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## The Ethics of Clinical Research in the Third World

[Editorials]

Angell, Marcia

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### Outline

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An essential ethical condition for a randomized clinical trial comparing two treatments for a disease is that there be no good reason for thinking one is better than the other. [1,2] Usually, investigators hope and even expect that the new treatment will be better, but there should not be solid evidence one way or the other. If there is, not only would the trial be scientifically redundant, but the investigators would be guilty of knowingly giving inferior treatment to some participants in the trial. The necessity for investigators to be in this state of equipoise [2] applies to placebo-controlled trials, as well. Only when there is no known effective treatment is it ethical to compare a potential new treatment with a placebo. When effective treatment exists, a placebo may not be used. Instead, subjects in the control group of the study must receive the best known treatment. Investigators are responsible for all subjects enrolled in a trial, not just some of them, and the goals of the research are always secondary to the well-being of the participants. Those requirements are made clear in the Declaration of Helsinki of the World Health Organization (WHO), which is widely regarded as providing the fundamental guiding principles of research involving human subjects. [3] It states, "In research on man [sic], the interest of science and society should never take precedence over considerations related to the wellbeing of the subject," and "In any medical study, every patient -- including those of a control group, if any -- should be assured of the best proven diagnostic and therapeutic method."

One reason ethical codes are unequivocal about investigators' primary obligation to care for the human subjects of their research is the strong temptation to subordinate the subjects' welfare to the objectives of the study. That is particularly likely when the research question is extremely important and the answer would probably improve the care of future patients substantially. In those circumstances, it is sometimes argued explicitly that obtaining a rapid, unambiguous answer to the research question is the primary ethical obligation. With the most altruistic of motives, then, researchers may find themselves slipping across a line that prohibits treating human subjects as means to an end. When that line is crossed, there is very little left to protect patients from a callous disregard of their welfare for the sake of research goals. Even informed consent, important though it is, is not protection enough, because of the asymmetry in knowledge and authority between researchers and their subjects. And approval by an

institutional review board, though also important, is highly variable in its responsiveness to patients' interests when they conflict with the interests of researchers.

A textbook example of unethical research is the Tuskegee Study of Untreated Syphilis. [4] In that study, which was sponsored by the U.S. Public Health Service and lasted from 1932 to 1972, 412 poor African-American men with untreated syphilis were followed and compared with 204 men free of the disease to determine the natural history of syphilis. Although there was no very good treatment available at the time the study began (heavy metals were the standard treatment), the research continued even after penicillin became widely available and was known to be highly effective against syphilis. The study was not terminated until it came to the attention of a reporter and the outrage provoked by front-page stories in the Washington Star and New York Times embarrassed the Nixon administration into calling a halt to it. [5] The ethical violations were multiple: Subjects did not provide informed consent (indeed, they were deliberately deceived); they were denied the best known treatment; and the study was continued even after highly effective treatment became available. And what were the arguments in favor of the Tuskegee study? That these poor African-American men probably would not have been treated anyway, so the investigators were merely observing what would have happened if there were no study; and that the study was important (a "never-to-be-repeated opportunity," said one physician after penicillin became available). [6] Ethical concern was even stood on its head when it was suggested that not only was the information valuable, but it was especially so for people like the subjects -- an impoverished rural population with a very high rate of untreated syphilis. The only lament seemed to be that many of the subjects inadvertently received treatment by other doctors.

Some of these issues are raised by Lurie and Wolfe elsewhere in this issue of the Journal. They discuss the ethics of ongoing trials in the Third World of regimens to prevent the vertical transmission of human immunodeficiency virus (HIV) infection. [7] All except one of the trials employ placebo-treated control groups, despite the fact that zidovudine has already been clearly shown to cut the rate of vertical transmission greatly and is now recommended in the United States for all HIV-infected pregnant women. The justifications are reminiscent of those for the Tuskegee study: Women in the Third World would not receive antiretroviral treatment anyway, so the investigators are simply observing what would happen to the subjects' infants if there were no study. And a placebo-controlled study is the fastest, most efficient way to obtain unambiguous information that will be of greatest value in the Third World. Thus, in response to protests from Wolfe and others to the secretary of Health and Human Services, the directors of the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) -- the organizations sponsoring the studies -- argued, "It is an unfortunate fact that the current standard of perinatal care for the HIV-infected pregnant women in the sites of the studies does not include any HIV prophylactic intervention at all," and the inclusion of placebo controls "will result in the most rapid, accurate, and reliable answer to the question of the value of the intervention being studied compared to the local standard of care." [8]

Also in this issue of the Journal, Whalen et al. report the results of a clinical trial in Uganda of various regimens of prophylaxis against tuberculosis in HIV-infected adults, most of whom had positive tuberculin skin tests. [9] This study, too, employed a placebo-treated control group, and in some ways it is analogous to the studies criticized by Lurie and Wolfe. In the United States it would probably be impossible to carry out such a study, because of long-standing official recommendations that HIV-infected persons with positive tuberculin skin tests receive prophylaxis against tuberculosis. The first was issued in 1990 by the CDC's Advisory Committee for Elimination of Tuberculosis. [10] It stated that tuberculin-test-positive persons with HIV infection "should be considered candidates for preventive therapy." Three years later, the recommendation was reiterated more strongly in a joint statement by the

American Thoracic Society and the CDC, in collaboration with the Infectious Diseases Society of America and the American Academy of Pediatrics. [11] According to this statement, "... the identification of persons with dual infection and the administration of preventive therapy to these persons is of great importance." However, some believe that these recommendations were premature, since they were based largely on the success of prophylaxis in HIV-negative persons. [12]

Whether the study by Whalen et al. was ethical depends, in my view, entirely on the strength of the preexisting evidence. Only if there was genuine doubt about the benefits of prophylaxis would a placebo group be ethically justified. This is not the place to review the scientific evidence, some of which is discussed in the editorial of Msamanga and Fawzi elsewhere in this issue. [13] Suffice it to say that the case is debatable. Msamanga and Fawzi conclude that "future studies should not include a placebo group, since preventive therapy should be considered the standard of care." I agree. The difficult question is whether there should have been a placebo group in the first place.

Although I believe an argument can be made that a placebo-controlled trial was ethically justifiable because it was still uncertain whether prophylaxis would work, it should not be argued that it was ethical because no prophylaxis is the "local standard of care" in sub-Saharan Africa. For reasons discussed by Lurie and Wolfe, that reasoning is badly flawed. [7] As mentioned earlier, the Declaration of Helsinki requires control groups to receive the "best" current treatment, not the local one. The shift in wording between "best" and "local" may be slight, but the implications are profound. Acceptance of this ethical relativism could result in widespread exploitation of vulnerable Third World populations for research programs that could not be carried out in the sponsoring country. [14] Furthermore, it directly contradicts the Department of Health and Human Services' own regulations governing U.S.-sponsored research in foreign countries, [15] as well as joint guidelines for research in the Third World issued by WHO and the Council for International Organizations of Medical Sciences, [16] which require that human subjects receive protection at least equivalent to that in the sponsoring country. The fact that Whalen et al. offered isoniazid to the placebo group when it was found superior to placebo indicates that they were aware of their responsibility to all the subjects in the trial.

The Journal has taken the position that it will not publish reports of unethical research, regardless of their scientific merit. [14,17] After deliberating at length about the study by Whalen et al., the editors concluded that publication was ethically justified, although there remain differences among us. The fact that the subjects gave informed consent and the study was approved by the institutional review board at the University Hospitals of Cleveland and Case Western Reserve University and by the Ugandan National AIDS Research Subcommittee certainly supported our decision but did not allay all our misgivings. It is still important to determine whether clinical studies are consistent with preexisting, widely accepted ethical guidelines, such as the Declaration of Helsinki, and with federal regulations, since they cannot be influenced by pressures specific to a particular study.

Quite apart from the merits of the study by Whalen et al., there is a larger issue. There appears to be a general retreat from the clear principles enunciated in the Nuremberg Code and the Declaration of Helsinki as applied to research in the Third World. Why is that? Is it because the "local standard of care" is different? I don't think so. In my view, that is merely a self-serving justification after the fact. Is it because diseases and their treatments are very different in the Third World, so that information gained in the industrialized world has no relevance and we have to start from scratch? That, too, seems an unlikely explanation, although here again it is often offered as a justification. Sometimes there may be relevant differences between populations, but that cannot be assumed. Unless there are specific indications to the contrary, the safest and most reasonable position is that people everywhere are likely

to respond similarly to the same treatment.

I think we have to look elsewhere for the real reasons. One of them may be a slavish adherence to the tenets of clinical trials. According to these, all trials should be randomized, double-blind, and placebo-controlled, if at all possible. That rigidity may explain the NIH's pressure on Marc Lallemand to include a placebo group in his study, as described by Lurie and Wolfe. [7] Sometimes journals are blamed for the problem, because they are thought to demand strict conformity to the standard methods. That is not true, at least not at this journal. We do not want a scientifically neat study if it is ethically flawed, but like Lurie and Wolfe we believe that in many cases it is possible, with a little ingenuity, to have both scientific and ethical rigor.

The retreat from ethical principles may also be explained by some of the exigencies of doing clinical research in an increasingly regulated and competitive environment. Research in the Third World looks relatively attractive as it becomes better funded and regulations at home become more restrictive. Despite the existence of codes requiring that human subjects receive at least the same protection abroad as at home, they are still honored partly in the breach. The fact remains that many studies are done in the Third World that simply could not be done in the countries sponsoring the work. Clinical trials have become a big business, with many of the same imperatives. To survive, it is necessary to get the work done as quickly as possible, with a minimum of obstacles. When these considerations prevail, it seems as if we have not come very far from Tuskegee after all. Those of us in the research community need to redouble our commitment to the highest ethical standards, no matter where the research is conducted, and sponsoring agencies need to enforce those standards, not undercut them.

Marcia Angell, M.D.

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