Chapter One

Ethical Issues in International Research—Setting the Stage

Introduction

Collaboration among peoples from different nations, whether in the form of engaging in trade, providing material assistance, or participating in cultural interchange, can substantially benefit all parties involved. However, these kinds of collaborations do not always proceed smoothly, particularly when controversy emerges regarding the nature of the collaboration and/or the distribution of benefits. Such controversies are perhaps more likely to occur when the nations involved do not share the same cultural, economic, political, and ethical perspectives, or when they are at different stages of development.

In recent years, the increasingly global nature of health research, and in particular the conduct of clinical trials involving human participants,[1] has highlighted a number of new ethical issues. This often happens when researchers or research sponsors from one country wish to conduct research in another country. The research in question might simply be one way of helping the host country address a public health problem, or it might reflect a research sponsor's assessment that the foreign location is a more convenient or efficient—or less troublesome—site for conducting a particular clinical trial. It might also represent a joint effort to address an important health concern faced by both parties. In any case, as the pace and scope of international collaborative biomedical research have increased during the past decade, long-standing questions about the ethics of designing, conducting, and following up on clinical trials have re-emerged. Some of these issues have begun to take center stage because of the concern that research conducted by scientists from more prosperous countries in poorer nations that are more affected by disease may, at times, be seen as imposing ethically inappropriate burdens on the host country and on those who participate in the research trials. For example, some commentators have denounced as unethical clinical trials to test drugs that might reduce perinatal transmission of HIV that were conducted in Africa, Asia, and the Caribbean and sponsored by parties from resource-rich countries (Angell 1997; Lurie and Wolfe 1997). (See Exhibit 1.1.)

In this case, concerns focused on two areas. First, using placebo-controlled trials when an effective treatment exists means that individuals in the control group are being treated differently than those in control groups in developed nations (where the control is an established effective treatment). This may imply that they are not considered equally worthy or worthy of equal concern. Second, some have claimed that an alternative research design could have addressed the health needs of those in the host country without using a placebo control.

The example of the AIDS trials is only one of the better-known cases of international research that has heightened ethical concerns. Recently, accounts have appeared in the popular media of troubling cases of drug testing conducted overseas in which participants allegedly were exposed to risky research—often without their voluntary informed consent—in studies of questionable value to the citizens in the host country (DeYoung and Nelson 2000; Flaherty et al. 2000; LaFraniere et al. 2000; Pomfret and Nelson 2000; Rothman 2000; Stephens 2000). The specter of exploitation raised by these allegations is cause for a concerted effort to ensure that protections are in place for individuals participating in international clinical trials.

Exhibit 1.1: Placebos—A Recent Ethical Controversy in International Research

In 1997, controversy arose over a series of placebo-controlled trials aimed at finding an affordable and implementable treatment to lower the rate of maternal-to-infant transmission of HIV in developing countries. The controversial studies followed an earlier National Institutes of Health (NIH)-sponsored study conducted in the United States (called "ACTG 076," after the number of the NIH protocol), which demonstrated that maternal-to-infant transmission of HIV could be reduced by two-thirds when AZT is administered continuously to women as early as the 14th week of pregnancy.

Although this treatment became the standard of care in the United States and other industrialized countries, several factors made it impossible to follow the regimen in developing countries, primarily cost and the lack of a health care infrastructure to administer the regimen. As a result, some of the clinical trials conducted in Thailand and Africa were designed to test a lower dose of AZT in HIV-positive women, which was much less expensive than the standard dose, in a placebo-controlled trial. In addition, these studies initiated the treatment much later in pregnancy, since women in these countries do not receive early prenatal care, and the AZT was administered orally rather than intravenously, in line with the availability of medical facilities. Moreover, newborns did not receive full treatment, if any. These departures from the proven ACTG 076 regimen aimed to establish a course of treatment that could reasonably be implemented for HIV-positive pregnant women in resource-poor countries.

For ethical reasons, placebo-controlled trials testing this experimental treatment regimen could not have been conducted in the United States and other developed countries once the efficacy of the ACGT 076 regimen had been established. In other words, it would be considered unethical to withhold from women in a research study an effective treatment that they could obtain as part of their routine medical care. The justification for conducting the research in developing countries was that it compared a new regimen with the existing level of care in those countries.

Critics of the study argued that it is wrong for researchers who come from a country where an effective treatment is used to withhold that treatment from any study participant and that infants in the study, who could be prevented from acquiring HIV, would become infected and die unnecessarily. These critics argued for the use of a different study design to compare the experimental treatment with the standard treatment rather than with the placebo, thereby avoiding these unnecessary deaths (Lurie and Wolfe 1997). Subsequently, such a study design was adopted in another NIH-sponsored study in another location in Thailand at the same time that the placebo-controlled trials were being carried out elsewhere in the same country.[2]

Defenders of the placebo-controlled studies replied with four arguments:

1) The "standard of care" for HIV-positive women in these developing countries is no treatment at all, so they are left no worse off as a result of participating in the study;

2) A placebo-controlled trial can be conducted with fewer participants and completed in a much shorter time than an AZT-controlled study, so useful information and effective interventions pertinent to this population will be available much sooner;

3) The ACTG 076 treatment regimen that has become standard in the West is not now, and will not in the foreseeable future, be available to this population because of its prohibitive costs. Therefore, use of this active control would render the results of very little relevance to the health needs of the developing country (Levine 1999; Wilfert et al. 1999); and

4) If it is proven to be effective, the less expensive and more appropriate regimen can be made available by governments to all HIV-positive pregnant women in these countries (Varmus and Satcher 1997).

These placebo-controlled trials (which have long since been completed, although follow-up is still occurring) did succeed in showing that the cheaper, short-course AZT regimen was significantly better than a placebo. Yet, the controversy surrounding the ethical principles relevant to such research has not abated.

Issues Prompting This Report

As with other National Bioethics Advisory Commission (NBAC) reports, several issues and activities prompted the Commission's decision to address this topic. First, several members of the public suggested that NBAC's mandate to examine the protection of the rights and welfare of human participants in research extends to international research conducted or sponsored by U.S. interests.

A second circumstance—the changing landscape of international research—also prompted the decision to prepare this report. Increasingly, scientists from developing countries are achieving more equal status as collaborators in research, as many of these countries have built their capacity for technical contributions to research projects and for appropriate ethical review of research protocols. Although the source of funding for such collaborative research is likely to continue to be wealthier, developed countries with experience conducting research outside their own borders (such as Canada, France, Germany, Japan, the Netherlands, the Scandinavian countries, the United Kingdom, and the United States), collaborators from developing countries are seeking—justifiably—to become more equal as partners in the research enterprise.

The current landscape of international research also reflects the growing importance of clinical trials conducted by pharmaceutical, biotechnology, and medical device companies. Over the last 40 years, U.S. funding of all research and development has seen a dramatic shift in its primary source from the public to the private sector. Although the U.S. government has continued to increase its investment in biomedical research, private industry funding has increased much more rapidly (AAAS 2000; PhRMA 2000).

Some observers believe that market forces have pressured private organizations to become more efficient in the conduct of research, which may—absent vigilance—compromise the protection of research participants (DeYoung and Nelson 2000; Flaherty et al. 2000; LaFraniere et al. 2000; Pomfret and Nelson 2000; Stephens 2000). Although the extent, relevance, and force of these pressures are widely debated, it is clear that such pressures can exist regardless of the funding source.

Third, NBAC also heard concerns from researchers, Institutional Review Board (IRB) members, and federal regulators about how U.S. regulations are "exported" to other countries and interpreted by researchers and institutions abroad. In other words, the U.S. government bundles its research regulations (and the ethical principles and commitments that underlie them) into research projects it conducts in other countries. In particular, most research sponsored by the U.S. government or regulated by the Food and Drug Administration (FDA) must comply with the Federal Policy for the Protection of Human Subjects (45 Part 46 of the *Code of Federal Regulations* [CFR], Subpart A, also known as the Common Rule) and/or parallel FDA regulations (21 CFR Parts 50 and 56). In previous reports, NBAC has noted that even for domestic researchers, the U.S. regulations are at times difficult to interpret and require clarification (NBAC 1998; NBAC 1999), so it is not surprising that understanding and interpreting U.S. research regulations in other settings could pose even more profound difficulties. Thus, another dimension to research conducted internationally deserves serious attention—whether the existing rules and regulations that govern the conduct of U.S. investigators or others subject to U.S. regulations are appropriate in the context of international research efforts, or whether they in fact unnecessarily complicate or frustrate otherwise worthy and ethically sound research projects.

Fourth, the Commission recognizes the importance of ongoing and vigorous international discussion concerning the most appropriate mechanisms for facilitating important and necessary international research, while at the same time ensuring the protection of the participants of research. In this regard, discussions already are under way in other countries (Nuffield Council on Bioethics 1999) within the context of an emerging international effort to harmonize regulations governing clinical trials under the auspices of the International Conference on Harmonisation (ICH 1996). Similarly, recent efforts by the World Medical Association (WMA), the Council for International Organizations of Medical Sciences (CIOMS), and the World Health Organization to revise and develop guidelines on international research ethics are a welcome contribution to this effort.

Finally, because attention will continue to focus on the ethical and policy issues that arise in international

research in general (Angell 1997; Angell 2000; Benatar 2000; Benatar and Singer 2000; Bloom 1998; Clarke et al. 1998; Levine 1999; Lurie and Wolfe 1997; Nuffield Council 1999; Tan-Torres Edejer 1999; Varmus and Satcher 1997) and regarding clinical trials in particular, this report provides another opportunity for ongoing public dialogue about how to provide appropriate protection to all research participants.

Scope and Limits of This Analysis

This report discusses the ethical issues that arise when research that is subject to U.S. regulation is sponsored or conducted in *developing* countries, where local technical skills and other key resources are in relatively scarce supply. Within this context, NBAC's attention primarily is focused on the conduct of clinical trials involving competent adults—in particular those trials, such as Phase III drug studies, that can lead to the development of effective interventions. Clinical trials are conducted to test and evaluate in human populations the safety and therapeutic efficacy of drugs, biologics, devices, and various other health-related interventions. Appropriately designed and conducted trials provide one of the most definitive and powerful techniques for evaluating existing clinical practices and developing innovative methods of diagnosis, treatment, and prevention. In addition, because complex and important ethical concerns are likely to be more pressing in clinical trials than in many other types of research investigations, the focus of this report has been limited accordingly.

However, limiting the scope of the report in this way precludes discussion of a wide range of analyses of other types of important international collaborative research initiatives subject to U.S. regulation, including observational and case-control studies, health services research, educational research, and various demonstration projects. Notably, this report does not focus on the important area of public health research. Although much of the discussion in this report is relevant to these other types of research, the particular characteristics of research endeavors other than clinical trials probably merit their own ethical assessment.

NBAC commissioned three separate research projects to provide empirical data to inform its deliberations.[3] One of the most ambitious of these reports, a survey of researchers involved in international research, was prepared by researchers at Johns Hopkins University. (See Exhibit 1.2.) In addition, NBAC heard testimony from a number of experts regarding scientific, cultural, and ethical aspects of international research. Finally, after the release of a draft version of this report in September 2000, NBAC received comments from 183 U.S. and international researchers and health experts, as well as from members of the public.

Exhibit 1.2: Survey of Researchers in Developing Countries and the United States

The largest empirical study commissioned by NBAC for this report was a survey of investigators who conduct biomedical research in developing countries. The study consisted of two parts: a survey of U.S. investigators directed by Nancy Kass and a survey of developing country investigators directed by Adnan Hyder, both of Johns Hopkins University. Both arms of the study used a written questionnaire and focus groups and involved questions about researchers' experiences with ethical issues in their research, ethical review in the United States and the host country, informed consent, and recommendations for change in U.S. and international guidelines for research in developing countries.

Two versions of the questionnaire were used—one for researchers from the United States and one for developing country researchers. The two versions differed only in the wording of some questions so that they would be compatible with the different locations of researchers. Similar focus group guides were used for each arm of the study as well. Data collection took place from December 1998 to September 2000.

More than 500 researchers completed the survey, including more than 200 from developing countries. Seventy-nine focus group respondents participated: 43 from the United States and 36 from developing countries. The results of the study (available in Volume II of this report) consist of quantitative data (from the survey questionnaire) and qualitative data (from the focus groups). Methods, results, and discussion are presented separately for each study component (U.S. and developing country respondents), and additional sections of the report compare the findings from the two groups and offer recommendations for policies concerning developing country research based on the overall study results.

Themes and Premises of This Report

The chapters in this report are organized to illustrate the ethical issues that arise in the design, review, and follow-up of clinical trials conducted abroad. In this chapter, NBAC makes recommendations that apply to all research sponsored or regulated by U.S. institutions and conducted in developing countries. The remaining sections of this chapter present general recommendations regarding research conducted by U.S. interests in developing countries and present an overview of issues raised in subsequent chapters. Chapter 2 focuses on ethical issues that arise in choosing a research question and appropriate study design of clinical trials and makes several recommendations in this area. Chapter 3 addresses the ethical issues pertinent to recruiting participants and obtaining voluntary informed consent and makes a number of recommendations toward improving these processes. Chapter 4 examines the difficult issue of the obligations of sponsors or others to provide post-study benefits to participants and host communities and countries and recommends approaches to providing such benefits once a trial is concluded. Chapter 5 recommends ways to enhance research collaboration between developing and developed countries, with a particular focus on ethics review, the processes of granting assurances and determining equivalency, and capacity building.

Essential Requirements for the Ethical Conduct of Clinical Trials

Many of the ethical concerns regarding the treatment of human participants in international research are similar to those raised in conjunction with research conducted in the United States.[4] They include, among others, choosing the appropriate research question and design; ensuring prior scientific and ethical review of the proposed protocol; selecting participants equitably; obtaining voluntary informed consent; and providing treatment to participants during and after the trial. These concerns are consistent with principles embraced in many international documents, such as the *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects* (WMA 1964, as amended in 2000) and the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS 1993), both widely acknowledged sources on the ethics of international research.

NBAC believes that two types of ethical requirements—substantive and procedural—must be carefully considered when human research is conducted, regardless of the location. The principles embodied in the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (National Commission 1979) serve as a foundation for our national substantive ethical requirements under the system of protection of human participants in the United States. The *Belmont Report* sets forth the following three basic ethical principles, which provide an analytical framework for understanding many of the ethical issues arising from research involving human participants: respect for persons, beneficence, and justice. Respect for persons encompasses two ethical notions. First, "individuals should be treated as autonomous agents" and their decisions should be respected; and second, "persons with diminished autonomy are entitled to protection" (National Commission 1979, 4). The principle of beneficence, the obligations of which affect both investigators and society at large, incorporates the rules of "do no harm" and "maximize possible benefits and minimize possible harms" (National Commission 1979, 6). Justice refers to a fair and equitable distribution of benefits and burdens, taking into consideration what is deserved or due and the fair selection of participants, as well as the idea that equals should be treated equally (National Commission 1979, 8–10). NBAC believes that in order to be ethically sound, research conducted with human beings in a foreign country must, *at a minimum*, be consistent with the ethical principles underlying the *Belmont Report*.

In addition, ethically sound research must comply with an important *procedural requirement*—prior ethical review by a body that is competent to assess compliance with these substantive ethical principles. U.S. regulations, which are designed to implement the substantive ethical principles embodied within the *Belmont Report*, also set forth more specific rules to guide ethics review committees (and researchers) in their work.

NBAC believes that when conducting clinical trials abroad, U.S. researchers and sponsors should comply with these substantive ethical requirements for the

protection of human research participants. Although the ethical standards that this report is recommending for conducting research in other countries are minimum standards, host countries are encouraged to adopt human research participant protections that go beyond those that are currently provided under the U.S. system. This will help to further promote the rights, dignity, and safety of research participants as well as the credibility of research results. Furthermore, explicitly stipulating these ethical requirements will facilitate efforts to harmonize international protections for human participants. Already, many national and international guidelines describe such protections, providing models for U.S. consideration. (See Appendix B.)

NBAC recognizes that the nature and understanding of these broad requirements might not be the same in all countries and regions. For example, although recognition of the importance of obtaining informed consent is increasing (Ijsselmuiden and Faden 1992), questions have been raised about whether voluntary informed consent as procedurally implemented in the United States is advisable or possible in some countries (Bankowski 1992; Karim et al. 1998). In addition, the need to provide *compensation* to individuals who have been injured as a result of research is an issue that has been discussed in many national and international guidelines and is the source of continuing discussion in the United States.[5] Many international guidelines require approval by a local ethics review committee and by an ethics review committee at the investigators' or sponsors' home institutions.[6] Because, in order to approve a study, U.S. IRBs must be satisfied that all U.S. regulatory requirements are met, it is appropriate to consider how these requirements should be understood and applied in the context of research conducted in developing countries.

The following protections, listed in Recommendation 1.1, are requirements of ethical research, whether conducted domestically or abroad.[7] Throughout the report, the Commission discusses the importance of context and describes, where appropriate, ethically acceptable levels of flexibility in the interpretation of the basic requirements outlined in this recommendation.

Recommendation 1.1: **The U.S. government should not sponsor or conduct clinical trials that do not, at a minimum, provide the following ethical protections:**

a) prior review of research by an ethics review committee(s);

b) minimization of risk to research participants;

c) risks of harm that are reasonable in relation to potential benefits;

d) adequate care of and compensation to participants for injuries directly sustained during research;

e) individual informed consent from all competent adult participants in research;

f) equal regard for all participants; and

g) equitable distribution of the burdens and benefits of research.

These requirements should extend to the private sector, which often has contact with U.S. regulations only through interaction with the FDA, for example, when seeking approval to license or market a drug in the United States.

Recommendation 1.2: **The Food and Drug Administration should not accept data obtained from clinical trials that do not provide the substantive ethical protections outlined in Recommendation 1.1.**

Choosing a Foreign Setting in Which to Answer a Research Question

Identifying the research question and the methodology necessary to answer that question is central to research design (Meinert and Tonascia 1986; Sackett 1983; Spilker 1991). (See Chapter 2.) In addition, when clinical trials are conducted in a developing country, it is ethically and scientifically important to justify why such a location has been chosen as the research site.

Sponsoring or conducting research in developing countries often poses special challenges arising from the combined effects of distinctive histories, cultures, politics, judicial systems, and economic situations (London et al. 1997). In countries in which extreme

poverty afflicts so many, primary health care services are generally inadequate, resulting from the collective effects of insufficient personnel (ranging from physicians to pharmacists), transportation and communication problems, and various logistical challenges, including the lack of basic medical supplies, the dearth of health facilities, and the inability of the population to pay for products and services. In addition, unsanitary living conditions and water supplies can make some medical therapies inappropriate or unproductive, and the high price of drugs often places them out of reach of both individuals and developing country governments.

Whether the research sponsor is the U.S. government—through such agencies as NIH, the Centers for Disease Control and Prevention, or the Agency for International Development—or a private sector organization (e.g., a nongovernmental organization [NGO] or private company), some justification is needed for conducting research abroad other than its less stringent or complex regulatory or ethical requirements, such as those regarding the speed with which ethics review occurs before initiating a study. Moreover, when the United States (or any developed country) proposes to sponsor or conduct research in another country when the same research could not be conducted ethically in the sponsoring country, the ethical concerns are more profound, and the research accordingly requires a more rigorous justification.

Typically, developed countries sponsor or conduct research in developing countries for some combination of the following four reasons. First, the host country might desire information about effective and affordable interventions for an indigenous health problem. For example, researchers from many other countries have collaborated with U.S. researchers and received NIH support for investigations of malaria or dengue, diseases that rarely occur in the United States, as well as for treatment of infectious diseases (e.g., tuberculosis, HIV/AIDS) or cancer, which are common in the United States.

Second, in order to be marketed in some developing countries, drugs and biologicals—even if already tested and approved in other countries—must be approved by national regulatory authorities. In some countries, this may require domestic testing. Third, it is more efficient to conduct research in a country in which the condition being studied is more prevalent. Certain diseases associated with particular environmental conditions—such as a tropical climate—can only be studied in locations where those conditions exist. Fourth, it might be less expensive and faster to conduct research in developing countries. Enrollment of participants, for example, can occur more quickly, or procedural requirements can be less burdensome (and protections for participants may not be as comprehensive).

Whatever the reason or combination of reasons for conducting research in developing countries, sponsors and researchers must ensure that these activities are conducted ethically and that they do not exploit either the participants or the population of the host country. When assessing justification for conducting research in a developing country, it is particularly important to determine whether the research is responsive to the health needs of the population of that country.

Responsiveness of the Research to the Health Needs of the Population

To meet the ethical principle of beneficence, the risks involved in any research involving human beings must be reasonable in relation to the potential benefits. Plainly, the central focus of any assessment of risk is the potential harm that may occur to research participants themselves (in terms of probability and magnitude), although risks to others also are relevant. The potential benefits that are weighed against such risks may include benefits that will flow to the fund of human knowledge as well as to those now and in the future whose lives may be improved because of the research. In addition, some of the benefits must also accrue to the group from which the research participants are selected. NBAC understands the principle of justice to require that a vulnerable population should not be the focus of research unless the potential benefits of the research will accrue to that group after the trial. Thus, in the context of international research—and particularly when the population of a developing country has been sought as a source of research participants—U.S. and international research ethics require not merely that research risks are reasonable in relation to potential benefits, but also that they respond to the health needs of

the population being studied. This is because, according to the principles of beneficence and justice, only research that is responsive to these needs can offer relevant benefits to the population.

Versions of this "responsive-to-needs" requirement appear in many international guidelines. For example, the influential CIOMS *International Ethical Guidelines* document states that "[b]efore undertaking research involving subjects in underdeveloped communities, whether in developed or developing countries, the investigator must ensure that the research is responsive to the health needs and the priorities of the community in which it is to be carried out" (CIOMS 1993, 25 [Guideline 8]). This requirement is echoed in *Ethical Considerations in HIV Preventive Vaccine Research: UNAIDS Guidance Document*, recently issued by the Joint United Nations Programme on HIV/AIDS (UNAIDS): "HIV vaccine development should ensure that the vaccines are appropriate for use among such populations, among which it will be necessary to conduct trials" (UNAIDS 2000, 12). The UNAIDS document carries the basic premise of the responsive-to-needs argument to the next level by insisting that when HIV vaccines are developed, "they should be made available and affordable to such populations" (UNAIDS 2000, 12).

Many researchers concur with this ethical premise. One scientist told NBAC that "research should only be conducted in a country if the results will potentially directly benefit the population. [Trials] should be conducted in a given country because the investigators have good reason for testing the intervention in the population and it is expected that the intervention will be used in that population."[8] The dean of a leading school of public health keenly stated his own pragmatic rule before undertaking a proposed study in the form of a question: "If this trial turns out positive, is there a reasonable likelihood that this will change governmental policy? Because if there is, that is the only real reason for doing the trial."[9]

Recommendation 1.3: **Clinical trials conducted in developing countries should be limited to those studies that are responsive to the health needs of the host country.**

Choosing a Research Design and the Relevance of Routine Care

It is generally accepted that the selection of an ethically appropriate research design when using clinical trials as a tool to evaluate an experimental intervention is critical. In this report, NBAC is especially interested in the following question: *Can a research design that could not be ethically implemented in the sponsoring, developed country be ethically justified in the country in which the research is conducted?* In addition, the Commission is interested in exploring whether offering potential participants better care or treatment than they could obtain outside the study would be an undue inducement to potential participants to enroll in a clinical trial. As a general rule, NBAC does not believe this to be the case, but the Commission recognizes that determining the level of treatment that should be provided to participants (including those in a control group, who are not receiving the experimental intervention) is a research design issue with ethical implications that must be addressed. A key question is, if the condition of an individual is improved as a result of participation in a study (whether due to the experimental intervention or overall improved medical care) is there some obligation on the part of sponsors and/or researchers to work toward maintaining that improved status after the study is completed?

The ensuing debate that arose following studies of maternal-to-infant transmission of HIV in developing countries (see Exhibit 1.1) set in motion efforts to revise the *Declaration of Helsinki*, first issued by the WMA in 1964 and amended several times (most recently in 2000), and the 1993 CIOMS *Guidelines*, the revision of which is currently under way. The revised *Declaration of Helsinki* calls for experimental interventions to be tested against the best current method, when one exists, and not against a placebo or any alternative intervention (WMA 1964, as amended in 2000). Principle 29 states 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. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists" (WMA 1964, as amended in 2000).

The CIOMS *Guidelines* document states that the ethical standards of the sponsoring agency's country should prevail when research is conducted in another country and that the ethical standards employed should be no less exacting than those in the sponsoring agency's country (CIOMS 1993, 43). Does this mean that every procedure stipulated in the U.S. regulations must be identical in the country collaborating in the research? Interpreting "ethical standards" in this way leads to the patently absurd conclusion that a country would somehow be applying a different ethical standard if its rules for prior independent review of research stipulated, for example, a different composition of research ethics committees than that required for U.S. research. Regarding informed consent, as noted below, Chapter 3 distinguishes between fundamental principles, specific ethical standards, and procedures mandated by U.S. regulations. It is important that each ethical issue be examined in light of the distinction between procedures and fundamental principles. Procedural requirements for informed consent, while important, are simply methodologies for implementing the ethical standards and are not themselves fundamental ethical principles.

Standard of Care

In many clinical trials, the standard of care for a given intervention often constitutes the control arm of the study. This report, for the most part, avoids the phrase *standard of care* in describing the interventions that people in a community or country normally obtain in the clinical setting. Instead, it refers in Chapter 2 to *treatment that is routinely available*, which is meant to apply to the majority of the population in that country. *Standard of care* is a concept borrowed from the medical-legal context that denotes the level of conduct against which a physician's or health provider's treatment of a patient will be judged in determining whether certain conduct constitutes negligence. It generally means, "what a reasonably prudent physician (or specialist) would do in the same or similar circumstances" (Annas 1993, 4). Defined in this way, it can meaningfully *describe* the types or level of treatments provided to patients in the clinical setting, but it might not serve as a justification for what *should* be provided to participants in research. Moreover, when most people in a country or a region routinely receive no care, that situation amounts to an absence of care rather than a standard of care.

Further, an ambiguity can be found in the term *standard*, which sometimes means, "what is normally done," or "standard practice." However, in some countries, a standard practice, such as reusing syringes or other disposable equipment, would not be acceptable to U.S. researchers and would not constitute a justification to employ the local unsafe practice. But a standard can also refer to a level that must be attained, as in "a standard for admission to medical school" or "the standard for maintaining hygienic practice in treatment and research." In this sense, U.S. researchers would be bound by the proper medical standard that prohibits the reuse of disposable equipment, even if reuse is standard practice in some countries. Other commentators have found similar discrepancies in the use of this term, including one group that has proposed an expanded concept that attempts to resolve some of these difficulties (Benatar and Singer 2000). Nevertheless, NBAC prefers where necessary to use the more cumbersome phrase, *treatment that is routinely available*, although, as noted below, even this phrase has certain limitations.

Established Effective Treatment

Before its most recent revision in October 2000, the *Declaration of Helsinki* required that "every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method" (WMA 1964, as amended in 1996). There has been much debate about the appropriateness of this requirement, particularly regarding the definition of the word *proven* and the expectation that anything less than providing the best treatment to patients (and by implication, research participants) will amount to treating them unjustly.

NBAC uses the phrase *an established effective treatment* to refer to a treatment that is *established* (it has achieved universal acceptance by the global medical profession) and *effective* (it is as successful as any in treating the disease or condition). Established effective treatments are not limited to what is routinely available in the country in which the research is being conducted, and NBAC

does not intend this phrase to refer to a *single best* treatment, since agreement may be lacking about what treatment is best. Although any phrase requires some interpretation, NBAC believes that the proposed phrase is reasonably clear and defines a concept that is useful in developing recommendations in this area. In particular, NBAC believes that it best conveys what is owed to research participants during a study, a topic discussed at length in Chapter 2.

This language is close to, but still somewhat different from, that found in the October 2000 revision of the *Declaration of Helsinki*, which states that "[t]he benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods" (WMA 1964, as amended in 2000). It is close to that found in *Helsinki* because NBAC also refers to providing a high quality of care. However, it differs in some respects, because it does not imply that there is only one best treatment. Indeed, NBAC recognizes that there are often many effective treatments for a given condition and that some controversy exists over which may be considered "best."

Without question, it can be difficult to determine whether an intervention constitutes an established effective treatment. Scientists may disagree regarding whether an intervention shown to be effective in one population is likely to be as effective in another that differs in significant ways (e.g., patients' age, patterns of susceptibility or resistance to drugs, or other medical conditions; stage of disease; or locally available medical or social resources needed for a successful intervention). Examples can be found in both the developing and developed world, such as differing drug susceptibilities of the parasite that causes falciparum malaria in Haiti as compared to East Africa and the differences among Canada, Europe, and the United States in guidelines for coronary artery bypass surgery and for chemotherapy in the treatment of solid tumors.

Fair and Respectful Treatment of Participants

Although many of the ethical issues that arise in international clinical trials also pose challenges to research conducted in the United States, some issues are particularly noteworthy in the international setting. Two such issues are the selection, recruitment, and enrollment of participants for research and the duty to obtain their voluntary informed consent to participate. (See Chapter 3 for a more extensive discussion and recommendations.)

In some countries, the methods used in U.S.-based studies for identifying appropriate groups for study and enrolling them in a protocol may not succeed because of different cultural or social norms. Meeting the challenge of developing alternative methodologies requires careful attention to the ethical issues involved in the recruitment of research participants, which is necessary in order to ensure justice in the conduct of research and to avoid the risk of exploitation. These are ethical concerns that echo an observation made by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in the *Belmont Report* more than 20 years ago:

> [T]he selection of research subjects needs to be scrutinized in order to determine whether some classes...are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied (National Commission 1979, 9–10).

As noted, researchers, ethics review committees, and relevant national and international guidelines agree broadly about the importance of satisfying certain substantive and procedural requirements for enrolling human participants in research. Although it is true that much international research sponsored by the U.S. government and private industry has conformed to these requirements, concern is ever present—both in the United States and abroad—that human participants not be exploited. In addition, exploitation may be more likely to occur when wealthy or powerful individuals or agencies take advantage of the poverty, powerlessness, or dependency of others to serve their own ends, without a sufficient benefit for the less advantaged individuals or group. Exploitation in any form can be construed as a human rights violation by virtue of its failure to recognize the inherent dignity of every human being, a precept embodied in the *Universal Declaration of Human Rights*.[10] It follows that all parties have a fundamental obligation to

avoid exploitation when conducting research, especially in poorer, less advantaged countries. In any case, exploitation is a serious moral wrong, and a fundamental obligation exists to refrain from behavior that constitutes or promotes it.

However, the circumstances in which exploitation occurs or might occur are not always apparent within the context of international research. One document that addresses international research in the context of HIV/AIDS identifies several factors that render countries or communities potentially vulnerable to exploitation in the conduct of research (UNAIDS 2000). These include:

- the level of the proposed community's economic capacity;
- limited experience with or understanding of scientific research in the country as a whole;
- limited local infrastructure, personnel, and technical capacity for providing health care and treatment options;
- limited experience and capacity for conducting ethical and scientific review; and
- an uncertain ability of individuals in the community to provide informed consent, for example, as a result of class, gender, or other social patterns (UNAIDS 2000, 8).

It is important to note, moreover, that these same concerns can and do arise in the context of research conducted in developed countries.

The requirement to obtain voluntary informed consent from human participants before they are enrolled in research is a fundamental tenet of research ethics and was the first requirement proclaimed in the Nuremberg Code (Nuremberg Code 1947). It has appeared in all subsequent published national and international codes, regulations, and guidelines pertaining to research ethics, including those in developing countries, such as India, Thailand, and Uganda. Nevertheless, there is an ongoing discussion about the value and importance of particular approaches to informed consent in other countries (Benatar and Benatar 1998; Edi-Osagie et al. 1998; Preziosi et al. 1997). Problems involving the interpretation and application of the requirement to obtain voluntary informed consent—and its underlying ethical principles—arise for researchers, ethics review committees, and others. For example, the CIOMS *Guidelines* specifically address the practical difficulties in dealing with informed consent as follows:

> Some [individuals] may be relatively incapable of informed consent because they are illiterate, unfamiliar with the concepts of medicine held by the investigators, or living in communities in which the procedures typical of informed-consent discussions are unfamiliar or alien to the ethos of the community (CIOMS 1993, 25).

In addition, in cultures in which men are expected to speak for their unmarried adult daughters and husbands are expected to speak for their wives, a woman may not be permitted to consent on her own behalf to participate in research. And, in many rural settings in developing countries, permission from a village leader is required before researchers may approach individuals to recruit them as volunteers.

In light of such cultural variation, the Commission was especially interested in problems that may arise from expecting researchers in developing countries to adhere strictly to the substantive *and* procedural imperatives of the U.S. requirements for informed consent. NBAC was particularly interested in exploring ways to deal with the situation that arises when cultural differences between the United States and other countries make it difficult or impossible to adhere strictly to the U.S. regulations that stipulate particular procedures for obtaining informed consent from individual participants. In general, it is important to distinguish procedural difficulties from those that reflect substantive differences in ethical standards. A number of procedural issues may arise during research, including variations (requiring written consent and permitting oral consent); substantive ethical considerations (withholding important and relevant information from potential participants); the need in some cultures to obtain a community leader's or a family member's permission before seeking an individual's consent; and standards of disclosure to research participants in cultures in which people lack basic information about modern science or reject scientific explanations of disease in favor of traditional nonscientific beliefs. Chapter 3

includes a series of recommendations that address these issues.

Access to Post-Trial Benefits

Among the many important issues that continue to be discussed in research ethics has been the concern about what is owed to research participants during a clinical trial. However, another question merits careful attention: *What products or services should be made available, and on what terms, to research participants and to others in the host country after completion of the research?* Although this question is relevant in ethical assessments of research regardless of where the research is conducted, it is being posed with special force, especially regarding serious diseases that affect large numbers of people in developing countries. Therefore, the question of what benefits research sponsors should make available to participants or others in the host country at the conclusion of a clinical trial is particularly significant for those developing countries in which neither the government nor the vast majority of the citizenry can afford the intervention resulting from the research. This question is discussed at length in Chapter 4.

A feature that distinguishes most developing from developed countries is the lack of access on the part of a large majority of the population to adequate health care. Many developed countries have long provided universal access to primary health care through a national health service or government-based insurance system. Although the United States is among a small number of developed countries that do not provide universal access to health care, most people who live in this country have access to an adequate basic level of medical services. Nevertheless, a sizable minority in the United States has only limited access to comprehensive health care services, and some have virtually no access, due to the complexities of U.S. health insurance coverage, the geographical distribution of health care resources, and the persistence of poverty and near-poverty conditions in some parts of the country. In the developing world, especially in the poorest countries in Africa and Asia, substantially fewer health care services are available (if any), and where they are available, access is severely limited. Despite some similarities, the conditions that limit access to health care in the United States and in developing countries are not comparable. In the United States, lack of access to adequate health care results from the decisions of policymakers, who have chosen not to use available resources to provide universal health coverage. In poor countries, most citizens lack access to health care because the resources simply are not available.

Access to health care is an important issue to consider in research ethics, because an ethically appropriate clinical trial design requires an assessment of the level and nature of care or treatment available outside the research context, as well as any possible future health benefits that might arise from the research. For example, if an effective treatment for a disease is generally available to patients outside the research context, it is not ethically acceptable to withhold it when studying a new treatment, because following the research trial, the participants would be left worse off than they otherwise would have been. In contrast, a research design that tests an experimental treatment against a placebo could perhaps be implemented in a developing country without participants becoming worse off, since those who receive the placebo would not otherwise receive an effective treatment for their condition. Whether it is sufficient from an ethical perspective merely to avoid making participants worse off than they would otherwise have been remains a matter of debate. This issue is addressed in Chapter 2.

These concerns also prompt the question of whether research sponsors should consider arrangements that would allow some of the fruits of research to be available in the host country when the research is concluded. Such arrangements would be responsive to the health needs of the host country. In this context, this report discusses the use of "prior agreements"—documents that refer generally to arrangements made before a clinical trial begins—that address the post-trial availability of effective interventions to the host community and/or country after the study has been completed. The parties to these agreements usually include some combination of producers, sponsors, and potential users of research products, including U.S. and international research organizations and development agencies, NGOs, and private corporations. Although only a limited number of prior agreements, either formal (legally binding) or informal, are in

place in international collaborative research today, it is useful to consider what role such agreements should play in the future.

Ensuring the Protection of Research Participants in International Clinical Trials

The two principal approaches to improving the protections of human participants in international clinical trials are 1) relying on reviews by U.S. IRBs and assurance processes to supplement and enhance local measures or determining that a host country or host country institution has a system of protections at least equivalent to that of the United States and 2) helping host countries build the capacity to independently conduct clinical trials and to carry out their own scientific and ethical review. Chapter 5 is devoted to exploring these approaches.

Ethics Review

It is now widely accepted that research involving human participants should be conducted only after an appropriate ethics review committee (a body that is independent of the investigators and sponsors of the research) has determined that several ethical issues have been addressed, including the following: 1) voluntary informed consent will be solicited; 2) risks will be assessed as reasonable in relation to potential benefits; and 3) evidence of a fair distribution of the benefits and the burdens of the research is present. When research is sponsored or conducted in accordance with U.S. research regulations (and within the boundaries of these regulations), an appropriately constituted and designated IRB is empowered to make these assessments. However, spokespersons from developing countries have maintained that people who live in the countries in which the research is to be conducted are in the best position to decide what is appropriate, rather than those who may be unfamiliar with local health needs and culture. These spokespersons state that committees that are familiar with the researchers, the institutions, potential participants, and other factors are more likely to provide a more effective and fully informed review than a geographically displaced or distant group. Only local committees, they argue, can exercise the kind of balanced and reasoned judgment required to review research protocols. In fact, the concept of local review is a cornerstone of the U.S. system for protecting human participants. Whether this standard can or should be applied to U.S. research conducted abroad was a focus of Commission deliberations.

NBAC found that the requirement for local review is occasionally tested and sometimes weakened when research is conducted in developing countries (something that can also happen within U.S. borders). In some cases, review by a local committee raises the potential for conflict of interest—or at least a heightened interest in approving research—when it means that valuable research funds would flow to the institution. Although several developing countries have instituted national research ethics guidelines, and ethics review in some countries is becoming more established, many difficulties and challenges to local review remain, including lack of experience with and expertise in ethics review principles and processes; conflict of interest among committee members; lack of resources for maintaining the committees; length of time it can take to obtain approvals; and problems involved with interpreting and complying with U.S. regulations.

In NBAC's view, efforts to enhance collaboration in research must take into account the status and capacity of ethics review committees in developing countries to review research and the need for U.S. researchers and sponsors to ensure that their research projects, at the very least, are conducted according to the same ethical standards and requirements applied to research conducted in the United States. This has led NBAC to conclude that when clinical trials involve U.S. and foreign interests, these protocols must still be reviewed and approved by a U.S. IRB *and* by an ethics review committee in the host country, unless the host country or host country institution has in place a system of equivalent substantive ethical protections. (See Chapter 5.)

Because U.S.-sponsored research undertaken in collaboration with other countries is increasing (including many studies that have different procedural requirements), there is a need to enhance the efficiency of those efforts through increased harmonization and understanding, without compromising the protection of research participants. We must find a way to adhere to widely accepted substantive ethical principles while at the same time avoiding the undue imposition of regulatory procedures that are peculiar to the United States.

Policy and Regulatory Issues

U.S. researchers or sponsors and their collaborators often encounter difficulties with procedural and administrative aspects of the U.S. research regulations or their implementation by the Office for Human Research Protections (OHRP) in the Department of Health and Human Services (DHHS).[11] U.S. and host country researchers at times perceive U.S. regulations as unnecessarily rigid. Among the many concerns NBAC heard were those relating to the process of negotiating assurances (45 CFR 46.103). The assurance document can be described as a commitment by the institution to conduct research ethically and in accordance with U.S. federal regulations; an approved assurance is a prerequisite to federally conducted or sponsored research. Some within the United States and abroad, however, view this as an excessively and unnecessarily paternalistic requirement.

A second important question concerns the nature of the variation in national and international ethical guidelines. Although many countries have promulgated extensive regulations or have officially adopted international ethical guidelines invoking high standards for research involving human participants, the former Office for Protection from Research Risks (OPRR) never has determined formally that guidelines or rules from any other countries afford protections equal to those provided by U.S. regulations—even those from countries such as Australia and Canada, where research ethics requirements closely parallel (and to some extent exceed) those of the United States.[12] Since its constitution in June 2000, OHRP has not done so either. The result is that researchers across the globe who are collaborating with U.S.-sponsored researchers must adhere to U.S. research regulations and obtain an assurance.

In its effort to more fully understand existing provisions for international collaborative research, NBAC reviewed 25 sets of guidelines, codes, and regulations from 14 countries and 7 organizations.[13] NBAC's analysis identified substantive ethical requirements of other countries that are absent from the U.S. regulations governing research. In contrast, NBAC found that all of the substantive ethical provisions in the U.S. regulations appear in other national or international rules. If these variations cannot be mediated by joint efforts, difficulties may arise in international research that will prevent important and ethically sound research from going forward. Unfortunately, some incompatibility remains, even within the U.S. regulations, both between the Common Rule and the FDA regulations and among the Common Rule agencies. FDA regulations are congruent with the Common Rule in most respects, but there are some differences stemming from the FDA's particular statutory authorities and regulatory mission. In contrast to the DHHS regulatory focus on institutions receiving DHHS funds, FDA regulations focus on the sponsors that develop the products, the investigators who perform the research studies, and the IRBs that review the research. In addition, in the international research context, the FDA does not make determinations of equivalent protection.

Addressing these inconsistencies should be a goal of U.S. regulatory policy. As discussed in Chapter 5, some actions can be taken at this time to make progress in this area, without the need for new regulations, such as developing policy guidance for determining whether the research policies of other nations provide protections equivalent to those provided in the United States.

Building Host Country Capacity to Review and Conduct Clinical Trials

Many international ethical guidelines, such as the 1993 CIOMS *International Ethical Guidelines* (CIOMS 1993) and UNAIDS' *Ethical Considerations in HIV Preventive Vaccine Research* (UNAIDS 2000), recommend that when developed countries sponsor research in developing countries, the sponsors have a responsibility to help build local and national capacity for designing and conducting trials and for the scientific and ethical review of proposed research projects. To enhance research collaborations between developing and developed nations, the capacity of resource-poor countries to become even more meaningful partners in international collaborative research must be increased. Making the necessary resources available for improving the technical capacity to conduct and sponsor research, as well as the ability to carry out prior ethical review, is one way to move forward in this effort. These issues are further addressed in Chapter 5.

Conclusions

The aim of this report is not to revisit past wrongs or to uncover a litany of examples in which participants in international research have been harmed or have had their rights violated. The intent, rather, is to examine the circumstances that make clinical trials that are conducted in developing countries ethically sound and to make recommendations to researchers, governmental and industrial sponsors, and other interested groups, where appropriate.

Ethical behaviors and commitments are not barriers to the research enterprise. Indeed, ethical behavior is not only an essential ingredient in sustaining public support for research, it is an integral part of the process of planning, designing, implementing, and monitoring research involving human beings. Just as good science requires sound research design, consideration of statistical factors, and a plan for data analysis, it must also be based on sound ethical principles. Only then can research succeed in being efficient and cost-effective, while at the same time embodying appropriate protections for the rights and welfare of human participants.

Most people believe that a world in which all have access to good medical care would be preferable to one in which many lack such access. Furthermore, most would agree that one should volunteer to participate in clinical research primarily for altruistic reasons and only secondarily for personal gain. In addition, it is widely believed that those who volunteer to be research participants should receive society's respect and gratitude, as manifested (at least in part) by ensuring they are treated fairly and respectfully and can enjoy the benefits of the research in which they participated. Researchers and sponsors should strive to conduct research in the United States and abroad in a way that furthers these aspirations, even though, regrettably, financial, logistical, and public policy obstacles often stand in the way of immediately achieving this goal.

This report makes recommendations for a beginning—a series of first steps toward achieving the aims discussed in this report. The Commission believes that the recommendations presented in this report are grounded in moral ideals, are tempered by reality, and are consistent with minimal ethical norms for distributive justice and respect for persons. However, abiding by these recommendations should not end efforts to improve the treatment of participants in research and the access of all peoples to the fruits of medical research. They provide a floor, not a ceiling, for ethical requirements.

Moreover, although the recommendations in this report focus principally on clinical trials conducted by U.S. researchers or sponsors in developing countries, it will be important to consider their application to other areas of research. Although many ethical issues that arise in clinical trials also arise in other types of research, the relevance, scope, and implications of NBAC's recommendations in other types of studies may be very different. Similarly, many of the issues and recommendations discussed in this report may equally apply to research conducted in the United States.

Notes

1 In past reports, the Commission has used the term *human subject* to describe an individual enrolled in research. This term is widely used and is found in the Federal Policy for the Protection of Human Subjects (45 CFR 46). For many, however, the term *subject* carries a negative image, implying a diminished position of those enrolled in research in relation to the researcher. NBAC recognizes that by merely changing terminology the desired goal of true participation by individuals who volunteer for research cannot be achieved, and the Commission does not imply that a truly participatory role is always the case. Nevertheless, for purposes of simplicity and from a desire to encourage a more equal role for research volunteers, in this report the term *participants* is adopted to describe those who are enrolled in research.

2 Varmus, H., Testimony before the Subcommittee on Human Resources, Committee on Government Reform and Oversight, U.S. House of Representatives. May 8, 1997. Washington, D.C.

3 See Kass, N., and A. Hyder, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations"; Marshall, P., "The Relevance of Culture for Informed Consent in U.S.-Funded International Health Research"; and Sugarman, J., B. Popkin, F. Fortney, and R. Rivera, "International Perspectives on Protecting Human Research Subjects." These background papers were prepared for NBAC and are available in Volume II of this report.

4 An upcoming NBAC report on the oversight of research conducted with human participants in the United States will address the implications of the findings and conclusions of this report in the context of domestic research.

5 In an upcoming NBAC report, the issue of compensation for injury is addressed in more detail.

6 In the United States, committees that review the ethics of human research protocols are referred to in regulation and practice as IRBs. In other countries, different names might be used, such as research ethics committees or ethics review committees. In this report, references and recommendations that are specific to the United States will refer to these committees as IRBs. References and recommendations that refer to such committees generally regardless of their geographic location will call them ethics review committees.

7 Although these protections are generally meant to apply to all research involving more than minimal risk, there are exceptions in certain guidelines for informed consent to be waived in research involving minimal risk.

8 Dickersin, K., Testimony before NBAC. December 2, 1999. Baltimore, Maryland. Meeting transcript, 138–139.

9 Sommer, A., Testimony before NBAC. September 16, 1999. Arlington, Virginia. Meeting transcript, 168.

10 Andreopolis, G.J., Testimony before NBAC. May 4, 2000. Madison, Wisconsin.

11 Until June 2000, the Office for Protection from Research Risks (OPRR) was the federal agency responsible for implementing U.S. regulations pertaining to protection of human research participants in other countries.

12 Letter from J. Thomas Puglisi, OPRR, to Eric M. Meslin, NBAC, December 16, 1999.

13 NBAC, "Comparative Analysis of International Documents Addressing the Protection of Research Participants." This analysis was prepared by NBAC staff and is available in Volume II of this report.

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