Clinical Research Should Not Be Permitted to Escape the Ethical Orbit of Clinical Care

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Clinical Research Should Not Be Permitted to Escape the Ethical Orbit of Clinical Care

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Miller and Brody's (2002) argument supporting the use of placebo-controlled clinical trials includes statements that are disturbing, particularly their claim of an "ethically fundamental distinction between clinical research and clinical care." Clinical research is a branch of clinical medicine that has been accorded dispensations such as the ability to use unapproved drugs and novel therapies. This license comes with obligations such as provision of a clear and detailed statement describing the research, institutional review board approval, and informed consent. Clinical investigators have not, as Miller and Brody seem to contend, been accorded broad immunity from the ethical standards of clinical practice in general.

Miller and Brody quite remarkably absolve clinical investigators of responsibility for the consequences of their experiments by advising physicians to avoid "the dual roles of treating physician and investigator." If a physician treats a patient with either an accepted or an experimental therapy, a physician-patient relationship is established that obliges the physician to care for that patient. It would be a violation of our common notion of responsibility if clinical investigators could administer an experimental therapy and then be absolved of the responsibility to manage the consequences of their intervention. This should particularly be true for clinical investigators who are likely to be using protocols and drugs less familiar to other physicians. Miller and Brody would allow physicians to accept clinical responsibility when their clinical trials pose "only slight risks"; I think they have it backward. It is even more important for a physician to care for a patient when the risks of their interventions are high.

Miller and Brody justify a schism between the ethics of clinical care and clinical research because "physician investigators are not offering personalized medical therapy for individual patients," but "seek to answer clinically relevant scientific questions by conducting experiments that test the safety and efficacy of treatments in groups of patients." The dominant goals of clinical research and clinical care may differ; however, the existence of a goal does not suffice as its moral justification. Having the predominant goal of obtaining scientific information on a large number of patients does not mean that clinical investigators are automatically immune from the ethical obligations of clinical care any more than a thief whose predominant goal is to rob banks is automatically entitled to immunity from laws that prohibit burglary. The degree to which investigators can deviate from the ethics of clinical care should be limited to what is precisely stated in their approved protocols.

Do Miller and Brody seriously mean, "Investigators have a duty to avoid exploiting research participants, not a therapeutic duty to provide optimal medical care?" If, after the data is analyzed, it is recognized that some participants in a therapeutic trial did not receive what ultimately proved to be optimal care, the investigators cannot be held morally responsible because they could not have known in advance which arm of the study would be the optimal one. But Miller and Brody do not limit the omission of optimal care to these restricted circumstances. The only obligation they impose on clinical investigators is "a duty to avoid exploiting research participants."

The notion that clinical investigators do not have a duty to provide optimal medical care is nonsense. People who agree to participate in clinical investigations do not relinquish the right to optimal medical care. If a patient on a cardiac study develops an arrhythmia, he or she should receive optimal medical care. If a patient on an oncology protocol develops febrile neutropenia, he or she should receive optimal medical care. If a patient on any study develops any problem, he or she should receive optimal medical care. Any investigator who accepts Miller and Brody's contention that they are not obligated to provide optimal medical care should note that fact in their consent form . . . which no rational person would sign.

Miller and Brody also justify the use of placebos in therapeutic trials because physician-investigators can ethically perform risky research procedures on healthy volunteers who obtain no medical benefit. If experiments of no possible benefit can be performed on healthy people, then, they contend, it should also be permissible to use placebos of no possible benefit in clinical research. Their analogy is strained because there is a difference between a healthy volunteer and a sick patient; a healthy volunteer is not in need of therapy and cannot benefit from therapy. The examples used to justify experimentation without therapeutic benefit include performing biopsies on healthy people and exposing healthy people to ionizing radiation. Acts of this sort are not appropriate moral role models for use in other situations.

Miller and Brody repeatedly use the phrase "proven effective treatment" without elaboration. That phrase would accommodate proofs based on anecdotal evidence, proofs

based on historical comparisons, and proofs derived from randomized clinical trials. Effectiveness might mean disease stability, a minor response, a complete response, or a cure. Rational patients might find the proof of a "proven effective treatment" insufficiently rigorous or the effectiveness of the treatment unacceptably minimal and for either of those reasons choose an experimental therapy even if that entailed the risk of drawing a placebo. It is neither wise, necessary, nor justified to compartmentalize the ethics of clinical research and the ethics of clinical care in a manner that relieves clinical investigators of the responsibility to provide optimal medical care. ■

References

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Exploitation and the Ethics of Clinical Trials

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In their essay "What Makes Placebo-Controlled Trials Unethical?" Frank Miller and Howard Brody (2002) argue that the ethical obligations in clinical research are different from those in routine clinical practice. While ordinary clinicians have obligations to provide optimal medical care for their patients, clinical researchers have no such duty. Instead, investigators have a duty not to exploit research subjects for the sake of medical research. According to Miller and Brody,

> enrolling patient volunteers in placebo-controlled trials that withhold proven effective treatment is not fundamentally unethical as long as patients are not being exploited . . . they are not being exploited if
>
> 1. they not being exposed to excessive risks for the sake of scientific investigation; and
> 2. they understand that they are volunteering to participate in an experiment rather than perceiving personalized medical care directed at their best interests.

Miller and Brody use this idea of avoiding exploitation to show why it is not unethical to enroll patients in a low-risk placebo-controlled trial, such as a trial for allergic rhinitis, since even those patients who are receiving no treatment will not be exposed to excessive risks. It would be unethical, on the other hand, to conduct a placebo-control study that exposes patients to excessive risks, such as a trial for a new medicine to control hypertension. Their view also implies that it would be unethical to enroll a patient in a placebo-control trial without adequately informing the patient that they have no guarantee of receiving a medically proven treatment and that they are participating in an experiment. Miller and Brody provide an analysis of "excessive risk" and say that this is based on a risk-benefit assessment conducted by the institutional review board (IRB) in charge of reviewing the research. Thus, their analysis of the ethics of placebo-control trials focuses on two well-established ethical principles in biomedical research, beneficence and respect for persons, which have guided federal (e.g., 45 CFR 46, 21 CFR 50) and international (e.g., World Medical Association 2000) research policy for many years (Levine, 1986; U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979).

Miller and Brody do not, however, incorporate another important principle in research ethics, the principle of justice, into their analysis of exploitation in research. The principle was mentioned prominently in *The Belmont Report* and has also influenced federal and international research policies. Although the principle of justice has often generated controversy in research ethics, it clearly plays an important role in the evaluation of clinical trials (see discussions in Kahn, Mastroianni, and Sugarman 1998; Macklin 2001). Indeed, many commentators have argued that injustice and unfairness in research can be found in several infamous studies, such as the Tuskegee Syphilis Study and the Willowbrooke Hepatitis Experiments.

In order to develop a thorough and complete analysis of exploitation in research, one must also address justice and fairness in research. Therefore, Miller and Brody should amend their definition of exploitation in research to include a clause dealing with justice. I would suggest the following addition:

3. the researchers are not taking unfair advantage of the social, economic, psychological, or cultural disadvantages of their subjects.

I will now briefly explain why I would modify their proposal.

I begin with a few words about exploitation. When people use the term *exploitation* in moral debates, they have