The New England Journal of Medicine

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Volume 345(2) 12 July 2001 pp 136-138

Research Involving Human Subjects in Developing Countries

[Editorials]

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Outline

The research community and the public have been engaged in a reexamination of the ethics and responsible conduct of research involving human subjects for many years. Since the 1995 report of the Advisory Committee on Human Radiation Experiments, [1] concern about these issues has intensified. Attention has recently focused on research carried out in countries where the requirements for review, approval, and oversight are much less stringent than they are in the United States. Some studies have exploited the unfortunate conditions in which some people live as a result of economic and cultural factors beyond their control - factors that make them vulnerable and convenient for study.

Concern about specific studies has stimulated widespread discussion of these issues. [2] As a result, the National Bioethics Advisory Commission has issued a report on ethical issues in the design and conduct of research in developing countries. [3] In this issue of the Journal, Shapiro and Meslin, the chairman and executive director, respectively, of the commission, discuss many of the issues addressed in its report. [4] According to Shapiro and Meslin, clinical trials in developing countries should meet all ethical and scientific standards of trials performed in developed countries. What, if any, grounds could there be for presuming otherwise? Some might argue that the ethical considerations are dependent on the actual situation in which the research is to be conducted. The international research community, however, already understands that rationalizing the application of less stringent ethical standards simply because a study is being performed in a developing country is untenable. Thus, Shapiro and Meslin conclude that the U.S. regulations governing clinical research, which are based on the 1978 Belmont report, [5] are sound and applicable in general to research conducted in developing countries. They argue that the ethical issues raised by such research are not unique but that how these issues are interpreted and handled may differ from the approach in the United States. Shapiro and Meslin point out that some aspects of the U.S. regulations might ethically be modified (e.g., accepting verbal instead of written informed consent in certain situations, with safeguards). What is less clear is when and how such deviations from the procedures mandated for the review, approval, and oversight of research in the United States should be permitted for a study sponsored by a U.S. entity but performed in another country.

There is increasing recognition of the need to establish international standards for the ethical and scientific conduct of clinical research. For example, over the past decade, the International Conference on Harmonization, a group composed of regulatory officials and industry experts from the European Union, Japan, and the United States, has developed uniform ethical and scientific guidelines for clinical trials and marketing-approval requirements. [6] In addition, the Council for International Organizations of Medical Sciences is revising its 1993 guidelines for the ethical conduct of research involving human subjects. [7]

Although these initiatives have been relatively free of controversy, another one has triggered sharp debate. In the October 2000 revision of the Declaration of Helsinki, [8] a statement of principles for the ethical conduct of medical research, the World Medical Association introduced new provisions that would prohibit almost all placebo-controlled clinical trials and would require that the best proved therapy be provided to the participants in a trial on its completion. Although these provisions were no doubt well intended, they have raised serious questions. Shapiro and Meslin [4] view the provision concerning placebo-controlled trials as too rigid. We agree. At an international conference on the implementation of the new provisions of the declaration, held in Pretoria, South Africa, in March, participants from a number of countries, including the United States, expressed serious concern. [9] The Department of Health and Human Services acknowledged the importance of the Declaration of Helsinki as a set of principles, as well as the value of certain new provisions - in particular, those pertaining to financial conflicts of interest. [10] It pointed out, however, that the declaration has limited scope and cannot encompass effectively the broad spectrum of clinical trials that are conducted internationally. With respect to appropriate research design, the department agreed that a study should be responsive to the health needs of the host country. Similarly, to be useful and ethical, the study should include a control group that is appropriate for the host country. The question of whether a control group is appropriate must be considered with the specific clinical trial in mind. The relevant factors include the disease or condition being studied, the research question, and the short- and long-term consequences of the use of placebo instead of active treatment. In some situations, the use of active treatment as a control may itself pose an ethical problem, if the use of such a control group makes the results unreliable or not useful.

To a large extent, the appropriateness of a clinical trial and of the control group used is based on two considerations. First, the research question should be posed in a manner that is relevant and meaningful to the host country, such as a comparison of an available treatment with the current standard of care in the host country (which might be no intervention in some cases). This approach may be necessary in order to avoid a situation in which the findings of the research are of interest to, or relevant to, only the scientists and health policy officials in the developed country sponsoring the study and would hold no promise for improving health in the host country. Second, the study should be designed to achieve maximal efficiency in producing meaningful data that could lead to improvements in health in the host country without leaving the study participants worse off at the end of the trial than they were when they entered it.

The Department of Health and Human Services also expressed concern that the provision in the revised Declaration of Helsinki to offer the "best proven prophylactic, diagnostic and therapeutic methods" to study participants after the study has been completed is well intended but simplistic. One trial rarely demonstrates that a given treatment is superior to all others, and there is often considerable disagreement about what the best methods are. Indeed, a single trial can rarely determine how best to treat or prevent a disease in all settings, or even in the setting in which it was conducted. Although the report by the National Bioethics Advisory Commission addresses these issues in detail, the Declaration of Helsinki provides no commentary on its stated principles, making their interpretation difficult. After the Pretoria conference, the leaders of the

World Medical Association indicated their willingness to consider further the issues that were raised. We applaud this effort. They subsequently announced the formation of a working group to examine these issues and to meet with other groups to "harmonize guidelines." [11]

Our greatest challenge is to realize and fully accept that in all research involving human subjects, ethics and science are not separable - a given study must conform to ethical standards or it should not be performed, and it must be scientifically sound or it cannot be ethical. The use of a good research design and adherence to sound ethical principles should result in the conduct of research that is valid, reliable, and ethically acceptable in any country. If we can embrace this seemingly simple concept, the ethical dilemmas will not vanish or suddenly become easier to resolve, but we will at least be less likely to conduct activities in the name of science that are disrespectful or harmful to others.

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Accession Number: 00006024-200107120-00011