

MODULE 3

Public Health Research and Practice in International Settings: Special Ethical Concerns

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Issue Essay

Scientific and technological advances in biomedicine mark the beginning of a new era in public health research. Now, more than ever before, public health research offers the promise of a greater understanding of human disease and its expression in populations throughout the world. Public health professionals working in international contexts face unique ethical dilemmas at all stages of research design and implementation. A number of important questions are raised: How should U.S. regulations for scientific research be applied in international settings? When there are disagreements about the application of federal regulations governing research, who should decide—American officials or local authorities? What is the meaning of “respect for cultural differences” in the context of international public health research? How should requirements for informed consent—with their strong emphasis on individual autonomy—be implemented in cultural settings that do not share this autonomy-oriented perspective? How are standards of care applied in international studies? What are the fundamental requirements for conducting ethically sound research with human subjects?

This module considers ethical issues in international public health research. This essay begins with a brief review of ethical guidelines for research with human subjects. A discussion of respect for cultural difference follows, describing notions of cultural relativism and ethical universalism. Ethical and social issues surrounding informed consent in public health research are also explored. Particular attention is given to challenges associated with comprehension, language barriers and beliefs about who should provide consent. The application of culturally specific standards of care and the meaning of “best proven therapeutic method” are discussed, drawing on controversial cases such as the recent AZT trials with pregnant women in developing countries to illustrate the myriad problems that confront public health researchers working in international settings. Particular attention will be given to the use of placebos in clinical trials. Finally, requirements for ethical conduct in research are outlined

Ethical Guidelines for International Health Research

International concerns with ethical issues surrounding human experimentation were heightened by the Nuremberg War Crime Trials following World War II. These proceedings judged medical experiments conducted by Nazis on prisoners of concentration camps. The Nuremberg Code, the first international code of ethics for research involving human subjects, was issued in 1947. The Nuremberg Code outlined a strong commitment to the informed and voluntary consent of research participants. The World Medical Association’s Declaration of Helsinki, adopted in 1964 and revised most recently in 2000, reiterated the importance of voluntary and informed consent to research. In the United States, in 1979, the *Belmont Report* was published by the National Commission for the Protection of Human

Subjects of Biomedical and Behavioral Research.¹ The Belmont Report outlines ethical principles underlying research with human subjects, and emphasizes informed consent, consideration of risks and benefits associated with scientific research, and the protection of vulnerable populations. Final regulations concerning policies governing research on human subjects were issued in 1981 by the U.S. Department of Health and Human Service and reissued a decade later. The federal mandates, generally referred to as *The Common Rule*, were clear: any research involving human subjects that is funded by a Department agency, with certain exemptions, must be evaluated by an Institutional Review Board (ORB). Eight criteria for IRB approval are listed, including documentation of informed consent and the protection of privacy and confidentiality.

In 1982, the Council of International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO) published the *Proposed International Guidelines for Biomedical Research Involving Human Subjects*.² These guidelines were developed in response to concerns raised about the particular circumstances surrounding the implementation of scientific research in developing countries. In 1991, in collaboration with WHO, CIOMS prepared a separate document addressing public health and epidemiological research (*International Guidelines for Ethical Review of Epidemiological Studies*). The *International Guidelines for Biomedical Research Involving Human Subjects*, revised in 1993, were endorsed by the WHO Global Advisory Committee on Health Research and the Executive Committee of CIOMS. The CIOMS guidelines consist of a description of general ethical principles and fifteen recommendations with commentary. As with the original guidelines, contributors to the revision were particularly concerned with the application of ethical standards and the establishment of mechanisms for ethical review of human subjects research in developing countries where local standards for scientific conduct may differ from those in western industrialized nations.

In recent years, reports of misconduct associated with international biomedical investigations have called into question research practices and the application of study results in medical care and health policy, particularly in resource poor nations. These controversies have influenced debates over the recent revision of the Declaration of Helsinki (2000) and discussions to finalize revisions of the CIOMS Guidelines.

In 2002, the Nuffield Council on Bioethics published the *Ethics of Research Related to Healthcare in Developing Countries*.³ This document provides specific recommendations for ethical issues related to standards of care, informed consent, obligations of researchers to individuals and communities, and independent ethical review.

Official international policies governing human subjects research such as the CIOMS Guidelines encourage cultural sensitivity in implementing research in non-western settings (see also International Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Guidelines for Good Clinical Practice⁴). In his systematic review of the ethics of biomedical research in international settings, Brody⁵ argues that policies such as those promulgated by CIOMS (1993) strengthen a commitment to transcending cross-cultural differences by mandating that the same standards be applied to research subjects from both developing and industrialized countries (e.g., research participants in any cultural setting should provide individual voluntary consent; research participants in the developing world should be advised of everything that would be told to research subjects in an industrialized country; research participants in any setting should be aware of their right of refusal).

Respecting Cultural Difference

The problem of balancing universal and local standards for ethical conduct in public health research is challenging for investigators facing the very real constraints of implementing a study in an area in which traditional customs may be in conflict with international guidelines and policies. Currently, there are ongoing debates over the importance of respecting cultural difference and simultaneously applying universal ethical standards in international scientific research. These issues are particularly complex when public health research is implemented in areas known for human rights violations. The situation is exacerbated by the economic and social disparities that exist between resource rich nations—who generally sponsor public health research—and resource poor nations—where the research may be conducted. Public and professional debates concerning health research in international settings often center around notions of cultural relativism and beliefs about ethical universalism.

Cultural relativism refers to the notion that because human social and psychological characteristics are culturally produced, the diverse representation of these characteristics across human groups is relative to cultural variability. From this perspective, the only normative judgment that is possible is one that recognizes the equal worth of culturally different moral standards. Thus, transcultural standards for the ethical assessment of cultural practices or human conduct are not objective or rationally valid, but always represent the imposition of one set of cultural values on another. Indeed, the term *ethical imperialism* has been used to refer to the application of western ethical standards in scientific research implemented in developing nations with different cultural norms concerning ethical conduct in research.⁶ Ethical relativism holds that the moral standards of different cultures cannot be rank ordered in terms of a common criterion of comparison; such standards are “incommensurable” with one another. Moreover, generalizations concerning human behavior may form a basis for ethical judgment within a given culture (although even there such generalizations are often problematic and lacking in empirical demonstration), but are so tenuous when made across different cultures that they cannot form the basis for a rational ethical system.

On the other hand, the problem with ethical relativism, in its broadest conceptualization, is that it seems to condone every permutation of human behavior, if the surrounding cultural context would also condone it. So neither internal critique of a malfunctioning culture nor outside critique on the basis of universal human standards--such as human rights—are possible if the theory of ethical relativism is accepted. Genocide, racism, violence against women and children, war crimes, and the like are highly problematic implications of the theory. There are certain situations in which an appeal of ethical universals, such as notions of human rights, seems both appropriate and essential to the very integrity of the international community.

At the heart of this debate over cultural relativism and ethical universals is the problem of *empirical fact* vs. *moral value*. How can an empirical description of what “is” influence the formulation of statements about what “ought” to be? In her recent book *Against Relativism*, Macklin argues for the existence of overarching principles that could be used to determine the rightness or wrongness of specific cultural beliefs and practices.⁷ Macklin’s articulation of a strong version of anti-relativism is based upon her adherence to the universalizing discourse of moral fundamentalism--the idea that certain ethical principles are applicable cross-culturally. However, Macklin acknowledges that, in some cases, it might be appropriate to consider cultural difference in the application of ethical standards, noting that flexibility in the application of ethical rules can be consistent with adherence to more fundamental ethical principles.⁷

What is especially troubling for investigators concerned about human rights is the reliance on cultural or ethical relativism to justify or in some way dignify social and political practices that condone the systematic oppression of individuals and groups based on their gender, ethnicity, religion or political affiliation.

Arguing from an autonomy perspective, Macklin is clearly committed to the notion of basic human rights and their global applicability.⁷ In his exploration of international bioethics, Baker offers instead a model for negotiating value differences relevant to science and health in a multicultural world.^{8,9} Thomasma takes a slightly different approach in his discussion of bioethics and international human rights.¹⁰ Rather than rely on the language of rights and the importance of autonomy and individual freedom, Thomasma proposes that we consider, alternatively, notions of the “common good” as a foundation for human rights.¹⁰ Thomasma distinguishes between procedural and substantive rules that could form the basis of an international multicultural bioethics.¹⁰

An important question concerns the way in which conflicts are resolved when there are disagreements about the ethical appropriateness of conducting particular public health studies. In these cases, the fundamental issue might be framed as: Who decides? Should it be local authorities, an international body, or the government represented by the funding agency? International guidelines provide sound advice for investigators, but often the guidelines are difficult to apply to specific contexts. Moreover, they are not legally binding. In some cases, the research sponsor imposes special requirements for ethical conduct. For example, all international research funded by the U.S. federal government is required to undergo review by an independent ethics committee constituted in the host country to insure that certain standards are met in the implementation research in international settings. Of particular concern is that the study design and procedures respect the welfare and rights of individuals participating in the study, and that participation is voluntary.

While public health researchers should be sensitive to local customs, they are never authorized to conduct research without regard to potential risks and without attempts to seek individual consent from potential study participants. In particular, public health researchers working in international settings must avoid the exploitation of non-western populations in research that would not be allowed in the investigator's home country. As the debates over cultural difference and ethical standards for research continue, it is likely that there will be further revisions to the existing guidelines for ethical conduct in international research, and greater efforts made to negotiate the more difficult obstacles to reaching consensus.

Informed Consent

National and international guidelines for ethical conduct in scientific research identify specific requirements for informed consent. These requirements include the following three key elements: provision of information, comprehension of information, and voluntariness. Informed consent describes a process in which an individual voluntarily agrees to participate in a research study after the purpose, procedures, risks, benefits and alternatives have been thoroughly described. Informed consent is based upon the notion that individuals are autonomous agents with the capacity for expressing a self-determined choice.

Offers of excessive financial compensation, bribes, or unrealistic promises to potential research participants in public health research can undermine autonomy and voluntary consent as much as lying or coercive threats do. Consent is truly voluntary only when the option reasonably exists to withhold consent. Additionally, the voluntary nature of participation in research is influenced significantly by the implicit or explicit power of investigators and the institutions they represent.

In international settings, particularly resource poor nations, individuals and communities involved in public health studies may be vulnerable to coercion because of their poverty and high rates of illiteracy. Moreover, challenges associated with implementing informed consent may be heightened because of language barriers that diminish effective communication, particularly regarding the translation of scientific or medical concepts, and because of differences in beliefs about who may provide consent to participate in research.^{11,12}

The following discussion of these factors and their influence on the process of informed consent is organized around three issues: 1) comprehension of information; 2) language barriers; and 3) location of decisional authority to provide consent to research.

Comprehension of information: Investigators often must explain sophisticated scientific concepts in international public health research, particularly in complex trials involving the use of placebos or randomization. Yet, studies have shown repeatedly that information included in informed consent documents is difficult for potential research participants or patients to understand. In the United States, most consent forms are written for someone educated at the college or graduate school level, although the average reading ability is significantly lower. Even when consent documents are simplified, higher rates of illiteracy in many resource poor nations contribute to problems associated with comprehension of informed consent documents. For example, in a study of informed consent for an influenza vaccine for children in The Gambia, although 90% of the 189 consenting parents knew the purpose of the vaccine was to prevent disease, only 10% understood the placebo control design.¹³

In addition to the length and complexity of consent forms, difficulties surrounding comprehension may also be associated with requirements for written consent, particularly among people who cannot read or write. The challenges of meeting U.S. requirements for written documentation of informed consent in international public health studies is particularly problematic when study participants are reluctant to formalize a document with their signature or thumbprint because of previous experiences that resulted in their victimization including the loss of personal property or land, when “legal” documents were used against them.

Language barriers: There are two dimensions of language that are relevant for informed consent. One dimension concerns the choice of words--the specific language that will be employed in the consent discussion. The second dimension concerns the language used to express concepts related to the research itself *and* concepts related to informed consent such as “voluntary participation” or “confidentiality.”

Misunderstandings and miscommunication about scientific research are more likely to occur when investigators and participants speak different languages and when informed consent documents must be translated, especially when there are no equivalent expressions for particular biomedical concepts or when the notion of informed consent is unfamiliar. For example, in Marshall’s case study of informed consent in genetic epidemiological research in Nigeria, investigators interviewed discussed problems

associated with back translation (translating a document from one language to another and then having an independent native speaker back translate the document into the original language).¹³ Several investigators reported an incident that occurred in which an English consent form was translated into Yoruba, and then back translated by language experts at the local university. Yet, when the final document was used with potential subjects in the field, individuals had difficulty understanding it. The investigators were required to revise the consent once more so that it could be used effectively.

Although the use of an interpreter may reduce linguistic barriers, potential problems remain. Translators are often portrayed as straightforward interpreters of information exchanged between health providers or researchers and patients. However, the translator must negotiate not only language, but also cultural and contextual factors. A broad range of problems are associated with medical interpretation: The inability to translate equivalent expressions across languages; paraphrasing language that results in omissions or erroneous substitutions of terms; different levels of comprehension among participants in the interaction; and the influence of conflicting cultural beliefs and values among participants.

Cultural norms governing the structure and content of discourse in medical encounters are vitally important to effective communication. Beliefs and expectations regarding what is considered to be "appropriate" discourse in medical interactions vary considerably across cultures and are affected by social factors that reinforce differences in the relative power experienced and expressed by the individuals involved in the interaction. For example, in cultural environments where women are subordinate to their husbands, fathers, or male heads of households, women might be expected to remain quiet and allow a male family representative to respond to questions or to ask them. Under these conditions, obtaining voluntary consent may be compromised if a woman does not believe she is able to make inquiries or if she believes she must acquiesce to the authority of the health care investigator and her husband, father or brother. Her voice is silenced in these communications, not necessarily because she cannot understand the "language" of the consent discussion, but because of normative behavior associated with "appropriate" discourse in medical interactions.

Public health investigators working in international settings must ensure that the research community and the individual participants understand clearly the nature of the research and its potential harms. The absence of linguistically equivalent terms is never a justification for minimizing the importance of communicating the essential aspects of a study and its implications for personal well-being; to do so would seriously jeopardize the ability to obtain voluntary *informed* consent.

Autonomy and Locus of Decisional Authority. Notions of personhood, individual autonomy and decisional capacity are embedded within the social and cultural patterns of family ties and community. In the United States and other western industrialized countries where personal autonomy is emphasized, individuals are expected to make decisions about medical treatments or research participation for themselves or through designated surrogates. However, in many non-western settings, religious or tribal leaders, or a patient's extended family may play a significant role in decisions concerning health care and medical research. Cultural differences regarding the nature of personhood and the location of decisional authority for consent have been problematic for investigators conducting international public health research.

In an early report on consent for smallpox vaccination research in five areas of West Africa, investigators found that in certain regions, the strongest factor influencing a community's receptivity to

the program was compliance with the decisions of tribal leaders.¹⁴ In her discussion of AIDS research in Africa, Barry addressed the challenge of translating the concept of autonomy in areas where personhood is defined by one's tribe, village, or social group.¹⁵ Before obtaining consent from individuals in these settings, tribal elders, community leaders, religious authorities or family members of the research participant may need to be approached.

It is important to note the distinction between consulting community authorities before approaching the individual and obtaining "approval" or "consent" only from community leaders. The former strategy is not problematic for researchers, but the latter poses inherent conflicts for investigators. An individual does not have a *right* to take part in research; she only has a right not to be forced to take part and a right not to take part under ignorant or deceiving circumstances. The key moral point is that rights exist even if the individual does not recognize or acknowledge those rights for himself.

More recently, Loue, Okello and Kawuma described the social context surrounding consent in Uganda.¹⁶ They note that according to Ugandan civil law an eighteen-year-old male living at home has the legal right to make his own decisions. However, it is customary for the son to obtain his father's consent prior to entering into any obligation or contract, including participation in research. In addition, Ugandan women often refuse to make a decision regarding their own or their child's participation in research without the consent of their partner. Loue and her associates describe the compromise solution that was reached at a workshop held in Uganda to discuss the issue of family consent for participation in research.¹⁶ Participants at the workshop suggested a waiting period of forty-eight hours between the time individuals were approached about participation and the time they signed the consent form. This would give them an opportunity to consult with family members if they chose before making the final decision about their participation in a research project. The groups recommendation for a delayed consent accommodates the cultural norms regarding family involvement in the decision making process without diminishing the importance of respect for the individual.

The problem of balancing universal and local standards for ethical conduct in scientific research is challenging for investigators facing the very real constraints of implementing a study in an area in which traditional customs regarding decisional authority may be in conflict with international guidelines for individual consent. Current recommendations (e.g., Nuffield Council on Bioethics³; National Bioethics Advisory Commission¹⁷) suggest that a tribal chief, village elder, or community leader may express approval of a research agenda, but sensitivity to cultural customs is secondary to honoring individual choice. When consent is viewed as a process, not a single event, there is greater flexibility in devising mechanisms that honor expressions of individual autonomy *and* cultural norms regarding the involvement of others in decision making, including for example, family members or community elders.

Standard of care

An important concept in biomedical research is the notion of equipoise. Equipoise refers to the general acceptance among scientists and health providers that patients or prospective research participants should not be subjected to greater risk through research than they would be if they were receiving standard therapy. Complex issues, however, surround interpretations of whether or not individuals actually would be exposed to greater harms in research than if they received conventional medical therapies; the pivotal question is: What is the force of the "if"? Does it mean that standard therapy is available? Or does it just mean that it is hypothetically available? The fact that a given area does not have financial resources or the clinical infrastructure to provide what might be considered standard

therapy never justifies subjecting individuals to experimental treatment without serious consideration of the social and ethical challenges involved in the study. Standard of care refers to the level of care provided to participants involved in biomedical clinical trials. There are two broad categories for deciding the level of care: 1) a universal standard refers to the best possible treatments that are available anywhere (any place in the world); and 2) a non-universal standard refers to the treatment that is actually available in a specific region of the world.³

A fundamental ethical principle underlying the application of standards of care in health research with human subjects is the avoidance of exploitation, particularly for individuals or communities who may be vulnerable because of their poverty or ethnicity. The issue of what standard to apply is especially complex when researchers conduct studies in international settings where health delivery systems are compromised because of lack of medical resources, including drugs, equipment, and personnel.

Debates over the meaning and application of standard of care in international scientific experiments are ongoing.^{18,19} International attention on this issue was heightened in 1997 as a result of the US-sponsored research on the prevention of maternal-fetal HIV transmission.^{20,21,22} In this study, researchers in Thailand, Uganda and other developing nations were criticized because control groups received a placebo, which would not have been acceptable if the study had been conducted in the US. Extensive discussion of this particular study, and its implications for other studies, has not resulted in a strong consensus among health professionals, bioethicists, and policy makers throughout the world. Views tend to be polarized—proponents of a universal standard argue strongly that anything less is inherently exploitative, suggesting that it is only the poor of the world, and usually poor people of color, who are placed at risk through their participation in studies. In sharp contrast, opponents argue that it is simply not realistic to apply a universal standard in locations where the existing infrastructures for health care delivery cannot support the “best proven therapy” for the local population. In the AZT study to prevent maternal-fetal transmission of HIV, for example, opponents of the universal standard of care point out that providing control groups with the placebo was, in fact, providing them with the locally available standard of care. Moreover, opponents of a universal approach call attention to the fact that local governments and health professionals were actively involved in reviewing and approving the study design. There was, in fact, broad approval for the study by the World Health Organization; a panel convened by WHO recommended that there was an urgent need to find less costly drug regimens for preventing HIV maternal-fetal transmission, noting that randomized controlled trials would be the most effective way to quickly produce scientifically valid results.

Determination of which approach to use for standard of care in clinical trials—universal or non-universal—remains one of the most contentious ethical issues in international public health research. The Declaration of Helsinki²³ states: “The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods...This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists” (paragraph 29). Recent recommendations proposed by the Nuffield Council on Bioethics for health research in developing countries generally agree with the revised Declaration of Helsinki.²³ Members of the Working Party for the Nuffield Council suggest that the appropriate standard of care for control groups can only be decided through consultation with representatives of the country where the study will be conducted, that whenever possible, control groups should be offered a universal standard of care, and that when it is not possible, the best intervention currently available as part of the national health system should be provided.

The Nuffield Council on Bioethics offer specific criteria for determining what standard of care should be used in international settings, acknowledging the complexities that exist in local contexts (e.g., available treatment, sustainability of treatment following the trial, health services infrastructure).³ Factors to consider include: a) the appropriate research design to answer the question; the severity of the disease and the effect of proven treatments; c) the existence of a universal standard of care for the disease being studied and the quality of the supporting evidence; d) the standards of care which can be afforded by the host and the sponsoring country ; and e) the standard of care which can be sustained in the host country.

Ethical Requirements for International Public Health Research

The promulgation of ethical guidelines for research, both nationally and internationally, provides frameworks for consideration of appropriate conduct in the design and implementation of research, including international research on public health issues. Recently, Emmanuel, Wendler, and Grady, outlined seven requirements for determining whether a research trial is ethical.²⁴ Although the authors focused their attention on biomedical clinical trials, their requirements have relevance for research in general, and international public health investigations specifically. The seven ethical points these authors consider are briefly outlined below:

1. Social or scientific value

Consideration of the social and scientific value of the study requires that investigators evaluate the treatments or interventions proposed to determine that they will improve the health and well-being of the individuals and communities involved. This requirement is justified by ethical concerns related to the scarcity of resources and the importance of not exploiting the populations who participate in the research.

2. Scientific validity

The requirement for scientific validity refers to the application of acceptable scientific principles and methodologies, including statistical techniques, in order to produce valid data. This requirement appeals to ethical concerns over the use of scarce resources and the importance of nonexploitation.

3. Fair subject selection

Fairness in choosing individuals and communities who participate in research requires that stigmatized and vulnerable populations will not be exposed to risky research, and conversely, that rich and powerful individuals will not be selectively chosen for potentially beneficial research. Fairness in subject selection appeals to the ethical principle of justice.

4. Favorable risk-benefit ratio

Consideration of a favorable risk-benefit ratio requires that investigators minimize risk and enhance benefits, and that risks for those who participate in research are proportionate to the benefits that may be derived for the subjects and for society. This requirement is justified by the ethical principles of nonmaleficence, beneficence, and nonexploitation.

5. Independent review

The requirement for independent review refers to the importance of an ethical review of the study design, potential research participants, and the risk-benefit ratio by a group unaffiliated with the study.

Independent ethical review is justified by the importance of public accountability and minimizing the influence of potential conflicts of interest.

6. Informed consent

Informed consent refers to the provision of information to potential research participants (study goals, procedures, risks, benefits, alternatives) using an approach that insures comprehension and understanding so that individuals can make a voluntary decision about their participation and continued enrollment. This requirement is based on the ethical principle of respect for individual autonomy.

7. Respect for potential and enrolled subjects

This requirement emphasizes respect for research participants by: a) permitting them to withdraw from the study; b) protecting privacy and confidentiality; c) providing information about newly discovered risks or benefits; d) providing feedback about the study results; and e) maintaining the welfare of study participants. This requirement is justified by the ethical principle of respect for persons.

In any public health investigation, establishing a collaborative relationship with local investigators and the host community contributes to the successful implementation of a project and the potential for insuring that the study results may have a long-term impact. Ideally, collaboration might be implemented throughout the duration of the study, beginning with community assistance in deciding on the topic to be examined and its relevance and significance for the local population. This is not always possible, although in most cases, the establishment of a Community Advisory Board before the study begins will assist public health investigators in determining the most effective approaches for implementing the study and providing feedback to the community.

Capacity building is an important aspect of instituting ethically sound international public health research. Capacity building refers to the efforts of investigators to provide assistance to host institutions and communities in establishing mechanisms and resources that promote the health and well-being of individuals. Educational programs designed to develop and enhance professional expertise, and financial support for technological resources, medical equipment, and administrative assistance represent various forms of capacity building that public health investigators might provide to the host community in international public health research.

Conclusion

The globalization of scientific and medical research has increased dramatically in recent years. Public and private sectors alike are engaged in multinational clinical trials, epidemiological community based research, and behavioral studies. The complexity of international politics and the economic disparities that exist between industrialized and “developing” nations create myriad challenges for public health investigators. In the future, institutional and governmental authorities will exercise greater authority over the regulation and management of public health research. While individuals and communities who participate in public health research may benefit from the stronger oversight, investigators may experience tighter regulations as administratively cumbersome and restrictive. Successful resolution of political and scientific challenges in international public health research will only occur when there is a solid foundation for the development of mutual trust. A vital measure of international cooperation will be the extent to which there is a strong commitment to capacity building and resource sharing among the various stakeholders involved in public health investigations, including governmental authorities, institutions, and individual researchers.

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Case Study: Clinical Trials of AZT to Prevent Maternal-Infant Transmission of HIV in Resource Poor Nations

The HIV/AIDS pandemic has been devastating for populations worldwide, particularly those in sub-Saharan Africa and Asia because of the personal and economic burdens for families and communities. Complex social and ethical issues surround the design and implementation of research on HIV/AIDS in any setting. However, transnational research on HIV/AIDS sponsored by resource rich countries and carried out in the developing world raise serious questions about the application of international guidelines for ethical conduct in biomedical studies regarding standards of care, placebo-controlled trials, informed consent, and the obligations of researchers to participants when a study has ended.

In 1994, investigators in France and the U.S. reported conclusive evidence that an AZT drug regimen administered to HIV-positive pregnant women and their babies after birth reduced the transmission of HIV to the infant. The findings were impressive: the difference in transmission rate between those who received AZT and those who received the placebo was significant (8% versus 25%). The new regimen was known by its study name, AIDS Clinical Trials Group (ACTG) 076. Based on the study conclusions, the U.S. Public Health Service recommended the 076 regimen as the standard treatment for all HIV-infected pregnant women in the U.S. This regimen represented a great breakthrough for those women with access to the drug, primarily those in wealthy industrialized nations. HIV-infected women in the developing world, however, were less fortunate, and their numbers were growing. In areas such as Uganda and South Africa, it was estimated that about 40% of pregnant women were HIV-positive and roughly one of every four or five children would be born infected with HIV.

The spread of the HIV/AIDS epidemic was, and continues to be, devastating for the developing world. In 1998, for example, 5.8 million new cases of HIV infection were reported by United Nations AIDS officials (1.2 million from South and Southeast Asia and 4 million from sub-Saharan Africa). Combination drug therapies for the millions of people infected with HIV in resource poor nations are largely unavailable because of their expense and the lack of health care resources. Drug regimens for HIV/AIDS treatment cost roughly \$15,000 per person each year in industrialized nations, a cost that far exceeds the annual income of most individuals in the developing world.

The cost of the 076 treatment protocol—at \$800-\$1000 for the AZT alone—was prohibitive for developing countries. Other barriers to the successful implementation of the 076 regimen included the costs of screening for HIV and complications associated with administering the protocol. The 076 regimen required five oral doses of AZT daily over approximately 12 weeks of pregnancy, intravenous AZT during labor and delivery, and six weeks of postpartum AZT for the infant. It was generally agreed that the 076 regimen was not a practical solution for areas such as sub-Saharan Africa where financial resources and the clinical infrastructure to manage the complicated protocol were not available. Moreover, women often did not seek prenatal care until their third trimester.

Following the publication of the success of the 076 regimen, in 1994, the World Health Organization convened a panel of over fifty experts from around the world to consider global recommendations for the use of this regimen for pregnant women. This panel acknowledged the potential impact of 076 for reducing maternal-infant HIV transmission but noted the practical limitations of the regimen for the developing world. However, The WHO panel called for innovative research to consider less complicated and less expensive regimens that would have the same effect as 076. Moreover, the WHO panel

recommended that the new research be coordinated at a global level to avoid duplication and to ensure that all aspects of the issue could be addressed in a robust and comprehensive manner.

By 1995, the United Nations AIDS program and agencies in the U.S., Belgium, France, Denmark, and South Africa agreed to sponsor sixteen clinical trials in Cote d'Ivoire, Uganda, Tanzania, South Africa, Malawi, Ethiopia, Burkina Faso, Zimbabwe, Kenya, Thailand, and the Dominican Republic. The National Institutes of Health (NIH) and the Centers for Disease Control (CDC) sponsored nine of the studies. The specific goals of the studies varied. The effectiveness of shorter courses of AZT or other antiretroviral drugs were assessed in about half of the investigations. Other studies focused on the impact of much less complex interventions such as Vitamin A supplements or vaginal disinfection during labor. Except for one study, these investigations were placebo-controlled trials. In Thailand, researchers compared three short course regimens with a control group receiving a protocol similar to 076.

All studies had been carefully examined by ethical review committees in the sponsoring and host countries, all studies were determined to meet international ethical standards for biomedical research and, in every case, individuals from the host-countries were involved in the design and implementation of the projects.

In February of 1998, the CDC reported the findings from a placebo controlled study in Thailand showing that the oral administration of AZT during the last four weeks of pregnancy as well as during labor, reduced maternal-infant transmission of HIV by fifty percent. A year later, the results of a placebo controlled trial conducted in three African nations (known as the PETRA trials) indicated that transmission rate was reduced by 37% at six weeks after birth when antiviral treatment drugs were administered at the time of delivery and continued for one week for both mother and infant. These results were heralded as a strong indication that alternative therapies—more practical and less expensive for women in developing countries—could be used to reduce maternal-infant transmission of HIV. Following the initial report of findings from the study in Thailand, the CDC suspended the placebo arm of the Thai investigation which was conducting equivalency trials to test the effect of reduced AZT therapy to prevent maternal-infant HIV transmission. Other clinical trials stopped recruiting women to placebo control groups.

While these studies were on-going, a debate ensued over the ethical appropriateness of the investigations, specifically in relation to the use of placebo control groups. The primary charge from critics was that researchers gave priority to their own research goals over the lives of the women participating in the studies.

Key Questions for Public Health Professionals

- What ethical review processes should be deemed acceptable for the implementation of multi-national clinical trials with vulnerable populations? Should the study move forward if host country researchers, along with other designated national and international review committees, approve the research for implementation, regardless of concerns raised by other individuals or groups (locally and internationally)? Whose views should be considered as the “final word”?
- In multi-national trials, what standards of care should be applied if the local standard means that pregnant women will not receive any treatment?

- What mechanisms ought to be considered to ensure that women in resource poor nations understand the nature and goals of the study and that consent to the research is voluntary?
- What procedures can or should be considered to ensure that pregnant women have access to appropriate AZT treatment during their pregnancy? What responsibilities do the researchers have in relation to the provision of care for women at the completion of the study?

Case Study: Analytical Discussion

Ethical Problems and Relevant Values

The collaborative international trials to investigate the effectiveness of alternatives to the 076 AZT protocol to reduce maternal-infant transmission of HIV resulted in heated debates among health professionals, ethicists, and policy makers worldwide. The primary ethical concern raised by critics was the use of placebo-controlled trials. Marcia Angell (1997), the editor of the *New England Journal*, suggested that the trials had the mark of the notorious Tuskegee study, a project funded by the U.S. Public Health Service to study the natural course of syphilis in poor African American men in the rural south. Angell believed that there was no need to compare shorter regimens of AZT with placebos. Lurie and Wolfe (1997) were equally harsh in their criticism of the studies. They argued that the research questions could be answered by equivalency studies in which the proven treatment was compared against alternative treatments and they also indicated that women and infants would die needlessly from HIV-infection if they were in the placebo control arms of the ongoing investigations.

Harold Varmus, director of NIH, and David Satcher, director of the CDC, countered these charges, noting that placebo-controlled trials are the definitive standard for determining the safety and efficacy of interventions (1997). Proponents of the placebo-controlled trials argued that the answers to the questions raised in the studies were not yet clear and therefore resulted in a state of equipoise, requiring the rigorous application of a placebo arm in the investigations. Moreover, proponents said that equivalency studies would require additional time because of the need for larger sample sizes, and they would be less conclusive.

Proponents and critics both evoked international guidelines for the ethical conduct of research with human subjects outlined in documents such as the Nuremberg Code, the Helsinki Declaration (being revised at the time of the debates), the Belmont Report, and the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (also in revision) in stating their arguments.

A fundamental issue in this case concerns the complexities surrounding the meaning of “best proven therapeutic method.” Should it refer to the highest attainable standard *anywhere in the world*, or the highest attainable and sustainable therapy in the country where a study will be conducted? Another important ethical issue in the AZT placebo control studies to prevent maternal-infant transmission of HIV concerns the obligations of researchers to consider the availability of therapeutic interventions for research participants and the community once a study is complete. The 1993 CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects emphasizes that research carried out in developing nations must be responsive to the health care needs, concerns and priorities of the host country. The intention of the AZT trials for HIV-infected pregnant women was an attempt to respond directly to the devastating effects of the AIDS epidemic for poor women and children whose access to medical care and treatment is often severely compromised. Proponents of the trials have argued that it is vitally important to provide the highest level of therapy possible given the circumstances of the study in the host country and that if a therapeutic intervention is not sustainable, findings or products from clinical trials will not be applicable or available for the research participants and their communities.

Critics of the studies charge that, even if the alternative interventions were successful, in most cases, the cost of providing treatment (even though it would be minimal) combined with the absence of

clinical infrastructures would severely diminish the possibility for effective application of the research findings. Proponents, however, note that at least two of the countries where the trials were being conducted had the financial resources to provide short term AZT therapy if it proved effective, and that other resource-poor nations would be assisted by international agencies in securing and providing the drugs.

Although placebo-controlled trials to reduce maternal-infant transmission of HIV have ended, the debate continues (see e.g. Levine 2001; Macklin 2001) In particular, the revision of the Declaration of Helsinki has become the focus of considerable controversy over the meaning, interpretation, and application of standard of care and the obligations of researchers to communities once a study has ended. The new wording of paragraphs 29 and 30 are especially contentious for those involved in the debate. Paragraph 29 now states: "The benefits, risk, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists." Paragraph 30 is a new addition to the Declaration of Helsinki, "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." Given the highly charged nature of the debates among health professionals, bioethicists, and policy makers internationally, it is unlikely that a general consensus on these issues will be reached in the near future.

Necessary Information

In this case, the necessary information to be considered in the decision-making process regarding implementation of placebo-controlled trials to reduce perinatal transmission of HIV include extensive examination of the scientific evidence available and a robust exploration of existing guidelines for ethical conduct in international biomedical research. Additionally, the investigators must involve researchers from host countries in the design and implementation of the study and initiate a comprehensive review of the issues among established ethical and scientific advisory panels at participating institutions, and with relevant national and international organizations. It is important to note that these activities were implemented by the investigators working on the placebo-controlled trials. Despite their efforts to systematically address the complicated dimensions of the studies, controversy arose over conflicting opinions about the ethical appropriateness of conducting the studies.

Stakeholders to the Decision

Public health professionals must be attentive to the views and concerns of the myriad stakeholders involved in the implementation of research such as the AZT trial to prevent maternal-infant transmission of HIV. The decision to go forward with the trial should be informed by the values and interests of: a) the pregnant women who would be directly effected by the study; b) the local community within which the study would be carried out; c) local researchers involved in the international collaboration; d) ethical review committees at the participating institutions, and if relevant, by national ethical advisory committees; and e) international advisory committees such as UNAIDS.

Available Options

Thoughtful consideration of the recommendations and concerns of all interested parties provides researchers with a range of potential plans of action. In this case, a number of alternatives were possible, including those outlined below:

- Move forward with the placebo-controlled trials as originally planned, but only after intense review and approval by ethical boards at participating institutions, and national and international ethical advisory committees.
- Design careful strategies to ensure that consent among the women was truly informed and voluntary.
- Ensure careful oversight of the study by establishing an Advisory Board comprised of local researchers, community leaders, and international representatives.
- Revise the study design in order to compare the full course of AZT with alternative treatments throughout the duration of the pregnancy and after the baby is born.
- Postpone the implementation of the study until consensus is reached following a thorough debate among health professionals, ethicists, policy makers, and governmental authorities both nationally and internationally.

Decision Process

In this case, the placebo-controlled trials of the effect of AZT on the prevention of maternal-infant transmission of HIV were implemented. The intense public and professional debate that followed was, and continues to be, reported in the media and scholarly publications. Consensus regarding the ethical appropriateness of these studies and others like it may not be attainable given the complexity of the issues involved and, in some cases, the sharp differences of opinions among interested parties. An important outcome of this study has been increased attention to ethical issues surrounding the design and implementation of biomedical international research, particularly in settings where individuals are vulnerable because of their poverty and lack of access to medical treatment.

References

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