Sounding Board

Ethical Issues in the Design and Conduct of Clinical Trials in Developing Countries

THERE has been considerable controversy about the ethics of clinical trials that are sponsored or conducted by groups in industrialized countries but carried out in developing countries.[1-8] The National Bioethics Advisory Commission, of which we serve as chairman and executive director, respectively, has recently addressed these and related issues.[9] International collaborative research covers a broad spectrum of methods, topics, and research strategies. In this essay, we discuss ethical issues in the design and conduct of clinical trials in developing countries. In particular, we focus on phase 3 and other drug trials that, if successful, can lead to the use of effective new treatments.

Clinical trials should not exploit the subjects who agree to participate in them.[10] The United States is one of several countries that have developed substantive ethical standards (based on the principles of justice and individual autonomy) for conducting clinical research, as well as a required set of procedures for implementing the standards.

These standards and procedures are embodied in regulations developed over two decades ago — the "common rule"[11] and parallel regulations of the Food and Drug Administration (FDA)[12] — which apply to research involving human subjects that is funded by many federal agencies or regulated by the FDA. Despite some noticeable shortcomings and its limited scope, this system for the protection of human subjects has worked reasonably well for clinical research conducted in the United States. Unfortunately, not all research conducted in the United States is subject to the common rule or the FDA regulations (e.g., some studies conducted in physicians' offices and any type of research at academic institutions that do not receive federal funds). There is also continuing concern about the capacity of ethics committees to meet fully their critical responsibilities to protect human subjects and to provide oversight of studies.[13-15]

For clinical trials that are sponsored by the U.S. government and conducted in developing countries by U.S.-based researchers, or otherwise carried out within the federal regulatory framework, two associated questions arise. The first question is whether it is appropriate to apply the same set of ethical standards and procedures that is used for trials in the United States to trials conducted in developing countries, where the context may be different. The second is whether such clinical trials pose unique ethical issues that must be addressed.

EXPORTING ETHICAL STANDARDS

We believe that clinical trials conducted abroad should meet all the ethical standards for trials based in the United States, including prior review and approval by ethics review committees, the minimization of risk to the participants, a favorable risk–benefit ratio, and the provision of individual informed consent by all competent adult participants. Arguably, there should be additional standards to ensure that participants are drawn from a broad cross-section of the population and to ensure that there is adequate medical care of participants during the trial, with compensation for any injuries directly related to participation, even though these provisions are not required in the United States. Within the framework of these ethical standards, however, procedures could be adopted in developing countries that might differ from those in the United States and that might be more in line with local custom, conditions, and culture.

An important additional safeguard is needed to avoid the exploitation of potentially vulnerable populations in developing countries — namely, clinical trials sponsored or regulated by U.S. groups should be limited to those that are responsive to the host country's health needs. If the intervention being tested is not likely to be affordable in the host country or if the health care infrastructure cannot support its proper distribution and use, it is unethical to ask persons in that country to participate in the research, since they will not enjoy any of its potential benefits. Research participants in developing countries are less likely to have continued access to the intervention being evaluated than are participants in developed countries. This raises the ethical question of whether any health care benefits will ever reach the citizens of the host country.[6-8] In addition, there is always a concern that the developed country may be exploiting a country that is poorer, less powerful, and therefore more vulnerable. Although it has long been recognized that collaboration between peoples of different nations has great potential to generate substantial benefits for both sides, there is often controversy over the nature of the collaboration and whether the distribution of any benefits will be equitable.

Given these issues, researchers, sponsors, and ethics review committees in developed countries must take great care to ensure that the justification for conducting a trial in a developing country is adequately articulated. This is especially important if the trial is to be conducted in a country or region where the population may be vulnerable to exploitation because of pervasive poverty and disease or lack of understanding of the scientific issues surrounding the health problem and the role of the clinical trial in the search for a solution.

A trial in a developing country might be justified in a number of ways. The research might address an important health problem in that country, or it

might represent a joint effort by the country sponsoring or conducting the study and the host country to address an important health problem in both countries. However, conducting a trial in a developing country because it is more convenient or efficient or less troublesome to do so is never a sufficient justification.

SPECIFIC ETHICAL ISSUES

There are specific ethical issues that arise when researchers from developed countries conduct clinical trials in developing countries. These issues are not unique — they pertain to all clinical research — but how they are interpreted and addressed may be unique.

The Process of Informed Consent

The particular procedures for obtaining voluntary informed consent in developing countries may need to be tailored to local custom and culture, even though we share the view that the principle of informed consent applies throughout the world.[16] For example, U.S. regulatory procedures focus on the informed-consent document itself, rather than on the process of informed consent, and require written consent. Such procedures may be impossible to implement in some areas, because persons may be illiterate or because signing a form may be considered dangerous in countries with oppressive regimes. In any case, obtaining a signature on paper — in the United States or elsewhere — does not ensure that a participant understands the proposed research. Although signed forms make it easy to audit informed consent — one useful dividend of this process — there are other ways to ensure that it has been obtained. An ethically sound alternative to written consent is oral consent that has been witnessed and verified.

In many countries, it is important to obtain permission from local leaders for researchers to seek individual informed consent and to discuss other aspects of the research. Although it may be difficult to identify the members of the community who should be consulted and to determine the level of authority they should have in permitting researchers to approach potential participants, we believe that such consultations can be helpful in improving both the informed-consent process and the overall research design.

Research Design and Ethics Review

One of the most controversial issues in the conduct of clinical trials in developing countries is whether the control group must receive the same intervention as that which would be provided if the study were conducted in a developed country. For example, trials that compared a short course of zidovudine with placebo for the prevention of perinatal transmission of human immunodeficiency virus (HIV) infection generated considerable controversy.[17-19] It was already known that a longer course of zidovudine reduced perinatal transmission,[20] so some argued that the use of a placebo in subsequent studies was unethical.[19] In our view, an experimental intervention should normally be compared with an established, effective treatment (defined as a treatment that has widespread acceptance by the medical profession throughout the world and that is as effective as any alternative treatment for the disease or condition), whether or not that treatment is available in the host country. Therefore, the presumption is that a placebo control, or any other control that is less effective than an established, effective treatment, is not ethically acceptable.

However, we would permit an exception in a situation in which the only useful research design, from the host country's perspective, required a less effective intervention in the control group, if the condition being studied was not life-threatening and if the trial received approval from an ethics review committee in the host country as well as one in the United States. We recognize that the requirement of approval by an ethics review committee is not without its own challenges — in the United States and abroad — particularly if the committee lacks the independence or capacity to conduct a thorough review. The research investigators and sponsors must therefore assume considerable ethical responsibility in determining whether an exception to the standard is warranted. It may not be feasible to design a study that both answers a question that is relevant for the host country and that would be ethically acceptable if it were conducted in the United States. An exception should be limited and should not be extended to trials that fail to meet these requirements and qualifications. It would not apply to the treatment of life-threatening diseases such as HIV infection. If our standard were adopted, many trials currently under way or in the planning stages might have to be stopped or redesigned.

Some of these issues are illustrated by a recent case. Earlier this year, a U.S. biotechnology company submitted a proposal to the FDA for a study of a new surfactant drug in premature newborn infants with the respiratory distress syndrome — a potentially fatal condition.[3] The study, which was to be conducted in several Latin American countries, was designed to include three groups of infants: those receiving the new drug, those receiving an FDA-approved surfactant drug, and those receiving placebo. In studies of this kind — involving a disease that is life-threatening and one for which an established, effective treatment is available — a placebo control is not permissible. Moreover, such a trial is not ethical if patients in the developed country would be the primary beneficiaries and if it is not clear that the trial would be responsive to the health care needs of the host country. Surfactant treatment in infants with the respiratory distress syndrome is widely used in de-

veloped countries but not in developing countries. In April, the company that proposed the placebo control redesigned the study so that no infants would receive placebo.

These issues are also addressed in the recent revision of the Declaration of Helsinki.[21] It states, "The benefits, risks, burdens and effectiveness of the new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods." This statement may, in our view, be too rigid. It could undermine ethically sound attempts to address critical health issues, such as the treatment of a disease that is extraordinarily burdensome — for example, lower respiratory tract infections, perinatal disorders, or diarrheal conditions. In many developing countries, other ethical concerns may compete with the commitment to protect participants in research — for example, the need to prioritize access to medical interventions and to make the most of limited resources. The Helsinki standard for the control group should be the presumptive standard for trial design. Nonetheless, ethics review committees should be able to approve a deviation from this standard, but only if it is required in order to address an urgent health problem in the host country.

Prior review and approval of a proposed clinical trial by an independent ethics committee is an internationally accepted ethical standard for research involving human subjects.[21-23] A review by ethics committees in both the host and sponsoring countries does not guarantee that the trial will be carried out in an ethical manner but does help ensure that both the ethical aspects of the trial and the local context are considered. There should be greater efforts to make sure that local ethics committees have the necessary expertise to carry out their responsibilities.[24]

Finally, it has been suggested that it is unethical to conduct clinical trials in a country that does not share the democratic traditions of the United States. For example, an editorial in the *Washington Post* stated, "At the least, the FDA should not accept trials conducted in non-democratic countries. . . ."[25] We believe that the ethical obligations of the United States as a participant in international collaborative research are not limited to countries that share our democratic system. The same editorial went on to suggest that the FDA should not "allow the export of drugs for trials if they have been rejected for such use in the United States." We support in part the sentiment behind this suggestion, but in our judgment it is too rigid and, like the recent Helsinki revision, might prevent ethically sound research from being conducted.

Post-Trial Benefits

Ethical issues arise at the conclusion of all clinical trials. The Declaration of Helsinki states (Principle 30), "At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study." Other international documents either require similar post-trial provisions or call for the best efforts of sponsors and researchers to secure benefits for the participants in the trial and, in some cases, for other persons who might be candidates for the successful intervention.[21,24]

Making a successful new intervention available to participants after a trial is an especially important ethical obligation. There is a related obligation to ensure that participants are no worse off during the trial than they were before it. In addition, we believe that research participants should not be made worse off as a result of their inability to have continued access to the successful intervention after the trial has ended. Although the researcher–participant relationship is different from the doctor–patient relationship, trust in the medical profession is central to anyone's willingness to participate in a trial. Any sense of abandonment is difficult to address adequately in the informed-consent process.

A plan for the routine provision of a successful new intervention to participants after a trial has been completed is one way to ensure that the study is responsive to the health needs of the host country. The ethical obligation to provide the intervention to others in the community who might benefit from it is considerably less strong, but a plan to do so would help reduce the risk of exploitation.

CONCLUSIONS

The unprecedented international movement of people, goods, and ideas has made people in developed countries more aware of the imbalance in the global burden of disease. This is sometimes referred to as the "10/90 gap" — less than 10 percent of global health care expenditures are devoted to diseases that account for 90 percent of the global burden of disease.[26] Initiatives to reduce the burden of disease in developing countries are urgently needed. Clinical trials that are responsive to the health care needs of these countries constitute one such initiative, but it is neither necessary nor desirable to relax our ethical standards in order to achieve this goal. On the contrary, the standards should be maintained, with circumscribed adaptations to the needs of developing countries.

HAROLD T. SHAPIRO, PH.D.
ERIC M. MESLIN, PH.D.
National Bioethics Advisory Commission
Bethesda, MD 20892-7979

We are grateful to members of the National Bioethics Advisory Commission and others for discussions and contributions.

REFERENCES

1. Stephens J. The body hunters: as drug testing spreads, profits and lives hang in the balance. Washington Post. December 17, 2000:A1.

2. Flaherty MP, Nelson D, Stephens J. The body hunters: overwhelming the watchdogs. Washington Post. December 18, 2000:A1.
3. Flaherty M, Stephens J. Pa. firm asks FDA to back experiment forbidden in U.S. Washington Post. February 23, 2001:A3.
4. Angell M. Investigators' responsibilities for human subjects in developing countries. N Engl J Med 2000;342:967-9.
5. Loue S, Okello D. Research bioethics in the Ugandan context. II. Procedural and substantive reform. J Law Med Ethics 2000;28:165-73.
6. Benatar SR, Singer PA. A new look at international research ethics. BMJ 2000;321:824-6.
7. del Rio C. Is ethical research feasible in developed and developing countries? Bioethics 1998;12:328-30.
8. Glantz LH, Annas GJ, Grodin MA, Mariner WK. Research in developing countries: taking "benefit" seriously. Hastings Cent Rep 1998;28(6):38-42.
9. Ethical and policy issues in international research: clinical trials in developing countries. Bethesda, Md.: National Bioethics Advisory Commission, 2001.
10. Gambia Government/Medical Research Council Joint Ethical Committee. Ethical issues facing medical research in developing countries. Lancet 1998;351:286-7.
11. 45 CFR 46 (Subpart A) (1981).
12. 21 CFR 56 (1981).
13. Advisory Committee on Human Radiation Experiments: final report. Washington, D.C.: Government Printing Office, 1995.
14. Scientific research: continued vigilance critical to protecting human subjects: report to the Ranking Minority Member, Committee on Governmental Affairs, U.S. Senate. Washington, D.C.: General Accounting Office, 1996.
15. Office of the Inspector General. Institutional review boards: a time for reform. Washington, D.C.: Department of Health and Human Services, 1998.
16. IJsselmuiden CB, Faden RR. Research and informed consent in Africa — another look. N Engl J Med 1992;326:830-4.
17. Angell M. The ethics of clinical research in the Third World. N Engl J Med 1997;337:847-9.
18. Varmus H, Satcher D. Ethical complexities of conducting research in developing countries. N Engl J Med 1997;337:1003-5.
19. Lurie P, Wolfe SM. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. N Engl J Med 1997;337:853-6.
20. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal–infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med 1994;331:1173-80.
21. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Edinburgh, Scotland: World Medical Association, October 2000. Accessed June 22, 2001. (See http://www.wma.net/e/policy/17-c_3.html.)
22. International ethical guidelines for biomedical research involving human subjects. Geneva: Council for International Organizations of Medical Sciences (CIOMS), 1993.
23. Operational guidelines for ethics committees that review biomedical research. Geneva: World Health Organization, 2000. (Report no. TDR/PRD/ETHICS/2000.1.)
24. Ethical considerations in HIV preventive vaccine research: UNAIDS guidance document. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS), 2001.
25. Testing drugs abroad. Washington Post. December 24, 2000:B6.
26. The 10/90 report on health research 2000. Geneva: Global Forum for Health Research, 2000.