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## Exploitation and the Ethics of Clinical Trials

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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. ■

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Miller, F. G., and H. Brody. 2002. What makes placebo-controlled trials unethical? *American Journal of Bioethics* 2(2):3–9.

## 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

in mind several different senses of the word. The word *exploit* has a morally neutral sense in which to exploit a thing is simply to “use the thing”; for example, “she exploited her artistic skills in designing the flower arrangement.” However, this is not the sense of the word I am concerned with here. The word also has a pejorative or value-laden sense, in which to exploit a thing is to “use a thing unethically or unjustly.” For the purposes of this essay, I would like to use the sense of *exploit* in which to exploit a person is to take “unfair advantage” of that person (Wertheimer 1996; Carling 1999).

Taking “unfair advantage” of someone has two components:

1. taking advantage of someone; and
2. doing so unfairly.

It is possible to take advantage of someone else without doing so unfairly. For example, a person who specializes in removing fallen trees who travels to the site of a recent hurricane may take advantage of this disaster and its victims to earn some money. Although he is taking advantage of the misfortunes and vulnerabilities of the hurricane victims, he is also providing them with an important and valued service, that is tree removal. As long as he offers a fair deal for his work and does not engage in price gouging, then we would say that he is not taking unfair advantage of the hurricane victims. However, if he engages in price gouging in order to reap a huge profit from the situation, we would say that he is taking unfair advantage of the victims and that he is exploiting them. What makes price gouging unfair is that the purchaser does not receive a fair, just, or equitable share of benefits in the bargain.

If we apply this analysis to clinical trials, one can see that there are many situations where researchers have the opportunity to take advantage of their subjects’ social, economic, psychological, cultural, or medical misfortunes and vulnerabilities. Subjects may be desperately ill, poor, uneducated, illiterate, in prison, or lack decision-making capacity due to age or mental illness or disability. There is nothing inherently wrong with conducting research on subjects that suffer from these misfortunes or vulnerabilities, provided, of course, that one does not take unfair advantage of those subjects and one observes other principles of research ethics, such as beneficence and respect for persons. (Indeed, federal research regulations have special rules and provisions for conducting research on vulnerable subjects, which we need not address here.)

But what does it mean to take unfair advantage of vulnerable research subjects? According to *The Belmont Report*, treating subjects fairly implies that the distribution of benefits and burdens in research is equitable; that is, that subjects that bear the burdens of research participation also obtain a fair share of the benefits. Although there are

disagreements about what makes the distribution of benefits and burdens in research fair or equitable, there is widespread agreement that this is an important consideration in the ethics of research, and various federal and international research policies reflect this concern for equity (Emanuel, Wendler, and Grady 2000). It is especially important to address issues of fairness and equity when conducting research on vulnerable populations, since these subjects may have difficulty giving informed consent and they may be unable to promote their own interests effectively.

Some of the recent debates about the ethics of clinical trials have involved questions about the distribution of benefits and burdens in research on vulnerable populations. For example, critics of HIV/AIDS placebo-control trials in developing nations have argued that the subjects are not getting a fair share of the benefits of research, because new medications developed through these studies will not be made reasonably available to patients in those countries due to the high costs of medications and a lack of a healthcare infrastructure (Macklin 2001). Critics of this research have argued that many of these studies exploit vulnerable research subjects in the developing world for the sake of science.

According to Miller and Brody’s analysis, a clinical trial in the developing world would not be unethical provided that the risks are not excessive and subjects give their informed consent to participate. Let’s consider their example of a study on allergic rhinitis. They hold that such a study would be an ethical placebo-control trial. If the trial takes place in the United States or some other developed nation, then I would tend to agree with their assessment. But suppose it is conducted in a developing nation (or some other setting where subjects are vulnerable and not expected to receive a fair share of the benefits of research, due to social, economic, or other factors). Suppose that subjects will participate in the trial but will have virtually no chance of receiving any additional benefits beyond those resulting from their direct participation. Suppose that the benefits will accrue mostly to pharmaceutical companies and to citizens of developed nations. Would such a trial be ethical?

I think most people would say that such research, even if low risk and fully informed, could still be viewed as unfair and exploitative and, hence, unethical. To avoid exploiting research subjects, researchers need to also ensure that subjects and participant populations are likely to receive a fair share of the benefits of research. Thus, Miller and Brody’s analysis of exploitation in research should be amended to reflect these concerns about benefit sharing and justice in research. Research cannot be ethical if it takes unfair advantage of research subjects. ■

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# I Thought We Were in This Together?

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Despite all of the unprecedented events occurring around the globe today, it is still very difficult to open up a newspaper without finding an account of another “disaster” in the world of clinical research. There is a steady drum beat of horror stories in which patients were allegedly misinformed or mistreated by doctors acting in ignorance or in violation of widely held ethical standards to the detriment of their patients. These include the tragic death of a young woman in a pulmonary physiology study at Johns Hopkins and the intervention by the Maryland State Court to halt a clinical study evaluating different methods for environmental lead abatement and to assert its legal authority over the assessment of risks involved in all clinical research in children.

One of the key issues around which much of the criticism of clinical research has revolved is the use of placebos. This discussion has become even more heated following the performance of a number of placebo-controlled trials in HIV-infected patients that were conducted in Third World countries but that did not incorporate the latest findings from ACTG investigations in the United States (Angell 1997; Lurie and Wolfe 1997; Varmus and Satcher 1997). This has culminated in the recent publication by the World Health Organization of a directive against the use of placebo-controlled trials for any disease in which there is a proven effective therapy. Miller and Brody (2002) succinctly summarizes the history of these developments, and the authors make a compelling argument in favor of judicious use of placebo-controlled trials. They demonstrate that clinical research is not synonymous with clinical care and that the same rules of conduct are not always valid in both domains. Moreover, they repeat the persuasive arguments of Temple and Ellenberg (2000a; 2000b) that validity may require a placebo-controlled study design. Miller and Brody conclude that valid science

is congruent with the most ethical approach to the problem.

While the essay by Miller and Brody is an admirable defense of a reasoned research strategy, I think there is an important element that is being overlooked in the discussion of this topic. The underlying assumption when problems arise in clinical research seems to be that the investigator alone is either guilty of willfully neglecting well-accepted ethical standards or is merely ignorant of how to protect the best interest of patients. Whether it is time pressure, inappropriate financial incentives, inattention to psychosocial complexities, or competition to succeed, the clinical researcher is viewed as prey to forces that compromise ethical conduct in research.

I suspect it was not always this way. Many clinical investigators probably began their careers when they realized the limits of their medical knowledge and capacity. Guided by senior mentors, they were motivated to figure out improvements in treatment that might help their patients. Clinical research was considered a worthy enterprise, an integral part of medical care, and not an afterthought. Some physicians may have made a legitimate profit, and others may have abused the system for personal gain. But these were usually egregious exceptions among the large group of clinical researchers. Most important, the investigators viewed themselves as allies of their patients working as a team to gain a deeper understanding and, hopefully, better therapy for disease.

It is hard to determine if this is a nostalgic look back at something that never actually existed. However, my vision of clinical research is based on a virtue that seems to be in short supply: a sense of duty. I speculate that a decade of economic plenty and nearly a generation of Pax Americana have worn down people's sense of a shared stake in handling medical problems. This is manifest in a persistent