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Clinical Equipoise and the Incoherence of Research Ethics

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The doctrine of clinical equipoise is appealing because it appears to permit physicians to maintain their therapeutic obligation to offer optimal medical care to patients while conducting randomized controlled trials (RCTs). The appearance, however, is deceptive. In this article we argue that clinical equipoise is defective and incoherent in multiple ways. First, it conflates the sound methodological principle that RCTs should begin with an honest null hypothesis with the questionable ethical norm that participants in these trials should never be randomized to an intervention known to be inferior to standard treatment. Second, the claim that RCTs preserve the therapeutic obligation of physicians misrepresents the patient-centered orientation of medical care. Third, the appeal to clinical equipoise as a basic principle of risk-benefit assessment for RCTs is incoherent. Finally, the difficulties with clinical equipoise cannot be resolved by viewing it as a presumptive principle subject to exceptions. In the final sections of the article, we elaborate on the non-exploitation framework for the ethics clinical research and indicate issues that warrant further inquiry.

Keywords: *clinical equipoise, exploitation, randomized controlled trials, risk-benefit assessment*

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I. INTRODUCTION

Equipose has gradually become accepted as a fundamental principle governing the ethics of clinical trials. By the turn of the 21st century, it had become entrenched as the conventional wisdom in bioethics in the form of “clinical equipose,” as articulated by Benjamin Freedman in 1987. What led us to challenge this principle? The genesis of our work may hold more than biographical interest, as it illustrates the ways in which bioethics scholarship addresses important and controversial issues of theory and practice.

A debate over the ethics of placebo-controlled trials that withhold proven effective treatment was sparked by the 1994 “Sounding Board” in the *New England Journal of Medicine* by Rothman and Michels. Those authors invoked the Declaration of Helsinki, the leading international code of ethics for clinical research, to condemn placebo-controlled trials of this type. One of us (FGM) was unpersuaded by the ethical reasoning of Rothman and Michels. He developed a rebuttal based on methodological considerations and risk-benefit assessment (Miller, 2000; Emanuel & Miller, 2001). As it became clearer that the line of argument defending some placebo-controlled trials was in direct conflict with clinical equipose, FGM invited HB to collaborate on a paper contending that this principle was not an absolute requirement for ethical clinical trials.

HB, for his part, had for many years not been writing about research ethics. Previously, in preparation for a new edition of a textbook of medical ethics (Brody, 1981), he had read and been persuaded by two seminal articles that argued for a strong distinction between the ethics governing therapeutic medicine and the ethics of research (Levine, 1979; Churchill, 1980). He was thus inclined to be suspicious of the position Freedman put forward in 1987, since Freedman viewed the ethics of research as simply a subcategory of the ethics of medical therapy. But he was not fully aware that clinical equipose had been elevated to such a high status as a principle until he was drawn back into the debate by being invited to collaborate with FGM.

Our first paper, focusing on the fallacy of relying on clinical equipose to condemn placebo-controlled trials, appeared as a “target article” in the *American Journal of Bioethics* (Miller & Brody, 2002). Many of the 15 accompanying commentaries were instructive in their strong reactions. Some attacked our rejection of clinical equipose as heretical, misguided, and dangerous (Weijer, 2002; Lemmens & Miller, 2002; Glass & Waring, 2002; Steinberg, 2002). Some offered constructive criticism by appealing to the historical underpinnings of the appeal to equipose (Weijer, 2002; Lemmens et al., 2002). Others noted that the alternative framework we had invoked as an alternative to clinical equipose—non-exploitation of research participants—was thinly developed and seemed inadequate (Jecker, 2002; Resnik, 2002).

These criticisms guided us in developing a more systematic critique of clinical equipoise (Miller & Brody, 2003). Here we focused on the basic disagreement between the critics and defenders of equipoise. Our argument is based on what we termed the “difference position,” that the ethical principles governing medical therapy are different from those governing clinical research. Defenders of equipoise rely on the “similarity position,” that the same ethical principles govern both activities. We first argued that numerous theoretical and practical difficulties arise from the similarity position. As a result, clinical equipoise is fundamentally incoherent. We next expanded somewhat on our advocacy of the non-exploitation framework as a set of appropriate guidelines for ethical and clinical research based in the difference position (Emanuel, Wendler, & Grady, 2000). In a follow-up paper, we argued that the basic distinction between the ethics of therapy and the ethics of clinical research has both theoretical and practical utility, even in cases where the same physician serves in the dual role of attending physician and principal investigator (Brody & Miller, 2003).

In what follows we will expand on our previous replies to critics. First, we will disentangle two components of equipoise that are often erroneously conflated. Next, we will argue that clinical equipoise’s basic appeal to the ethics of therapeutic medicine is in fact misguided and incoherent, since no ethical physician would treat patients in the way that clinical equipoise would allow research participants to be treated. After that we will expand on the incoherence of clinical equipoise as it is applied to risk-benefit assessment within clinical trials. We will next argue that clinical equipoise cannot be rendered coherent merely by carving out exceptions. We will elaborate on the non-exploitation framework by addressing the criticisms of our argument recently offered by Jansen (2005). In conclusion, we will suggest matters that require future study.

II. DISENTANGLING THE COMPONENTS OF EQUIPOISE

One point discussed in our critical analysis merits further elaboration. We suggest that much of the appeal of clinical equipoise derives from its combining a scientific principle indicating the epistemic prerequisites for conducting a clinical trial—a state of uncertainty regarding a valuable clinical question—with an ethical norm concerning the design and conduct of randomized trials—no patient should be randomized to an intervention known to be inferior either to one of the treatments under investigation or the established, scientifically validated standard of care. These two components can be described as

1. the honest null hypothesis principle and
2. the no inferior treatment principle. Because the honest null hypothesis principle appears unassailable—there is no point in conducting a clinical

trial without a valuable research question to answer—clinical equipoise as a whole, including the no inferior treatment principle, may seem to have unquestionable validity. Indeed, Freedman and colleagues (Freedman, Glass, & Weijer, 1996b) conflated these two principles, although they are not identical in meaning.

Everyone agrees with the honest null hypothesis principle. Randomized controlled trials seek to answer clinically valuable questions by testing hypotheses concerning the safety and/or efficacy of treatments under investigation. As long as the answers to these research questions are unknown, there is a state of uncertainty in which it is reasonable to posit the null hypothesis. However, the honest null hypothesis principle is not equivalent to, nor does it logically imply, the no inferior treatment principle. Thus, the manifest validity of the former does not establish the validity of the latter.

To illustrate the lack of equivalence between these two component principles of clinical equipoise, consider a “proof of concept” randomized trial evaluating a novel agent to treat depression compared with a placebo control. Suppose that scientific knowledge and a previous open-label trial in depressed patients suggest that this agent may have antidepressant efficacy. Yet, it is unknown, and worth knowing, whether it would prove to be superior to a placebo control in a double-blind, randomized trial. In other words, there is an honest null hypothesis. Nevertheless, this trial would violate clinical equipoise by virtue of contravening the no inferior treatment principle, since a range of established drugs have been demonstrated to be effective in treating depression in prior placebo-controlled trials.

It might be objected that the null hypothesis in this case is not really “honest,” because the clinically valuable question to answer is whether the new agent is as good or better than existing antidepressants, not whether it is better than “nothing.” Freedman and colleagues (Freedman, Glass, & Weijer, 1996a) have recommended active-controlled non-inferiority trials as an alternative to placebo-controlled trials that violate clinical equipoise. However, several scientifically valid questions may arise in connection with a new treatment, each of which generates an honest null hypothesis. Practitioners may wish to know how the new treatment compares to the existing standard therapy; but it may still be scientifically valid to ask how the new therapy stacks up against a placebo control.

Moreover, as several commentators have noted, non-inferiority trials lacking a placebo control present serious methodological problems when they are employed to evaluate treatments for chronic conditions (such as depression) with waxing and waning symptoms and high rates of placebo response (Temple & Ellenberg, 2000; Emanuel & Miller, 2001). A finding that the novel agent is not inferior to the standard drug may mean either that both treatments were effective or that neither was effective in the sense of being superior to a placebo intervention. In the absence of a placebo-controlled trial, valid conclusions

about efficacy may be impossible to draw. Moreover, use of placebo controls in early phase efficacy trials is desirable in order to obtain rigorous data and expose the least number of subjects to an experimental agent. Thus, there is an honest null hypothesis that the experimental agent is no better than a placebo.

Failure to disentangle these two component principles of clinical equipoise has sown confusion. For example, a recent examination of the state of clinical research ethics highlighted and discussed major issues of consensus and of controversy (Brody, McCullough, & Sharp, 2005). With respect to clinical trials, the authors claimed that there is consensus that clinical trials should satisfy equipoise but controversy over the ethics of placebo-controlled trials that withhold proven effective treatment. This account illustrates another version of the incoherence in the ethics of clinical trials that we diagnosed. If the robust principle of equipoise is posited (including both the honest null hypothesis and the no inferior treatment principles), then the controversy over placebo-controlled trials should be resolved: those trials conducted in the face of proven effective treatment would be judged unethical. Strictly speaking, this account of the state of the ethics of clinical trials is not necessarily inconsistent. For the definition of equipoise that they formulated appears to capture the honest null hypothesis principle but not the no inferior treatment principle: "There is consensus that clinical trials should be launched only when there is sufficient promise for the new intervention but insufficient evidence to justify broad use, a condition called equipoise." However, because equipoise, as generally understood, includes both of these nonequivalent principles, this characterization of the consensus and controversy in the ethics of clinical trials is not accurate. It fails to note the theoretical controversy over the ethical validity of equipoise and the incoherence between the prevailing endorsement of equipoise in theory and the common practice of IRBs approving placebo-controlled trials that violate equipoise, i.e., those that contravene the no inferior treatment principle.

III. INCOHERENCE OF THE THERAPEUTIC ORIENTATION

There is yet another reason to regard clinical equipoise as fundamentally incoherent. The proponent of clinical equipoise assents to both the following:

1. The physician-investigator is held to the same ethical standards, in treating the research subject, as is the physician in the purely therapeutic physician-patient relationship.
2. It is ethically appropriate to enroll a subject in a double-blind, randomized trial, so long as the trial meets the criteria of clinical equipoise (i.e., there is genuine uncertainty within the professional community as to which of the two treatment arms is superior).

Proponents of clinical equipoise appear not to have noticed that their theory depicts the therapeutic duty owed by the physician to the patient in an extraordinarily odd way. The physician, on this theory, appears to be nothing more than a medication-dispensing machine. It does not matter that the physician selects the medication administered to the “patient” by tossing a coin. It does not even matter that the physician dispenses a medication to the “patient” while remaining ignorant of precisely what medication is being dispensed. All that presumably matters is that the patient, in the end, receives a treatment that is not inferior to the accepted standard treatment. The methods by which the physician arrived at that treatment decision are apparently of no ethical concern.¹

We would assert, in contrast, that clinical equipoise proponents cannot have it both ways. Although physicians are obliged to practice in accordance with the established communal standard of care, the essence of the *therapeutic* obligation owed by the physician to the patient is that the physician must make an *individualized judgment* as to what treatment is in the patient’s best interests. Physicians, in arriving at this judgment, must employ the best standard methods of medical decision-making in order to fulfill their ethical obligation. There can be no place for randomization and for double-blinding in the “care” that the treating physician gives to the “patient.” Therefore, if the therapeutic orientation to clinical trials is adopted, no such research methods can ever ethically be used, regardless of what medication the patient ends up receiving (Hellman & Hellman, 1991).

The more reasonable alternative is that it *is* ethical to conduct randomized, double-blind clinical trials. But if that is so, then it *cannot* be the case that the ethical obligations of the investigator to the subject are essentially *the same as* those of the therapeutic physician to the individual patient. We find it extraordinary that clinical equipoise has become so popular among physician-investigators, given that it embodies a demeaning portrayal of the physician’s role in therapeutics. We speculate that what underlies this puzzling incoherence is that scientific and therapeutic norms inherently conflict in the context of clinical trials, creating deep moral discomfort. Many physician-investigators and ethicists attempt to ward off this moral discomfort via the doctrine of clinical equipoise. As we have demonstrated, however, this maneuver aiming to bridge scientific and therapeutic norms leads to multiple forms of incoherence in clinical research ethics. The solution is to jettison clinical equipoise and develop a sound ethical framework for clinical research that is appropriate to the nature of the activity.

IV. INCOHERENCE IN RISK-BENEFIT ASSESSMENT

Another theoretical objection to clinical equipoise, which has not received sufficient attention, is the way that appeal to this principle introduces

incoherence in risk-benefit assessment (Miller & Brody, 2002). The method of risk-benefit assessment in clinical research suggested by defenders of clinical equipoise, known as “components analysis,” advocates a two-track approach (Weijer, 2000; Weijer & Miller, 2004). Therapeutic procedures are assessed by the test of whether they satisfy clinical equipoise. Non-therapeutic procedures are justified if their risks are minimized and reasonable in view of the knowledge anticipated to be gained by the research.

The major theoretical problem posed by this two-track assessment is the following. Clinical equipoise derives its ethical force from the assumption that clinical research should be governed by the ethical standards of medical care (Miller & Brody, 2003). The therapeutic obligations of physicians in medical practice are held to be operative as well in clinical trials. Clinical trials, however, often include research procedures, such as blood draws, lumbar punctures, imaging procedures using radiation, and biopsies, to measure trial outcomes that pose risks to subjects without any compensating medical benefits. These interventions, which admittedly may pose no more than minor risks, would not be justifiable within the ethical framework governing medical care.

How, then can they be justified in clinical trials? Of course, everyone agrees that they are justifiable; yet it is difficult to see how they can be justified within the ethical framework for clinical research that embraces clinical equipoise. Why should treatment interventions be held to a different standard of risk-benefit assessment than non-therapeutic interventions? If non-therapeutic interventions are justified in research, then why not placebo controls that pose minor risks of discomfort or harm from withholding effective symptomatic treatment?

Components analysis merely asserts that there are two standards of risk-benefit assessment; no argument is provided to support this approach. The theoretical problem can be illustrated concretely by comparing the following two studies (Litton & Miller, 2005). Consider a study of the pathophysiology of depression that recruits subjects diagnosed with major depression who are not currently receiving anti-depressant treatment. The scientific protocol requires that they remain without treatment for depression for 6 weeks, during which various research assessments are conducted, including brain imaging. Compare this study with a placebo-controlled six-week trial of a novel medication to treat major depression. Both studies carry the risk of symptom exacerbation while treatment is being withheld. However, according to components analysis this same risk is assessed in terms of two different standards, which may yield divergent judgments. The placebo-controlled trial would be ruled out on account of contravening clinical equipoise. The withholding of treatment in the pathophysiology study might be justified, provided that the risks have been minimized and the anticipated scientific yield is sufficient to justify the risks. This is incoherent. Moreover, the placebo-controlled trial arguably should be easier to justify,

as those receiving placebo may benefit from a placebo effect, which is unlikely to be evoked in the pathophysiology study in which no masked placebo treatment is provided.

It is possible that components analysis might be amended so that studies such as this research on the pathophysiology of depression would not be acceptable. Non-therapeutic procedures might be assessed by an additional standard, analogous to clinical equipoise, which prohibits any interventions that would compromise the health or medical care of research participants. This might be called “the principle of therapeutic nonmaleficence.” Just as physicians would not defer recommending anti-depressant treatment to a patient with major depression pending additional diagnostic assessment over a six-week period, or would not recommend a watch-and-wait option to see if the depression remits on its own, so six weeks without medically indicated treatment for major depression should not be allowed in research. Although the research in question is not a treatment study, it does involve withholding standard effective treatment, making it contrary to therapeutic nonmaleficence.

This move suffers from practical and theoretical difficulties. It is not clear when non-therapeutic procedures that pose risks to subjects without compensating medical benefits count as compromising their health or medical care. Everyone would agree that a single blood draw for research purposes would not qualify. But consider another type of research, which has been frequently employed to study the pathophysiology of depression and the mechanism of action of pharmacologic treatment. Euthymic patients with a history of major depression are given a tryptophan depletion procedure that causes temporary recurrence of depressive symptoms, typically lasting several hours, but no more than one or two days. Does it compromise the health or medical care of the research participants? Provoking symptoms of depression, albeit temporarily, certainly seems counter-therapeutic, and therefore difficult to square with therapeutic nonmaleficence.

Consider also “infection challenge studies” that expose healthy volunteers to viruses, bacteria, or parasites in order to improve the understanding of infectious diseases and conduct early phase testing of candidate vaccines. This research is typically limited to induced infections that are either self-limiting or fully eradicable by (delayed) drug treatment. Such research seems all the more difficult to justify in terms of therapeutic nonmaleficence, as it makes healthy volunteers into sick patients who suffer symptoms of infectious disease and often require a course of medical treatment to return to health. We contend, however, that, although controversial, both types of challenge studies are justifiable, provided that they have scientific merit, receive IRB approval, institute careful monitoring of subjects, and obtain their informed consent (Miller & Rosenstein, 1997; Miller & Grady, 2001).

The theoretical difficulty with this amendment to components analysis is the same that characterizes clinical equipoise. Requiring that all research

interventions are governed by a standard of not compromising the health or medical care of research participants applies the ethical standards of therapeutic medicine to the fundamentally different activity of clinical research. In contrast to components analysis, the risks of all interventions in research, whether treatments or not, should be assessed in terms of whether they are compensated by the prospect of any direct medical benefit to the participants; if not, it must be judged that the uncompensated risks are not excessive and that they can be justified by the value of knowledge to be gained from the research. Appeal to clinical equipoise, or a norm of *therapeutic nonmaleficence*, is not necessary to ensure adequate protection of research subjects. Nor is it desirable, because it would prohibit socially valuable research that does not expose participants to undue risks of harm.

V. EXCEPTIONS TO EQUIPOISE

One response to our critique of clinical equipoise, particularly as it relates to the justifiability of some placebo-controlled trials that violate this standard, is to modify the doctrine developed by Freedman and colleagues so as to recognize some exceptions to clinical equipoise, or situations in which clinical equipoise is outweighed by competing considerations, such as scientific validity. Placebo-controlled trials of “minor” conditions such as allergic rhinitis, non-migraine headache, and perhaps mild depression or anxiety, might be assessed as ethically justifiable despite the clinical availability of proven effective symptomatic relief. One rationale for this is that physicians do not always recommend treatment for such mild conditions, thus suggesting that there is no therapeutic obligation that is violated by such placebo-controlled trials (Weijer, 2002; Lemmens et al., 2002). Alternatively, the therapeutic obligations of physicians with respect to patients suffering from these conditions might be seen as sufficiently weak to be overridden by the methodological considerations favoring the use of placebo controls (Lemmens et al., 2002; Ackerman, 2002).

Whereas the former stance might be consistent with the original conception of clinical equipoise espoused by Freedman and colleagues, the latter is not. In criticizing the position of those who claim that withholding effective treatment does not expose subjects to risks of real harm, Freedman, Glass, & Weijer (1996b), p. 253, ask, “But how much harm to subjects, short of these end points [mortality and permanent disability] should be cause for concern?” Contrasting trials of treatments for allergic rhinitis with those for schizophrenia, they write,

In other cases of placebo-controlled trials, for example, of allergy medicine, the harm is incomparably less. Yet even then, consider that many subjects are enrolled when they seek treatment at a health facility. Does

the mere fact that the patient is sufficiently troubled to seek medical attention not indicate that, *from the subject's own point of view*, these symptoms should be treated? (p. 254)

The thrust of their argument, therefore, is to reject exceptions or overrides to clinical equipoise in the case of minor conditions, given that patients are seeking treatment and physicians have a duty to treat. Accordingly, it is not clear how this sort of modification to clinical equipoise can be squared with the theory of therapeutic responsibility that underlies it. In sum, we see no merit in this ad hoc effort to preserve clinical equipoise in view of the theoretical problems associated with this principle—especially the conflation between the ethics of clinical research and the ethics of medical care—and the availability of adequate ethical guidance that does not appeal to or presuppose equipoise.

VI. EXPLOITATION

We have recognized that our account of exploitation in clinical research, drawing on the seminal conceptual analysis of Alan Wertheimer (1996), remains thin and needs further development—a weakness noted by our critics. In particular, Jansen (2005) discusses clinical equipoise and exploitation in terms that initially appear to be congenial to our analysis. She argues quite appropriately that before we can accept non-exploitation as an alternative ethical framework, we must carefully elaborate its implications. But her eventual conclusion seems to undermine our arguments. She claims that if we were to take non-exploitation seriously, we would be forced to implement some extreme measures such as a compulsory draft for research subjects. In the end we might conclude that we were better off with clinical equipoise as an ethical paradigm.

Jansen, in our view, misunderstands two basic features of our argument. First, and most fundamentally, she fails to grasp the logical structure of research ethics. We claim that a basic feature of clinical research ethics is utilitarian or consequentialist. However, an adequate ethical framework requires that the utilitarian component must be constrained by non-utilitarian norms aimed at avoiding exploitation and promoting respect of research participants. The utilitarian feature, in short, is the following: The eventual gain in health information and health outcomes for the larger population produced by clinical research justifies what is being done to a few individuals today, who may or may not derive any personal health (or other) benefits from participation, and who may face risks. Can such a utilitarian ethical component be tolerated in this sort of public institution? We know that the utilitarian calculus is prone to subject a small number of individuals to

unacceptable risks and to violations of individual rights in the name of a greater public good (Rawls, 1971).

This undesirable feature of strict utilitarianism leads to the role of norms aimed at avoiding exploitation (Emanuel, Wendler, & Grady, 2000). They are intended to function as a series of “side constraints” on pursuit of the social good (Nozick, 1974; Morreim, 2005). These norms form a deontological check within an institution that serves a utilitarian purpose. The goal of clinical research is to discover new knowledge to aid future patients; but one must respect the basic rights of, and avoid exploiting, individual research subjects while seeking this worthy goal.

Seeing norms of non-exploitation as side constraints explains the extent to which (if ever) protection for the individual research subject can be traded off against greater good for future patients. Perhaps the most troublesome of the provisions we have proposed are the twin ethical principles of social value and scientific validity. If these were interpreted to mean that the high future value of the research results generated by rigorous studies justified otherwise unacceptable risks of harm to the present subjects, then non-exploitation side constraints would have ceased to function, and the ethics of research would be unalloyed utilitarianism. Therefore, in practice, social value and scientific validity are critical in protecting participants from exploitation when their valence is negative. If a study is not directed to a valuable question or is poorly designed scientifically, it will not matter whether subjects give consent and are fairly selected; there is no justification to subject them to even minor risks or inconveniences. If the social value and scientific validity of the research protocol are high, however, we still have to ask whether subjects are free of exploitation in other ways.

The second basic feature of our argument that we believe that Jansen misunderstands is the appeal of “non-exploitation” as redirecting attention to the practical context of a research study. Clinical equipoise is appealing as an ethical principle because of its abstractness. It claims to be able to tell us whether a study is ethical or not based on only one feature—whether any subjects will be given a type of care currently viewed as less than optimal therapeutically. Jansen chimes in with this general approach, offering for the most part only very sketchy accounts of the various sorts of research trials she discusses.

A hint of this problem is her rhetorical move in calling trials that violate clinical equipoise “bad deal trials.” In one sense this is a circular argument. Trials that violate clinical equipoise are, by assertion, bad deals for the subject. If a subject is stuck with a bad deal, she is being exploited. Therefore any trial that violates clinical equipoise also violates non-exploitation. Therefore, according to this approach, we can retain clinical equipoise as a principle of research ethics, since it does the same practical work as non-exploitation.

Is any trial that violates clinical equipoise truly a “bad deal” for the subject? Answering that question requires more than applying an across-the-board

label. It requires that we carefully investigate all aspects of the design of the trial, along with the social and cultural context within which it is conducted, including the reasonable motivations of research participants. That is the deep contextual inquiry that we intend to encourage by adopting “non-exploitation” as central to clinical research ethics. Applying this strategy to some of the placebo-controlled trials that Jansen would label as “bad deals” by virtue of violating clinical equipoise will, we believe, show that they are not bad deals at all, at least for some subjects—and there may be enough subjects like that to provide a respectable sample size for a research study. But such a point-by-point refutation of Jansen is beyond the scope of this article.

VII. CONCLUSION

We have examined instances of theoretical and practical incoherence in research ethics attributable to endorsing clinical equipoise as a fundamental principle. Additionally, we have responded to criticisms of our critique of this principle and of the non-exploitation ethical framework that we have proposed as an alternative. We conclude by alluding to some questions that we believe worthy of consideration in the future.

Several have challenged our insistence on the sharp division between the ethics of clinical research and the ethics of therapeutic medicine. We agree that a systematic account of a sound ethical framework for research with patient-subjects would need to address the basic distinction between the ethics of research and the ethics of therapy, as well as areas of overlap between the two. It might be helpful here to recall that a *distinction* need not necessarily imply a *dichotomy*. We consider it vital at all times to retain the conceptual distinction between the ethics of research and of therapy, respectively. But we do not suggest by this that the two activities never co-exist in practice. Although we have argued that it is a mistake to see investigators as having the same obligations as physicians and research participants as merely patients in need of medical care, it would also be a mistake to see the latter as no different from healthy volunteers and the former as “scientists only” (Miller, Rosenstein, & DeRenzo, 1998; Miller & Rosenstein, 2003).

So far, the specific theoretical and practical problems linked to the misguided enshrinement of clinical equipoise have caused us to focus almost all of our attention on the distinction between research and therapeutic ethics. In the future, however, two key ideas of convergence require explication. First, understanding that the process of clinical research requires a dynamic perspective. There is a trajectory from being a patient with a certain medical condition which makes one eligible for a clinical trial; to being a research subject who nevertheless requires ongoing medical attention within the scientific constraints imposed by the trial protocol; to becoming a

patient again, though perhaps with new clinical insights that have been gained as a result of trial participation.

The second key idea is to note that this trajectory does *not* describe a transition from patient to subject, but rather the transition from (mere) patient to patient-subject. Avoiding exploitation will remain an important guiding orientation toward the ethics of this transition. But non-exploitation might in the end prove insufficient. It seems reasonable to propose, for instance, that a physician-investigator has an obligation to maximize therapeutic benefits to the patient-subject, *provided that* this benefit can be attained within the scientific constraints imposed by the protocol (Emanuel, Wendler, & Grady, 2000). How to supplement a pure non-exploitation framework with some account of this duty to provide protocol-consistent therapeutic benefits, without falling back into the incoherence of the therapeutic orientation to clinical trials or clinical equipoise, is a challenge for the future.

NOTE

1. This odd depiction of the way that the attending physician selects treatment for the patient is also foreign to the conception of Charles Fried, who is credited with having first introduced the concept of 'equipoise' into research ethics in 1974 (Fried, 1974). Fried laid great emphasis on "rights in personal care," which assumed that the physician made an *individualized* judgment about what treatment would be best for each patient. While Benjamin Freedman, like Fried, grounded his view of equipoise in what we call the "similarity position," he appears to have neglected Fried's earlier admonitions about what the ethics of therapeutic medicine require of the physician (Freedman, 1987).

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