

## Ethical Framework in Multi-National Clinical Research

**Summary:** To provide a comprehensive ethical framework that can be used to guide decision making about the appropriate standard of care, reasonable availability, and other major ethical controversies for multi-national clinical research, and to explore specific ethical issues that arise in the international setting.

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**Background:** Since 1997 and the publication in the New England Journal of Medicine of the criticism of the short course AZT trials to reduce perinatal HIV transmission in developing countries, the ethics of multi-national clinical research have been widely debated. In general, the controversy has focused on two issues: 1) standard of care and 2) reasonable availability.

The standard of care debate has focused on when it is permissible to include an intervention that is known to be less than the world-wide best intervention in a clinical research study. Some claim that the world-wide best intervention must be provided. Multiple justifications are cited. One justification is that to provide less than the world-wide best intervention would violate the Declaration of Helsinki (provision 29) which requires that “the benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods.” Others argue that to provide less would create a double standard—one standard of care for research participants in the developed countries and a lower one for poor participants in developing countries. Still others claim that a therapeutic relationship between researchers and participants requires researchers to do what they know is in the best interests of the participants, which would be to

provide the intervention known to be best at promoting health of the participant, that is the world-wide best intervention.

There are multiple critics of this view who also raise many arguments. One line of argument claims that requiring the world wide best intervention be provided in developing countries would frequently make the results of the clinical research conducted in developing countries irrelevant to those countries because it could not be implemented. Indeed, such a standard would lead to exploitation of participants in developing countries because the results would be more relevant for developed countries. Still others argue that requiring the world-wide best intervention violates requirements of justice because it is legitimate for countries not to provide certain interventions if the resources can be used more effectively for other services. Finally, it is noted that the critiques are “aiming at the wrong target.” While the poverty of developing countries is both tragic and unjust, the critique of the standard of care of biomedical research is a misguided ethical argument; the real issue is poverty not the behavior of scientists.

The reasonable availability debate centers around the CIOMS provision that “ the sponsoring agency should agree in advance of the research that any product developed through such research will be made reasonably available to the inhabitants of the host community or country at the completion of successful testing.” Debate has mainly focused on two issues. First, how extensive should the guarantee be—how firm or contract-like should the agreement be? Second, who needs to be covered? Some guidelines, such as those from National Bioethics Advisory Commission (NBAC), have advocated that research collaborators should work out "a prior agreement" before a research collaboration is initiated. Such a "prior agreement" might include an agreement to provide the interventions should it prove to be successful, but it might also include agreements about other benefits to the community in which the trial takes place. The justification of this provision is that without the guarantee of reasonable availability of the proven intervention then people in the developing country cannot “benefit from the research” and therefore will be exploited by the research.

The Department initially became involved in the ethics of multi-national research in late 1997. Harold Varmus, then director of the NIH, asked Dr. Emanuel to convene a group to help develop general guidelines that could be used by the NIH for evaluating the ethics of multi-national research proposals. At the September 1998 meeting of the Institute Directors a very preliminary description of the group’s thinking was presented. Subsequent to that meeting, Dr. Varmus asked that the group’s work be stopped but permitted the Department to continue to study the topic.

**Objectives:**

- 1) To evaluate critically arguments regarding the standard of care and to delineate an ethically coherent position regarding the standard of care.
- 2) To evaluate critically arguments regarding reasonable availability and delineate an ethically coherent position regarding reasonable availability.
- 3) To delineate a comprehensive framework for determining the ethics of multinational clinical research.
- 4) To elucidate the concept of exploitation in the context of multi-national clinical research.
- 5) To develop a book of cases and commentaries on ethical issues in multi-national clinical research.

**Methodology:** Initially, the Department collected all articles and some unpublished manuscripts on the standard of care and reasonable availability debates as well as other articles related to the ethics of multi-national research. The arguments in the articles were analyzed and discussed among members of the Department in various settings, informally, at research team meetings, and at works-in-progress meetings.

The Department began to identify the central ethical issues surrounding these debates as debates about the ethical issues of international justice and exploitation. To obtain richer understandings of the underlying ethical concepts the Department made them the focus of the Joint Seminar Series. The Joint Seminar Series is organized by the Department in conjunction with the Bioethics Institute of Johns Hopkins University and the Kennedy Institute and Department of Philosophy of Georgetown University. Each semester the seminar series focuses on one topic and invites distinguished scholars in the area to assign readings and lead a seminar. In the Spring of 2001 the topic of the joint seminar was international justice; speakers included Charles Beitz, Thomas Pogge, Hilary Bok, and Nancy Kass. In the Fall of 2001 the topic was exploitation; speakers included Alan Wertheimer and Richard Arneson. Through these seminars and the discussions among faculty and fellows afterwards, the Department evolved more refined understandings of these key ethical concepts.

To make a general ethical framework more practical and focused, the Department discussed something called the “benchmarks approach.” Originally, this approach was articulated to provide a systematic approach to elucidating how general principles related to establishing funding priorities in health care systems apply to specific contexts and choices. Members of the Department then discussed whether the benchmarks could be adapted to the case of multinational research ethics. Four people discussed each principle, trying to articulate as concretely as possible what actions would constitute fulfilling the

principle. This approach was useful in systematically specifying the practical considerations necessary to evaluate the ethics of research studies.

At one training conference in Africa a session was devoted to discussing the issue of reasonable availability. Spontaneously evolved into a delineation of the problems with this approach as well as articulation of an alternative way to ensure participants in developing countries received a fair level of benefits from research and, thereby, avoid exploitation.

Finally, the Department began identifying cases of research studies that presented ethical challenges. These cases were used to test the ethical framework as well as ethical arguments developed by the Department members. Then the Department began to develop formally a database of cases, with a standardized format.

**Results:** The Department provided a comprehensive critical analysis of the 2000 revision of the Declaration of Helsinki, a major document in the debates over multi-national research. This analysis made four major points. First, the worldwide controversy of the revision had focused exclusively on the provision related to standard of care, but we observed there were many other important modifications. Second, there were some notable improvements especially in identifying ethical issues, such as including investigator conflicts of interest in the Declaration. Third, beyond the question of the standard of care there were many problems, especially regarding how to resolve many of the ethical issues raised. Finally, the analysis pointed out some of the less frequently discussed problems with the standard of care perspective.

Members of the Department participated in a summary of ethical issues in HIV research in developing countries. Again this perspective emphasized how the issues go well beyond the question of standard of care.

In 2000, the Department published an ethical framework that delineated 7 major principles necessary for ethical evaluation of clinical research. The focus of that project was domestic clinical research. Building on that framework, the Department delineated a framework for multi-national clinical research. This framework added an 8<sup>th</sup> principle—collaborative partnership. More importantly, it characterized 31 benchmarks that “specify the practical consideration needed to fulfill the 8 principles...[and] for determining how well research studies realize the 8 principles.” Such a list of benchmarks should help researchers, IRBs, health organizations and others develop consensus on the considerations important in evaluating the ethics of clinical research studies and in developing ethical research studies themselves.

From the Department’s 2001 training conference of African researchers, bioethicists, and IRB members in Malawi arose the outlines of an analysis of

reasonable availability. This analysis included three components. First, it delineated a deeper understanding of how reasonable availability was intended to address the ethical problem of exploitation. Second, it delineated a comprehensive critique of reasonable availability. The central elements of that critique are that reasonable availability emphasizes the kind of benefits to be provided to communities in developing countries whereas to address the problem of exploitation the emphasis should be on the level or amount of benefits and in this regard a broader conception of benefits from clinical research is needed. Furthermore, we argue that reasonable availability is a limited response to exploitation because it is only applicable to successful Phase III research, not to all types of clinical research. Finally we offer an alternative conception to avoid exploitation called the Fair Benefits framework. The fair benefits framework emphasizes three principles, 1) benefits—a comprehensive delineation of all benefits from research; 2) collaborative partnership—entrusting the decision whether the benefits are sufficient to the local community being approached to enroll in research; and 3) transparency—there should be a repository of fair benefit agreements that can be independently evaluated for their fairness. A virtue of this contribution is that it included all the conference participants, especially the Africans, as co-authors as it was a true consensus of all participants.

The Department also felt that the concept of exploitation and especially exploitation from research in developing countries was used quite variably and inconsistently in the literature. As a consequence of the seminar series on exploitation, the Department sought to analyze the concept of community exploitation and to delineate safeguards to minimize the possibility of exploitation. Further, the Department is editing a book on exploitation. We asked the experts who participated in the seminar series to discuss their conception of exploitation and how it might apply to two controversial cases—hepatitis A vaccine trial in Thailand and a surfactant trial planned for Bolivia, Ecuador, Mexico, and Peru. Wertheimer will develop his deontological conception of exploitation; Arneson will offer a utilitarian view; Pogge will discuss how conceptions of cosmopolitanism relate to exploitation from research, especially how they focus on ameliorating poverty rather than criticizing the conduct of research.

Finally, the Department felt that a deeper understanding of the standard of care was possible. One approach was to analyze the arguments offered for making the world-wide best standard required—such as the double standard argument and the claim about researcher's obligations to participants. This analysis showed that while each of these arguments has some truth, the logical conclusion of the arguments is not a requirement for the world-wide best standard. Another approach has been to demonstrate that the standard of care used in a research study must be linked to the health care services people in a country are entitled to receive as a matter of justice. In other words, entitlement based on justice determines what services must be provided to people in a

research study. The controversy about standard of care can then be seen as a controversy about justice. There is no agreement about a theory of international distributive justice. Some theorists, such as Rawls, contend that beyond a very basic level economic development is not a key part of international justice and therefore developed countries are not obligated, as a matter of justice, to provide developing countries money that would increase the entitlements to health care services. On this view, standard of care should be what is currently provided in developing countries. At the other extreme, utilitarians argue for strict equality among all people regardless of country of residence. On this view, the standard of care in research should be the world-wide best intervention. There are several other conceptions of international justice between these two extremes and that provides more subtle determinations of the standard of care.

**Future Directions:** It will take approximately one and a half years to complete the work laid out. The book on exploitation should be submitted to a publisher in Fall 2002. The outline for the casebook includes 30 cases which have been identified to cover the full range of ethical issues that arise in the conduct of research developing countries. By the end of the summer 2002, 10 were complete with the cases written up and two commentaries solicited per case. The editors are emphasizing obtaining cases and commentaries from people in developing countries to ensure their perspective is included in international discussions of these issues. This requires substantial work and time, as few clinical researchers and bioethicists in developing countries have experience developing the cases and writing such commentaries. The editors are devoting substantial time working with contributors.

The work on the analyses of the standard of care is just beginning and will take several more months to complete.

The Department has articulated and advocated the principle of collaborative partnership as fundamental to ethical multi-national research and avoiding exploitation. This principle is probably the least developed ethical principle for research. In order to elucidate it more fully, the Department is interested in developing case studies of collaborative partnership to see how the proposed benchmarks actually work. One preliminary possibility that is being explored is with the Rakai Project in Uganda. Rakai is the district on the southwest side of Lake Victoria where HIV was first described in Africa. The Rakai Project is an NIH funded on-going cohort study involving approximately 18,000 individuals in research on HIV and sexually transmitted diseases. The Rakai Project has worked with the Rakai community for more than 12 years and developed an extensive partnership. We are exploring the possibility of developing this in a case study of collaborative partnership.

Another future project is to work on the question of what are the obligations of researchers to provide for the health care needs of subjects that

fall outside the objectives and interventions of the research. For instance, if researchers are conducting a study of HIV vaccines in sub-Saharan Africa many participants are likely to have or develop diseases unrelated to HIV or the vaccine, such as malaria or diarrhea, during the course of the research study. A key question becomes: What are the obligations of the researchers to treat the malaria or diarrhea of study participants? Further questions arise as to whether the researchers have any obligations beyond the study participants to the community from which the study participants were selected.

In its report on international research, NBAC provides several examples of prior agreements for research. However, these agreements are not examined in great detail, nor very critically. The Department will critically examine previous examples of such agreements, identifying their strengths and deficiencies. Based on this analysis, the Department will suggest a template for prior agreements that will provide more specific guidance than embodied in guidelines such as NBAC.

## **Publications**

Forster HP, Emanuel E, Grady C. The 2000 revision of the Declaration of Helsinki: a step forward or more confusion? Lancet 2001;358:1449-53.

Killen J, Grady C, Folkers GD, Fauci AS. Ethics of clinical research in the developing world. Nature Reviews 2002;2:210-215.

Emanuel EJ, and Particpants in Ethical Aspects of Research in Developing Countries. Beyond Reasonable Availability: Ensuring Fair Benefits for Research in Developing Countries. Science 2003 (in press).