

Avoiding a Jekyll-And-Hyde Approach to the Ethics of Clinical Research and Practice

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Franklin G. Miller and Howard Brody (2002) clearly recognize two things: that there is an important tension between the aims of clinical care and research and that research practices can differ from those of clinical care. They err, however, when conferring normative ethical force to this observation. It is one thing to say that clinical care and research are not the same. It is quite another to state that, therefore, moral obligations of physicians and researchers differ fundamentally.

Recognition of the tension between the ends of clinical research and practice forms the bases of research ethics and research regulation. Some of the most outrageous historical examples of research misconduct involved clinician-researchers who ignored their primary obligations to care for the sick. The fact that physicians were involved in such misconduct has shocked us as much, if not more so, than the fact that research subjects were sometimes seriously harmed and often uninformed. In response to these episodes of misconduct, statements of principle, guidelines, professional codes, and regulatory frameworks have been promulgated, virtually all of which impose on physician-researchers not only a negative duty to respect research subjects but also a positive duty to protect and promote their well-being. In the *Belmont Report*, for example, the members of the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979) formed a consensus on three ethical principles that continue to be widely recognized to guide the conduct of research and institutional review board (IRB) review: respect for persons, beneficence, and justice. Though requirements based on the principle of respect for persons became overemphasized, the *Belmont Report* enunciates as equally essential obligations based on beneficence. The National Commission was clearly aware that some might consider the principle of beneficence to indicate merely supererogatory obligations. In anticipation of this, it stated that the principle is not to be understood in this way:

The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: 1) do not harm and 2) maximize possible benefits and minimize possible harms.

This conception of beneficence clearly goes *far* beyond Miller and Brody's negative obligation to avoid exploitation. Other well-known guidelines include formulations of a positive obligation on physician-researchers to protect and promote the well-being of individual research subjects (Council for International Organizations of Medical Sciences 1993; International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use 1996; and World Medical Association 2001).

In short, the tension between the ends of research and practice has been recognized and responded to, not by way of dividing off the ethics of research from the ethics of practice, but rather by way of forceful statements of the positive therapeutic obligations of researchers to research subjects.

Given their inclination to a minimally intrusive research ethic, it is ironic that Miller and Brody should react strongly to a concept developed with the intention of providing a research-friendly solution to this tension. The concept of equipoise was originally introduced by Charles Fried (1974). Fried argued that it is only ethical for researchers to ask subjects to submit to randomization where they are personally "genuinely uncertain" as to the relative merits of the study arms to which subjects are to be randomly assigned. Other commentators agreed that individual uncertainty is a crucial condition for physician-researcher involvement in randomized controlled trials (RCTs) (Shaw and Chalmers 1970). Benjamin Freedman (1987) reacted against these claims, arguing that requirements for individual uncertainty set impossibly demanding conditions for the conduct of RCTs. He pointed out that attempts to adhere to such conditions would unduly cripple the conduct of research. Recognizing the importance of the therapeutic obligation on physician-researchers, he felt that the obligation should be embodied in a condition more in line with the social nature of standards for clinical practice and for the acceptance of research results in communities of scientists. With his "clinical equipoise" condition, Freedman provided a moral argument showing how physician-researchers' therapeutic obligations can be reconciled with their commitment to scientific standards. According to the condition of clinical equipoise, individual physicians, even if they have a clinical preference, can continue randomization as long as they

have reasonable grounds for believing that available scientific evidence has not established the superiority of one treatment intervention.

Obviously, clinical equipoise, as any theoretical concept, is not a panacea. There is still plenty of room for refinement, interpretation, and debate (over, for instance, the appropriate reference community, what is to count as standard treatment, or the nature and extent of evidence sufficient to give rise to an obligation to halt the RCT). However, Miller and Brody have been hasty and all too drastic in dismissing this concept without recognition of or engagement with its historical origins and by positing an unprecedented and unargued for redefinition of the ethics of research. Where Freedman sought to provide a moral compass to physicians-researchers caught in the tension between the ends of research and practice, Miller and Brody suggest the adoption of split personalities in recognition of correspondingly split moral worlds and constitutive moral obligations. Researchers and clinicians inhabit different moral worlds, they argue, and are thus not bound by the same moral commitments. The researcher is morally committed to research; the clinician morally bound by a duty of care. This Jekyll-and-Hyde approach to ethics clearly offers an easy solution to the moral discomfort of a research community that is increasingly under pressure to perform placebo-controlled trials. However, physician-researchers who seek to adhere to a coherent moral code should find only false comfort in their solution. The realization of the tension between clinical research and practice in the debate surrounding the use of placebo controls is not genuinely solved through a sheer re-definition of the ethics of clinical research and practice which, without argument, finds in the differences between the activities grounds for their moral divorce.

In any other walk of life we tend to believe that people ought not to conduct themselves as professionals in a way that they would normally deem to be morally problematic. We tend to value moral integrity in all spheres of human activity. If anything, our expectations of moral integrity are only heightened with respect to professionals with whom we have relationships of care and trust. When meeting physicians in a medical context, patients expect that their best medical interests will be protected and promoted. They do not expect that physician-researchers will hold their therapeutic obligations in suspense at their discretion, whenever they believe they are involved in "research activities." Yet Miller and Brody invite physician-researchers to do precisely that—to hang their fiduciary duty on the hook when they approach patients as researchers.

Miller and Brody might object to this characterization by stressing that it is their view that placebo controls are

acceptable only when people are fully informed and not exposed to excessive levels of risk. The first part of this argument reflects an inordinate reliance on individual autonomy and ignores the real-life circumstances of research participation. The entire research review process is clearly an explicit, sustained, and systematic recognition of the insufficiency of informed consent. Many have pointed out how informed consent is an ideal that is hardly realized. And Freedman himself argued that we must be careful not to conflate the ethics of research with the ethics of consent (Freedman 1987). Any defensible ethic of research must account for the fact that many patients will be in a vulnerable and dependent position vis-à-vis their caregivers. Particularly when institutionalized, patients assume that those who show medical interest in their case are professional caregivers in whom trust is rightfully placed. Many patients may be under pressure to enter clinical trials as an alternative means by which to obtain access to needed care. One of us has received personal accounts of patients being offered participation in placebo-controlled trials as an alternative to waiting several months for standard treatment of a psychiatric condition. Even when recruited through advertisements, research subjects are often lured with alarming descriptions of the serious problems they have. Those who respond to well-designed publicity campaigns often do so because they long for medical attention and care. Still others participate in research because they lack health insurance and want to have at least a chance of receiving treatment. Although these circumstances may not necessarily be coercive and thus invalidate consent, they nevertheless call into question the appropriateness of relying on informed consent as the primary condition for the conduct of research. As Robin West eloquently stated,

{c}onsensual acts of commerce, labor, or sexual intercourse are not morally good simply because they are not coerced: a bad trade is still bad, even if it is not theft; a bad job is still bad, even if it is not slavery; and bad sex is still bad sex, even if it is not rape. (1985, 399)

Despite their positing of a clear distinction between the ethics of clinical research and practice, Miller and Brody recognize that clear lines are drawn with much difficulty in practice. In attempting to mollify the implications of their earlier insistence that placebos be considered nontherapeutic procedures, Miller and Brody point out that "placebo controls are typically combined with interventions that have therapeutic potential. These include clinical attention from investigators and members of the research team {and} the therapeutic milieu of research hospitals." Even if Jekyll could feel morally comfortable clothed in Hyde's hide, can one really expect the research subjects to be aware of such subtle and continuous trans-

formations? Jekyll and Hyde wear the same white coat, speak the same language, and handle the same instruments. They seem the mirror image of one another to the unsuspecting patient.

As to the second part of their argument, we agree with Miller and Brody that some notion of significant/nonsignificant risk may play a role in determining the ethical acceptability of certain placebo-controlled trials, but only exceptionally. The relevance of the degree of risk exists not in isolation, however, but rather in sorting out the implications of clinical equipoise in marginal situations, as, for instance where there might be some doubt as to the nature and extent of the superiority of "effective standard treatment." There are numerous minor conditions in society for which standard treatment is available but often avoided. Hay fever is often left untreated or is sometimes treated with alternative treatments that have not been scientifically validated. The risk of not taking any medication for these conditions is small, and this often influences peoples' decisions about whether to seek treatment or not. They may feel indifferent about the available treatments and feel happy to participate in a trial that could offer something better. The issue of the significance of the risk is in such cases not an independent condition but is rather intimately bound up with the questions surrounding what is to count as standard treatment and when the availability of standard treatments is to have normative force on the conduct of physician-researchers. In these conditions it is generally fine for physician-researchers to leave the decision of whether or not to participate solely in the hands of their patients, who often vote with their feet when determining what are acceptable treatments. Where the risks posed by the use of placebo controls are slight in light of available treatments, the therapeutic obligation must be felt with correspondingly decreased force, and the clinical-equipoise condition may thus be applied with some latitude.

Recognition of the need for latitude is not novel. In the Canadian Tri-Council Policy Statement, for instance, it is provided that placebo controls may be used in circumstances where: "Patients have provided an informed refusal of standard therapy for a minor condition *for which patients commonly refuse treatment* and when withholding such therapy will not lead to undue suffering or the possibility of irreversible harm of any magnitude" (Medical Research Council of Canada, Natural Sciences and Engineering Council of Canada, and Social Sciences and Humanities Research Council of Canada 1998; emphasis added).

These exceptions to the rule of clinical equipoise on the use of placebo controls are just that—exceptions, or even less than that: subtle variations on the theme of what constitutes standard treatment. We find in the argument of Miller and Brody worrisome indication of the ease with

which one can minimize the risks posed by many conditions and overstate the limited popularity of treatments for these conditions in order to justify placebo-controlled trials. Miller and Brody give us a taste of this in their suggestion that if nonsignificant risks can justify a placebo control, then it "is an open question whether they are justifiable in conditions such as depression and anxiety disorders, migraine . . . and asthma." This statement makes clear the importance of our insistence that flexible applications of the rule be of the nature indicated in the Tri-Council Policy Statement. We are unclear as to why Miller and Brody would argue for the importance of introducing a distinction between significant and nonsignificant risk in considering the acceptability of the use of placebo controls, only to later abandon it in suggesting that to accept placebo controls in cases posing nonsignificant risk (e.g., hay fever) is to "open the door" of acceptability to the use of placebo controls in conditions where risks of deprivation of treatment would clearly be significant (e.g., asthma). The latter exception (minor conditions for which people often refuse treatment) indicates a sensible limit on the application of the clinical-equipoise condition, but Miller and Brody have misread it to defend abandoning the clinical equipoise condition.

This brings us to our last point, with respect to the scientific foundation of the concept of clinical equipoise. Miller and Brody argue that there can be no scientific reason upon which to reject the use of placebo controls. An implication of this argument must be that there is no scientific foundation for the clinical-equipoise condition. We find neither the argument nor its implication to be persuasive. In fact, clinical equipoise seems to have a strong scientific foundation.

For research to be relevant, it has to mimic treatment conditions that would (comparator arm) or will (experimental arm) occur in clinical care. Research design is "implemented to promote scientific validity" but with the fundamental *expectation that this will promote therapeutic benefit* when research results are applied in a clinical context. If scientific validity and value are fundamental requirements for the ethics of clinical research, research design must be relevant for clinical care. There can be a tension between research and clinical care, but they cannot be fundamentally separated.

Miller and Brody are right to note that scientific validity is a crucial precondition for the conduct of research. The "note of clarification" to the Declaration of Helsinki would open the door to placebo controls despite the availability of proven effective treatment when there are "compelling and scientifically sound methodological reasons" to use it. However, Miller and Brody's interpretation of this clarification as constituting a fundamental departure can be questioned from a legal perspective, based on rules of

interpretation related to the need for cohesion and the need to interpret provisions in the spirit of the general text. Furthermore, the Note of Clarification indicates a highly exceptional justification for the use of placebo controls where researchers can either *prove* that placebo controls are scientifically *necessary* to the conduct of the research, or alternatively, where the condition investigated is so minor that *no* additional risks are posed by deprivation of treatment. Researchers are held to a much higher standard than indicated by Miller and Brody's interpretation. Others may comment more knowledgeably about the methodological limitations of placebo controls. It is sufficient here to invite those arguing for scientific necessity of placebo controls when standard therapy is available to provide a clear example that cannot be captured under the flexible interpretation of the equipoise condition. We still have not seen any sound argument explaining the clinical importance of research results that indicate that a new compound is better than nothing but tell us little about how it compares to existing compounds. If scientific merit is to be taken seriously, and if scientific necessity is a precondition for placebo-controlled trials when proven effective treatment is available, then attempts to justify the use of placebo controls under normal circumstances ought to continue to prove exceedingly difficult. While such attempts may not prove so difficult under the parallel moral universes of research and practice imagined by Miller and Brody, they will rightly continue to be so as long as we continue to recognize the primacy of therapeutic obligations in clinical care and research. ■

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Are Concerns about the Ethics of Placebos a Stalking Horse for Other Issues?

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Where conditions are severe, as in amyotrophic lateral sclerosis, or mild, as in allergic rhinitis, the issue of placebo controls in clinical trials provokes few disputes. The problem appears to lie in the midground, and there are few areas of therapeutics in which the debate about placebo controls has been fought as keenly as in the case of antidepressants. Some have argued that depressed patients may lack the capacity to consent to clinical trials (Elliott 1997). Others have argued that clinical trials may be unethical because of the very serious, if relatively rare, risk of suicide from untreated depression (Weijer 2000).

Table 1, consisting of trial data from submissions to the U.S. Food and Drug Administration for agents licensed as antidepressants during the 1990s, have been adapted from Khan, Warner, and Brown (2000). The data have been modified in the light of reports obtained under freedom of information provisions (Brecher 1991; Lee 1990; 1991), which indicate that more than 50% of the suicidal acts categorized as occurring while a patient was on placebo during trials of sertraline and paroxetine in fact occurred during the placebo washout period. The washout period is the five to seven days between discontinuation of