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IN THE LITERATURE
Clinical Trials in Developing Countries
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The past year has seen much discussion on participation by physicians from developed countries in research conducted in less-developed countries. The World Medical Association revised its Declaration of Helsinki, a statement of principles for the ethical conduct of medical research, in October 2000. Earlier this year, the National Bioethics Advisory Commission (NBAC) issued a report on ethical and policy issues in international research, and the AMA passed a new recommendation on ethical considerations in international research at its 2001 Annual Meeting in June. The Council for International Organizations of Medical Sciences is currently revising its 1993 guidelines for the ethical conduct of research involving human subjects.

Harold Shapiro and Eric Meslin, NBAC's chair and executive director, respectively, summarize their committee's position in *Ethical Issues in the Design and Conduct of Clinical Trials in Developing Countries*. In *Research Involving Human Subjects in Developing Countries* Greg Koski and Stuart Nightingale comment on the NBAC report and on the Declaration of Helsinki, and draw some conclusions of their own.

There is much agreement among NBAC, Helsinki, and AMA guidelines on many aspects of clinical research ethics. All subscribe to the need for fully informed consent; all require that the proposed research address a health problem within the host country, and that research protocols be approved by ethics review boards or committees. The main sticking point among various groups is over the study design—particularly the design of the trial's control arm. The authors of both articles cited here suggest that the Helsinki demand for a control that employs "the best current prophylactic, diagnostic, and therapeutic methods" available may be too rigid. Shapiro and Meslin grant that the "an experimental intervention should normally be compared with an established, effective treatment . . . whether or not that treatment is available in the host country." That, they say, is the "presumed standard." However, they can envision situations in which the condition being studied is not life threatening and the only useful research design (from the host country's point of view) may require a less effective control intervention than the current "best therapy" in developed countries. The authors stipulate that such an exception to the Helsinki Declaration would have to be approved by ethics review committees in both the host and visiting countries.

There is also disagreement over the necessity to make a successful new intervention available to research subjects after the trial is over. The Helsinki Declaration requires this, and, to the NBAC authors, it is "an especially important ethical obligation." Koski and Nightengale agree with the spirit of the requirement but believe that it will be difficult to implement for many reasons, not least of which is that "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."

Questions for Discussion

1. The revised *Declaration of Helsinki* 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." Is Shapiro and Meslin's exception to this standard reasonable, or does it undermine the protection for research subjects intended in the provision?
2. Regarding the close of a trial, the *Declaration of Helsinki* reads, "At the conclusion of the study, every patient entered in the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study." Is there a difference between an obligation to not abandon subjects at the close of a clinical trial, and a requirement to provide the best proven methods? How is this obligation reconciled with an objective to improve health for everyone in a developing country?
3. Who should develop and enforce ethics standards in foreign countries? Is there enough of a global obligation to justify an international policy, or should standards for clinical trials be left to self-determined relativism? How does one avoid ethical imperialism in this case?

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