions such as blood draws, lumbar punctures, radiation imaging, or biopsies that measure trial outcomes but in no way benefit participants. RCTs often contain a drug “washout” phase before randomization to avoid confounding the evaluation of the investigational treatment with the effects of medication that patients were receiving prior to the trial. These various features of research design promote scientific validity; they carry risks to participants without the prospect of compensating therapeutic benefit.

Writing in 1993, Jay Katz affirmed the vital importance of the distinction between research and therapy and deplored its blurring in practice: "The astronomical increase in clinical research has, in practice, not led to a clear demarcation between therapy and research, bioethical theories notwithstanding. This vital distinction remains blurred when physician-investigators view subjects as patients, and then believe that patients' interests and not science's are being served by participation in randomized clinical trials that are so commonly conducted in today's world."<sup>16</sup> One of the reasons investigators (and bioethicists) have failed to appreciate the distinction between research and therapy is that the similarity position has conceived the ethics of clinical trials within the context of the physician-patient relationship.

### **Charles Fried and the Similarity Position**

In 1974, Fried published *Medical Experimentation: Personal Integrity and Social Policy*, which launched the similarity position within bioethics.<sup>17</sup> Fried assumed that answers to ethical dilemmas in research would have to be found within the ethics of therapeutic medicine. He defended fidelity to the interests of the individual patient against a model in which "medicine is to be viewed as caring for populations."<sup>18</sup> What made the RCT ethically suspect was that it seemed to him a prime example of population-focused—rather than individualized—and utilitarian medicine.

Fried devoted most of his book to defending patients' "rights in personal care."<sup>19</sup> Returning to medical research, he took issue with trials in which patients were randomized to receive either the experimental intervention or standard care. Fried coined the term " equipoise " to describe the ethically necessary condition for conducting an RCT: physician-investigators must be indifferent to the therapeutic value of the experimental and control treatments evaluated in the

trial. The basic idea of equipoise had previously been articulated by Bradford Hill, a pioneer in the development of RCTs.<sup>20</sup> But what Fried objected to primarily in RCTs was not randomization per se, but the fact that no informed consent had been obtained. Fried saw the threat of "care for groups" (instead of "care for individuals") as residing primarily in the idea that it was legitimate to enroll subjects in an RCT without explicit, informed consent because the results of the trial would provide new medical knowledge that would improve the lot of future patients.<sup>21</sup> Because Fried was concerned chiefly about informed consent, an essential ingredient of both medical research and therapeutic medicine, he saw no problem in applying the ethics of medical therapy to medical research.

In the 1970s, the "respect for patient autonomy" movement was gaining steam as a replacement for the old Hippocratic ethic of paternalistic beneficence. Since both Fried and the National Commission seemed on the surface to be championing patient autonomy, it was easy to miss the point that they were proposing two fundamentally different strategies for approaching the ethics of clinical trials. Put another way, so long as the bioethics debate of the moment has to do with whether research ethics requires all competent subjects to give fully informed consent, any fundamental divergence between the similarity and the difference positions is likely to be obscured.

### **The Emergence of Clinical Equipoise**

During the 1980s, philosophers interested in research ethics recognized a tension between the obligation of physicians to offer optimal care to their patients ("the therapeutic obligation") and the provision of medical treatment in the context of clinical trials. Don Marquis addressed this problem in a 1983 essay, "Leaving Therapy to Chance."<sup>22</sup> The title is significant, suggesting that the RCT

is a form of therapy rather than an ethically distinct activity. Marquis began his essay, "Consider this dilemma: according to an argument that is hard to refute, the procedure for conducting randomized clinical trials of anticancer drugs is incompatible with the ethics of the physician-patient relationship. If this problem is to be resolved, then either a key procedure for achieving scientific knowledge in medicine must be given up or unethical behavior by physicians must be tolerated."<sup>23</sup> In framing this "RCT dilemma," Marquis assumed that the appropriate ethic for clinical trials was that of the (therapeutic) physician-patient relationship.

Fred Gifford, following the lead of Marquis, examined the RCT dilemma in greater depth: "The central dilemma concerning randomized clinical trials (RCTs) arises out of some simple facts about causal methodology (RCTs are the best way to generate the reliable causal knowledge necessary for optimally-informed action) and a *prima facie* plausible principle concerning how physicians should treat their patients (always do what it is most reasonable to believe will be best for the patient)."<sup>24</sup> Neither Marquis nor Gifford found what they regarded as a satisfactory solution, and neither considered the possibility that the difference position could dismiss the "RCT dilemma" as misguided to begin with.

In a landmark 1987 article, Benjamin Freedman offered a solution to the RCT dilemma that gained widespread acceptance within bioethics. He argued that the tension between ethically legitimate scientific experimentation and the therapeutic obligation of physicians could be overcome by the principle of "clinical equipoise."<sup>25</sup> Freedman agreed with Fried and Marquis that ethical clinical trials had to be compatible with therapeutic beneficence and non-maleficence. But he argued that Fried's formulation of equipoise was too constraining. Freedman called Fried's original concept "theoretical equipoise" (sometimes called "indi-

vidual equipoise”) and contrasted it with his favored concept of “clinical equipoise” (sometimes called “collective equipoise”). In the latter sense of equipoise, any individual investigator or physician might have reasons to believe that one arm of the RCT offers a therapeutic benefit over the other arm, but the medical profession as a whole remains divided. According to Freedman, an RCT is ethical so long as the professional community has not yet reached a consensus, which recognizes that “medicine is social rather than individual in nature.”<sup>26</sup> When, and only when, clinical equipoise is satisfied will patients enrolled in a clinical trial be assured that they will not be randomized to treatment known to be inferior. Freedman thus asserted in a later article that clinical equipoise is “grounded in the normative nature of clinical practice, the view that a patient is ethically entitled to expect treatment from his or her physician—an entitlement that cannot be sacrificed to scientific curiosity.”<sup>27</sup>

The bioethics community perceived Freedman’s concept of clinical equipoise as both a theoretical and a practical advance. Theoretically, it appeared to offer a more intellectually compelling argument than Fried’s initial formulation. Practically, it would permit useful RCTs that would otherwise be ethically proscribed to go forward. Since it appeared to solve the RCT dilemma by accommodating the conduct of clinical trials with the therapeutic obligation of physicians to offer optimal medical care, clinical equipoise gained wide currency as a fundamental concept of the ethics of clinical trials.<sup>28</sup> The persuasive way in which Freedman fortified the similarity position diverted attention from the fact that clinical equipoise collapsed the distinction between research and therapy.

The similarity position and clinical equipoise have been popular not only among bioethicists, but also among investigators. We speculate that this ethical perspective helps to address investigators’ psychological

needs. Physician-investigators, after all, went to medical school, not investigator school. To think of research with patients outside the ethical framework of the physician-patient relationship, as the difference position requires, may be difficult and threatening to them. Clinical equipoise offers a formula that seems to allow them to mix both physician and investigator roles—even if the psychological comfort is purchased at the price of ethical obfuscation.

The anomaly therefore exists that much of today’s bioethical thinking accepts clinical equipoise as an outgrowth of the similarity position, while the Federal regulations grew out of the work of the National Commission, which largely endorsed the difference position. One would imagine that sooner or later proponents of clinical equipoise would realize the need to defend this doctrine from the charge that it conflates the ethics of clinical trials with the ethics of medical care. But this is precisely what has not yet happened.

### **The Case of Placebo-Controlled Trials**

Although the similarity position, bolstered by clinical equipoise, became the reigning paradigm in the ethics of clinical trials, its dominion over practice was limited. This divorce between theory and practice has been particularly pronounced in the case of placebo-controlled trials. Freedman and his colleagues argued that the use of placebo controls is unethical whenever proven effective treatment exists for the medical condition under investigation in a clinical trial because those randomized to placebo would receive treatment known to be inferior.<sup>29</sup>

Despite the clear implications of clinical equipoise for the ethics of placebo-controlled trials, numerous trials, such as the hypericum-sertraline trial, continued to use placebo controls despite proven effective treatment. Placebo controls have typically been used in trials of new treatments

for a wide range of chronic conditions—including mood and anxiety disorders, asthma, stable angina, hypertension, and migraine headaches—all of which can be treated with medication of proven efficacy.

There are two explanations for this incoherence between theory and practice. First, the FDA has encouraged the use of placebo controls in trials concerning these and other chronic conditions.<sup>30</sup> Active-controlled trials designed to test the equivalence of the experimental treatment with a standard treatment suffer from serious methodological limitations. Whenever active-controlled trials show no statistically significant difference between the investigational treatment and an active comparator, two conclusions are possible. Either both were effective in the trial sample of patients, or neither was effective. Without the use of a placebo control, such trials lack internal validity. Accordingly, the FDA has insisted that pharmaceutical companies use placebo controls in trials of new treatments for conditions characterized by fluctuating symptoms and high rates of placebo response.<sup>31</sup> Second, the U.S. federal regulations governing human subjects research do not provide any explicit guidance on the use of placebo controls.<sup>32</sup> IRBs have been free to approve such placebo-controlled trials, provided that they meet regulatory requirements for a favorable risk-benefit ratio, including the potential value of knowledge to be gained and informed consent.

For the most part, this lack of fit between theory and practice received little critical attention until the publication in 1994 of an article in the *New England Journal of Medicine* entitled “The Continuing Unethical Use of Placebo Controls.”<sup>33</sup> Kenneth Rothman and Karin Michels castigated the practice of placebo-controlled trials in the face of proven effective treatment and the role of the FDA in encouraging these trials. They cited the Declaration of Helsinki, which relies heavily on the similarity posi-

tion, as prohibiting this widespread “unethical” practice.

Their article stimulated a lively debate over the ethics of placebo-controlled trials. Freedman and his colleagues attacked “the placebo orthodoxy” in a two-part article that challenged the scientific value of placebo-controlled trials and reiterated that they are unethical when proven effective treatments exist because they contravene clinical equipoise.<sup>34</sup> Other commentators, writing in leading medical journals, defended more or less extensive use of placebo-controlled trials on methodological and ethical grounds.<sup>35</sup> Without directly challenging the doctrine of clinical equipoise, they implied that clinical equipoise provides erroneous ethical guidance for placebo-controlled trials. Accordingly, the debate over placebo-controlled trials jeopardizes the reigning ethical paradigm of the similarity position and clinical equipoise.

#### **Critique of the Similarity Position and Clinical Equipoise**

Our reconstruction of the recent history of the ethics of clinical trials has traced the emergence and dominance of the similarity position. This history also reveals cracks in the foundation of this ethical paradigm. Simultaneous endorsement of the difference position, reflected in the federal regulatory system and the Belmont Report, and the similarity position, which invokes the doctrine of clinical equipoise, has left the ethics of clinical trials in a state of incoherence. Although this incoherence has not received critical attention, it becomes apparent once the assumptions underlying the similarity position and clinical equipoise are challenged. In addition, the divorce between research ethics theory and clinical trials practice in the case of placebo-controlled trials suggests that a critique of the similarity position and clinical equipoise is overdue.

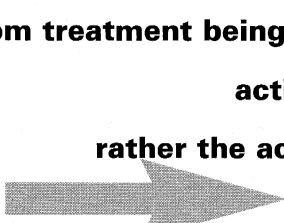
We contend that clinical equipoise is fundamentally mistaken

because “the RCT dilemma,” for which it was proposed as a solution, is false. Clinical equipoise and all other forms of equipoise make sense as a normative requirement for clinical trials only on the assumption that investigators have a therapeutic obligation to the research participants. The “therapeutic obligation” of investigators, forming one horn of the RCT dilemma, constitutes a therapeutic misconception about the ethics of clinical trials. The presumption that RCTs must be compatible with the ethics of the physician-patient relationship assumes erroneously that the RCT is a form of therapy, thus inappropriately applying the principles of therapeutic beneficence and nonmaleficence that govern clinical medicine to the fundamentally

ate to clinical research, which are distinct from therapeutic beneficence and therapeutic nonmaleficence.

Clinical equipoise is neither necessary nor sufficient for ethically justifiable RCTs. The use of placebo controls when proven effective treatment exists violates clinical equipoise; however, when methodologically indicated, their use is no different in principle from any research intervention that poses risks to subjects without the prospect of benefiting them.<sup>37</sup> In many cases, the risks of withholding effective treatment are excessive, and the use of placebo controls would thus be unethical. Nevertheless, it is the unacceptable level of risk, not the violation of investigators’ alleged “therapeutic obligation,” that makes these

**Even though the patient may derive benefit from treatment being evaluated, the basic goal of the activity is not personal therapy, but rather the acquisition of generally applicable scientific knowledge.**



different practice of clinical research. It is impossible to maintain fidelity to doing what is best medically for patients in the context of RCTs because these are not designed for, and may conflict with, personalized care. Although ethically appealing, the project of bridging the gap between therapy and research via the doctrine of clinical equipoise is doomed to fail.

The insight that the RCT contravenes the ethics of the physician-patient relationship led Samuel Hellman and Debra Hellman to argue that the RCT is unethical and that other methods of evaluating treatments should be employed.<sup>36</sup> This stance, however, would deprive patients and society of the benefits that flow from rigorous scientific evaluation of experimental and standard treatments. The more reasonable conclusion is that RCTs should be governed by ethical norms appropri-

trials unethical. In other cases, including the hypericum-sertraline trial, use of placebo controls when proven effective treatment exists is ethically justifiable.

By conflating the ethics of clinical trials with the ethics of therapeutic medicine, proponents of the similarity position may also contribute to the lack of adequate informed consent. If investigators view the ethics of clinical trials through a therapeutic lens, they may explicitly or implicitly foster the therapeutic misconception among research participants—that is, the tendency of participants in trials to confuse clinical trials with medical care. Research participants need to know that the overall activity is aimed not at their own ultimate benefit, but at discovering new knowledge to help future patients. If they think that clinical trial participation is a form of therapy, then they cannot

give informed consent. Moreover, unlike the therapeutic context, the patient-subject cannot delegate the decision to the physician-researcher. In the therapeutic setting, a patient can decide to trust the physician to choose the best treatment because the

already do with increasing frequency. Payments would add to the cost of conducting clinical trials, but it might help prevent the therapeutic misconception among trial participants.<sup>38</sup> To be paid signifies that the trial participant is not merely a patient seeking

dorsement of clinical equipoise renders incoherent any account that arises from the difference position. The most important next step for research ethics is to develop this “non-exploitation” framework systematically in a way that avoids any conflation of clinical research with medical care.

Those who agree that physician-investigators who conduct clinical trials are not governed by therapeutic beneficence still might argue that clinical equipoise provides important methodological guidance for justifying clinical trials. Freedman and his colleagues have argued that clinical equipoise is both an ethical and a scientific principle: “That principle can be put into normative or scientific language. As a normative matter, it defines ethical trial design as prohibiting any compromise of a patient’s right to medical treatment by enrolling in a study. The same concern is often stated scientifically when we assert that a study must start with an honest null hypothesis, genuine medical uncertainty concerning the relative merits of the various treatment arms included in the trial’s design.”<sup>40</sup> Nevertheless, whatever is valid methodologically in clinical equipoise—the honest null hypothesis—can be stated more clearly and without confusion with the therapeutic obligation, by appeal to the requirement of scientific value: no research participants should be exposed to the risks of valueless research. Clinical trials must be designed to answer valuable scientific questions. If the answer is already known or the question is trivial, then there is no honest null hypothesis, and a clinical trial should not be conducted. But this is logically independent of whether all the patients enrolled in the trial would receive medical treatment that is believed by the expert medical community to be at least as good as the standard of care.

This alternative framework provides accurate ethical guidance concerning clinical research without presuming that the ethics of therapeutic medicine should govern clinical trials.

**To be trustworthy, investigators must themselves understand clearly the ways in which clinical research differs from clinical practice and convey this forthrightly to potential research subjects.**

physician has the patient’s best interests at heart. The investigator has the interests of future patients at heart, and so cannot decide for the subject whether or not to participate in the research. To be trustworthy, investigators must themselves understand clearly the ways in which clinical research differs from clinical practice and convey this forthrightly to potential research subjects.

It is worth pondering, however, the practical consequences that might ensue if physicians, investigators, patients, and ethicists understood clinical trials without distortion by therapeutic misconceptions. Would recruitment of participants for valuable clinical trials become substantially more difficult, slowing progress in medical care? The fact that clinical trials are no longer seen as a mode of therapy leaves unchanged the real prospect of therapeutic benefits offered to patients from trial participation, including the opportunity to receive promising investigational agents, ancillary medical care, expert diagnostic evaluations, and education about their disorder. Nonetheless, some patients might be less inclined to participate in clinical trials when they appreciate the differences between these scientific experiments and medical care.

To attract enough subjects, researchers might have to pay people for their participation, as researchers in industry-sponsored clinical trials

therapy. If additional expenditure is necessary to motivate clinical trial participation, then this is a price worth paying for enhanced professional integrity and informed consent.

**An Alternative Ethical Framework**

In view of the theoretical and practical problems associated with the similarity position and its logical offspring, clinical equipoise, an alternative framework for the ethics of clinical trials is needed. The most promising recent treatment of research ethics has been developed by Ezekiel Emanuel, David Wendler, and Christine Grady.<sup>39</sup> They propose seven ethical requirements for all clinical research: (1) scientific or social value; (2) scientific validity; (3) fair subject selection; (4) favorable risk-benefit ratio; (5) independent review; (6) informed consent; and (7) respect for enrolled research participants. This framework is built on the difference between research and therapy and on the core value of *protecting research participants from exploitation*.

Yet even this formulation of an ethical framework appropriate to clinical research testifies to the hold of the similarity position. The authors endorse clinical equipoise, claiming it is implied by the requirements of value, validity, and risk-benefit ratio. We contend, by contrast, that the en-

We illustrate this by applying the seven ethical requirements to the example of the hypericum-sertraline trial.

**Scientific or social value and scientific validity.** The study has social value owing to the widespread use of herbal remedies. Since the efficacy of hypericum in treating depression (especially major depression) was uncertain, there was an honest null hypothesis that hypericum would be no better than placebo. It would have been unreasonable to design the trial as an active-controlled superiority trial, since it is highly unlikely that hypericum could be shown to be more effective than sertraline. An active-controlled equivalence trial would lack "assay sensitivity" because the finding that the reduction in symptoms of depression experienced by those trial participants receiving hypericum was not significantly different for those receiving sertraline would not validly support the inference that hypericum was effective.<sup>41</sup> It would remain possible that neither treatment was effective in the study sample—as was in fact shown. The study, therefore, was properly designed as a three-arm placebo-controlled trial.

**Fair subject selection.** There is no evidence to suggest that particularly vulnerable patients were recruited inappropriately for this study, which included a sample representative of depressed patients.

**Favorable risk-benefit ratio.** Risk-benefit assessment of research protocols ultimately comes down to a matter of judgment. With respect to the use of the placebo control—the aspect of the trial that violated clinical equipoise—the risks to participants from an eight-week trial, with careful exclusionary criteria and monitoring, were not excessive and were justifiable by the anticipated value of the knowledge to be gained from the research. Hence, the placebo component of the study had a favorable risk-benefit ratio. Eliminating the placebo would have made the risk-benefit ratio unfavorable by virtue of undermining the scientific validity of the research.

**Independent review, informed consent, and respect for enrolled research participants.** The report of the study asserted that IRB approval was obtained at all sites and that all subjects gave informed consent. In addition, the described procedures for monitoring subjects for possible risk of harm indicated an acceptable level of respect.

In sum, this study was ethically justifiable despite violating clinical equipoise; moreover, had it been designed in accordance with clinical equipoise, it would have been methodologically deficient and therefore ethically questionable.

Charles Weijer, a leading advocate of clinical equipoise and the similarity position, has recently claimed that "Placebo-controlled trials in the context of serious illnesses such as depression or schizophrenia are ethically egregious precisely because no competent physician would fail to offer therapy to a patient with the condition."<sup>42</sup> Although we agree that depression is a serious illness, the hypericum-sertraline trial demonstrates that there is nothing "ethically egregious" about the use of placebo controls in trials of treatment for depression, as long as the ethical requirements for clinical research are satisfied. Whether or not one agrees that, all things considered, the placebo control was ethical in this trial, the ethical justification of placebo controls has nothing to do with the therapeutic practice of competent physicians. In any case, the alternative ethical framework with its seven requirements provides adequate guidance for clinical trials without appeal to the incoherent doctrine of clinical equipoise and without conflating the ethics of research with the ethics of therapy.

#### Disclaimer

The opinions expressed are the views of the authors and do not necessarily reflect the policy of the National Institutes of Health, the Public Health Service, or the U.S. Department of Health and Human Services.

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