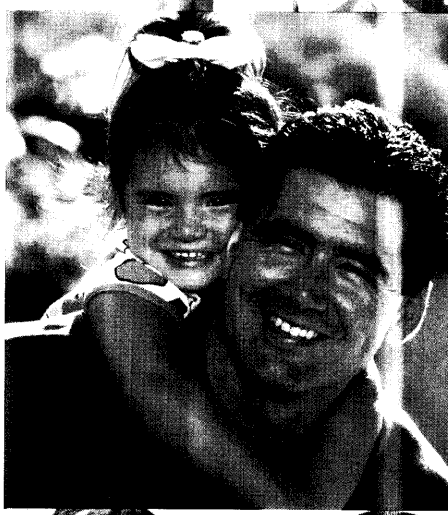

Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries

VOLUME I

Report and Recommendations of the National Bioethics Advisory Commission

Bethesda, Maryland
April 2001

The National Bioethics Advisory Commission (NBAC) was established by Executive Order 12975, signed by President Clinton on October 3, 1995. NBAC's functions are defined as follows:

a) NBAC shall provide advice and make recommendations to the National Science and Technology Council and to other appropriate government entities regarding the following matters:

   1) the appropriateness of departmental, agency, or other governmental programs, policies, assignments, missions, guidelines, and regulations as they relate to bioethical issues arising from research on human biology and behavior; and

   2) applications, including the clinical applications, of that research.

b) NBAC shall identify broad principles to govern the ethical conduct of research, citing specific projects only as illustrations for such principles.

c) NBAC shall not be responsible for the review and approval of specific projects.

d) In addition to responding to requests for advice and recommendations from the National Science and Technology Council, NBAC also may accept suggestions of issues for consideration from both the Congress and the public. NBAC also may identify other bioethical issues for the purpose of providing advice and recommendations, subject to the approval of the National Science and Technology Council.

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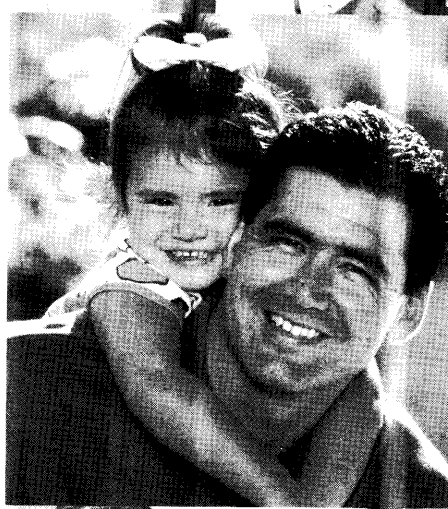

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April 18, 2001

The President
The White House
Washington, DC 20500

Dear Mr. President:

On behalf of the National Bioethics Advisory Commission (NBAC), I am pleased to submit our fifth report, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries*. This report caps 18 months of study on a topic of both domestic and international policy importance to the United States.

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 international clinical trials have re-emerged. Some of these issues have begun to take center stage because of the concern that research conducted by investigators and sponsors from more prosperous countries in poor nations that are heavily burdened 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. The potential for such exploitation is cause for a concerted effort to ensure that protections are in place for all persons participating in international clinical trials.

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, our attention is focused on the conduct of *clinical trials*; in particular those trials—such as Phase III drug studies—that can lead to the development of effective new treatments. 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.

The Commission proposes 28 recommendations that center on the principal ethical requirements surrounding the conduct of clinical trials conducted by U.S. interests abroad, and in particular the need for such trials to be directly relevant to the health needs of the population of the host country. Other major issues addressed include ethical issues surrounding the choice of research designs, especially in situations in which a placebo control is proposed when an established effective treatment is known to exist; issues arising in the informed

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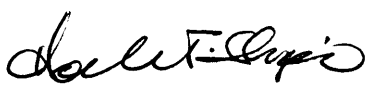
consent process in cultures whose norms of behavior differ from those of the United States; issues regarding what should be provided to research participants, and by whom, after their participation in a trial has ended; and issues involving what benefits, if any, should be made available to others in the host community or country. In addition, we make recommendations about the need for developed countries to assist developing countries in building the capacity to become fuller partners in international research. Until this goal can be reached, however, we offer recommendations regarding how the United States should proceed in settings in which systems for protecting human participants equivalent to our own have not been established. Finally, we recommend that the Food and Drug Administration should not accept data obtained from clinical trials that do not provide the substantive ethical protections outlined in this report.

Our international report comes at a time when NBAC is completing another report, one that focuses specifically on the federal system of protecting human participants in research conducted in the United States. Taken together, we believe that the recommendations contained in both reports will offer a policy framework that will assist both federally and privately sponsored researchers who conduct research here and abroad. We will be submitting this latter report to you in the coming weeks.

I would like to take this opportunity to thank the Commissioners, who worked tirelessly over the past 18 months, and the many members of the public (expert and lay alike) who provided valuable input for the Commission's deliberations.

We appreciate the opportunity to submit this report to you.

Sincerely,



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Executive Summary

Introduction

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 ethical issues, especially in those situations in which researchers or research sponsors from one country wish to conduct research in another country. The studies in question might simply be one way of helping the host country address a public health problem, or they might reflect a research sponsor's assessment that the foreign location is a more convenient, efficient, or less troublesome site for conducting a particular clinical trial. They might also represent a joint effort to address an important health concern faced by both parties.

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 international 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 heavily burdened 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. The potential for such exploitation is cause for a concerted effort to ensure that protections are in place for all persons who participate in international clinical trials.

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. In this respect, one particular dimension of research conducted internationally has attracted a great deal of attention, namely whether the existing rules and regulations that normally govern the conduct of U.S. investigators or others subject to U.S. regulations remain appropriate in the context of international research, or whether they unnecessarily complicate or frustrate otherwise worthy and ethically sound research projects.

A second circumstance—the changing landscape of international research—also is relevant. Increasingly, scientists from developing countries are becoming more involved as collaborators in research, as many of the countries from which these investigators come have developed 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 the wealthier, developed countries, collaborators from developing countries are seeking—justifiably—to become fuller and more equal partners in the research enterprise. Finally, the current landscape of international research also reflects the growing importance of clinical trials conducted by pharmaceutical, biotechnology, and medical device companies. Some observers believe that market forces have pressured private companies to become more efficient in the conduct of research, which may—absent vigilance—compromise the protection of research participants. 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.

Scope of This Report

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, the Commission's attention was 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 new treatments. Complex and important ethical concerns are likely to be more pressing in clinical trials than in many other types of research investigations; thus, the focus of this report has been limited accordingly. Although much of the discussion in this report is relevant to other types of research, the particular characteristics of research endeavors other than clinical trials probably merit their own ethical assessment.

This report centers on the principal ethical requirements surrounding the conduct of clinical trials conducted by U.S. interests abroad, and in particular the need for such trials to be directly relevant to the health needs of the host country. Other major topics addressed include ethical issues surrounding the choice of research designs, especially in situations where a placebo control is proposed when an established effective treatment is known to exist; issues arising in the informed consent process in cultures whose norms of behavior differ from those in the United States; what benefits should be provided to research participants and by whom after their participation in a trial has ended; and what benefits, if any, should be made available to others in the host community or country. Finally, it makes recommendations about the need for developed countries to assist developing countries in building the capacity to become fuller partners in international research. Until this goal can be met, however, recommendations are made regarding how the United States should proceed in settings in which systems for protecting human participants equivalent to those of the United States have not yet been established.

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.[2] 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 appropriate treatment to participants during and after the trial. These concerns are consistent with principles endorsed in many international research ethics documents.

NBAC believes that two types of ethical requirements—substantive and procedural—must be carefully considered and distinguished 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* serve as a foundation for the substantive ethical requirements incorporated into the system of protection of human participants in the United States. The *Belmont Report* sets forth 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. NBAC believes that in order to be ethically sound, research conducted with human beings must, *at a minimum*, be consistent with the ethical principles underlying the *Belmont Report*. In addition, ethically sound research must satisfy a number of important *procedural requirements*, including prior ethical review by a body that is competent to assess compliance with these substantive ethical principles. U.S. research regulations also set forth more specific rules to guide ethics review committees[3] (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.

Recommendation 1.1 lists protections that should be provided for individuals participating in U.S. government-sponsored clinical trials, whether conducted domestically or abroad.[4] Although existing U.S. law and regulations impose limits on the extent to which nonfederally funded research is subject to oversight, the Commission believes that these requirements should extend to all clinical trials, regardless of who sponsors or conducts them.

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.**

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.**

Responsiveness of the Research to the Health Needs of the Population

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. In addition, in countries in which extreme poverty afflicts so many, primary health care services generally are inadequate, and a majority of the population is unable to gain access to the most basic and essential health products and services. As a result of these difficult conditions, the people in these countries are often more vulnerable in situations (such as clinical trials) in which the promise of better health seems to be within reach.

Whether the research sponsor is the U.S. government or a private sector organization, some justification is needed for conducting research abroad other than a less stringent or troublesome set of regulatory or ethical requirements. 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.

To meet the ethical principle of beneficence, the risks involved in any research with human beings must be reasonable in relation to the potential benefits. Plainly, the central focus of any assessment of risk is the potential harm 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 those 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 population, especially a vulnerable one, should not be the focus of research unless some of 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.

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

Making a determination about the appropriate design for a clinical trial depends on various contextual considerations, so that what might be an ethically acceptable design in one situation could be problematic in another. For example, it might be unethical to conduct a clinical trial for a health condition in a country in which that

condition is unlikely to be found. In comparison, the same trial might be quite appropriately conducted where the trial results could be important to the local population. A more challenging question is whether a research design that could *not* be ethically implemented in the sponsoring country can be ethically justified in a host country when the health problem being addressed is common to both nations.

In this report, NBAC is especially interested in exploring 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 all cases, there is an ethical requirement to choose a design that minimizes the risk of harm to human participants in clinical trials and that does not exploit them. Because the choice of a study design for any particular trial will depend on these and other factors, it would be inappropriate—indeed wrong—to prescribe any particular study design as ethical for all research situations. Nevertheless, under certain, specified conditions, one or another design can be held to be ethically preferable.

> *Recommendation 2.1:* **Researchers should provide ethics review committees with a thorough justification of the research design to be used, including the procedures to be used to minimize risks to participants.**

Providing Established Effective Treatment as the Control

From the perspective of the protection of human participants in research, one of the most critical issues in clinical trial design concerns the use and treatment of control groups, which often are an essential component in methodologies used to guard against bias. Although placebos are a frequently used control for clinical trials, it is increasingly commonplace to compare an experimental intervention to an existing established effective treatment. These types of studies are called *active-control* (or positive control) *studies*, which are often extremely useful in cases in which it would not be ethical to give participants a placebo because doing so would pose undue risk to their health or well-being.

Within the context of active treatment concurrent controls, it is useful to consider whether, and if so under what circumstances, researchers and sponsors have an obligation to provide an established effective treatment to the control group even if it is not available in the host country. This report adopts the phrase *an established effective treatment* to refer to a treatment that is *established* (it has achieved widespread acceptance by the global medical profession) and *effective* (it is as successful as any in treating the disease or condition). It does not mean that the treatment is currently available in that country.

Investigators must carefully explain and ethics review committees must cautiously scrutinize the justification for the selection of the research design, including the level of care provided to the control group. If in a proposed clinical trial the control group will receive less care than would be available under ideal circumstances, the burden on the investigator to justify the design should be heavier. Furthermore, representatives of the host country, including scientists, public officials, and persons with the condition under study, should have a strong voice in determining whether a proposed trial is appropriate.

> *Recommendation 2.2:* **Researchers and sponsors should design clinical trials that provide members of any control group with an established effective treatment, whether or not such treatment is available in the host country. Any study that would not provide the control group with an established effective treatment should include a justification for using an alternative design. Ethics review committees must assess the justification provided, including the risks to participants, and the overall ethical acceptability of the research design.**

Community Involvement in Research Design and Implementation

Over the past three decades, researchers increasingly have deliberately involved communities in the design of research. In addition, research participants, health advocates, and other members of the communities from which participants are recruited have requested, and in some cases demanded, involvement in the design of clinical trials. By consulting with the community, researchers often gain insight about whether the research question is relevant and responsive to health needs of the community involved. In addition, community consultation can improve the informed consent process and resolve

problems that arise in this process because of the use of difficult or unfamiliar concepts. Such discussions can provide insight into whether the balance of benefits and harms in the study is considered acceptable and whether the interventions and follow-up procedures are satisfactory. Community consultation is particularly important when the researcher does not share the culture or customs of the population from which research participants will be recruited.

Recommendation 2.3: **Researchers and sponsors should involve representatives of the community of potential participants throughout the design and implementation of research projects. Researchers should describe in their proposed protocol how this will be done, and ethics review committees should review the appropriateness of this process. When community representatives will not be involved, the protocol presented to the ethics committee should justify why such involvement is not possible or relevant.**

Fair and Respectful Treatment of Participants

The requirement to obtain voluntary informed consent from human participants before they are enrolled in research is a fundamental tenet of research ethics. It was the first requirement proclaimed in the Nuremberg Code in 1947, and it has appeared in all subsequent published national and international codes, regulations, and guidelines pertaining to research ethics, including those in many developing countries.

Nevertheless, discussion is ongoing about the value and importance of particular procedural approaches to informed consent in other countries. 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. In some countries, the methods used in U.S.-based studies for identifying appropriate groups for study, enrolling individuals from those groups in a protocol, and obtaining informed voluntary consent might 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 recruiting research participants and obtaining their consent, which is necessary in order to ensure justice in the conduct of research and to avoid the risk of exploitation.

Recommendation 3.1: **Research should not deviate from the substantive ethical standard of voluntary informed consent. Researchers should not propose, sponsors should not support, and ethics review committees should not approve research that deviates from this substantive ethical standard.**

Disclosure Requirements

The basic disclosure requirements for satisfying the informed consent provisions in U.S. research regulations focus on the information needed by a potential participant in order to decide whether or not to participate in a study. Requirements for disclosure of information in the research setting usually exceed those for disclosure in clinical contexts. Indeed, the extent of disclosure of medical information to patients in clinical settings differs among cultures and can influence judgments about the amount and kind of information that should be disclosed in research settings. In the United States, the requirements for disclosure of information to potential participants in research are specific and detailed (45 CFR 46.116). The Commission has found some evidence that disclosures relating to diagnosis and risk, research design, and possible post-trial benefits are not always clearly presented in clinical trials conducted in developing countries, even though the current U.S. regulations include such requirements. For example, one disclosure requirement in the U.S. regulations focuses on potential benefits: "a description of any benefits to the subject or to others which may reasonably be expected from the research" (45 CFR 46.116(a)(1)). Traditionally, such a disclosure has been required to ensure that potential participants understand whether there is any possibility that the intervention itself might benefit them while they are enrolled in the study. There is, however, no specific mention of any possible *post-trial benefits* in current U.S. regulations. The Commission believes that, because this information is relevant to participants' decisions to participate in the trial, prospective participants should be informed of the potential benefits, if any, that they might receive after the trial is over.

Recommendation 3.2: **Researchers should develop culturally appropriate ways to disclose information that is necessary for adherence to the substantive ethical standard of informed consent, with particular attention to disclosures relating to diagnosis and risk, research design, and possible post-trial benefits. Researchers should describe in their protocols and justify to the ethics review committee(s) the procedures they plan to use for disclosing such information to participants.**

Recommendation 3.3: **Ethics review committees should require that researchers include in the informed consent process and consent documents information about what benefits, if any, will be available to research participants when their participation in the study in question has ended.**

Ensuring Comprehension

In some cultures, the belief system of potential research participants does not explain health and disease using the concepts and terms of modern medical science and technology. However, despite this potential barrier to adequate understanding, if they are willing to devote the time and effort to do so, researchers are often able to devise creative measures to overcome this barrier. Despite the acknowledged difficulties of administering tests of understanding, NBAC supports the idea of incorporating these tests into research protocols.

Recommendation 3.4: **Researchers should develop procedures to ensure that potential participants do, in fact, understand the information provided in the consent process and should describe those procedures in their research protocols.**

Recommendation 3.5: **Researchers should consult with community representatives to develop innovative and effective means to communicate all necessary information in a manner that is understandable to potential participants. When community representatives will not be involved, the protocol presented to the ethics review committee should justify why such involvement is not possible or relevant.**

Recognizing the Role of Others in the Consent Process

In some cultures, investigators must obtain permission from a community leader or village council before approaching potential research participants. Yet, it is important to distinguish between obtaining permission to enter a community for the purpose of conducting research and for obtaining individual informed consent. In their reports, NBAC consultants all noted that the role of community leaders or elders is an integral part of the process of recruiting research participants. Although these reports typically use the terminology of *consent* to refer to the community's permission or a leader's authorization for the researchers to approach individuals, NBAC will use this term to refer to the permission or authorization given by the individual being recruited as a research participant.

The need to obtain permission from a community leader before approaching individuals does not need to compromise the ethical standard requiring the individual's voluntary informed consent to participate in research. Gaining permission from a community leader is no different, in many circumstances, from the common requirement in this country of obtaining permission from a school principal before involving pupils in research or from a nursing home director before approaching individual residents. An ethical problem arises only when the community leader exerts pressure on the community in a way that compromises the voluntariness of individual consent. In NBAC's view, if the political system in a country or the local situation makes it impossible for individuals' consent to be voluntary and that fact is known in advance, then, because U.S. researchers cannot adhere to the substantive ethical standard of informed consent, it would be inappropriate for them to choose such settings.

Recommendation 3.6: **Where culture or custom requires that permission of a community representative be granted before researchers may approach potential research participants, researchers should be sensitive to such local requirements. However, in no case may permission from a community representative or council replace the requirement of a competent individual's voluntary informed consent.**

Recommendation 3.7: **Researchers should strive to ensure that individuals agree to participate in research without coercion or undue inducements from community leaders or representatives.**

Family Members

It is customary although not required in some societies for other members of a potential research participant's family to be involved in the informed consent process. For example, 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. In most instances, the need to involve the family is not intended as a substitute for individual consent, but rather as an additional step in the process. In many cases, family members may be approached before an individual is asked directly to participate in a research project. However, seeking permission from family members without engaging the potential research participants at all clearly departs from the ethical standard of informed consent. On the other hand, potential participants might also choose to involve others, such as family members, in the consent process. Indeed, involving family or community members in the informed consent process need not diminish, and might even enhance, the individual's ability to make his or her own choices and to give informed consent (or refusal).

It is often possible to obtain individual informed consent, which may require and indeed benefit from the involvement of family or community members, while at the same time preserving cultural norms. Such involvement ranges from providing written information sheets for potential participants to take home and discuss with family members to holding community meetings during which information is presented about the research and community consensus is obtained. When the potential participant wishes to involve family members in the consent discussion, the researcher should take appropriate steps to accommodate this desire.

Recommendation 3.8: **When a potential research participant wishes to involve family members in the consent process, the researcher should take appropriate steps to accommodate this wish. In no case, however, may a family member's permission replace the requirement of a competent individual's voluntary informed consent.**

Consent by Women

A strict requirement that a husband must first grant permission before researchers may enroll his wife in research treats the woman as subordinate to her husband and as less than fully autonomous. In reality, it may be impossible to conduct some research on common, serious health problems that affect only women without involving the husband in the consent procedures. In such cases, a likely consequence would be a lack of knowledge on which to base health care decisions for women in that country. The prospect of denying such a substantial benefit to all women in a particular culture or country calls for a narrow exception to the requirement that researchers use the same procedures in the consent process for women as for men, one that would allow for obtaining the permission of a man in addition to the woman's own consent.

Recommendation 3.9: **Researchers should use the same procedures in the informed consent process for women and men. However, ethics review committees may accept a consent process in which a woman's individual consent to participate in research is supplemented by permission from a man if all of the following conditions are met:**

a) **it would be impossible to conduct the research without obtaining such supplemental permission; and**

b) **failure to conduct this research could deny its potential benefits to women in the host country; and**

c) **measures to respect the woman's autonomy to consent to research are undertaken to the greatest extent possible.**

In no case may a competent adult woman be enrolled in research solely upon the consent of another person; her individual consent is always required.

Minimizing the Therapeutic Misconception

One barrier to understanding the relevant, important aspects of any proposed research is what has been called the *therapeutic misconception*. This term refers to the belief that the purpose of a clinical trial is to benefit the

individual patient rather than to gather data for the purpose of contributing to scientific knowledge. The therapeutic misconception has been documented in a wide range of developing and developed countries.

It is important to distinguish the confusion that arises from the therapeutic misconception from a related consideration. In the research setting, participants often receive beneficial clinical care. In some developing countries, the type and level of clinical care provided to research participants may not be available to those individuals outside the research context. It is not a misconception to believe that participants probably will receive good clinical care during research. But it is a misconception to believe that the purpose of clinical trials is to administer treatment rather than to conduct research. Researchers should make clear to research participants, in the initial consent process and throughout the study, which activities are elements of research and which are elements of clinical care.

Recommendation 3.10: **Researchers working in developing countries should indicate in their research protocols how they would minimize the likelihood that potential participants will believe mistakenly that the purpose of the research is solely to administer treatment rather than to contribute to scientific knowledge (see also Recommendation 3.2).**

Addressing Procedural Requirements in the Consent Process

A number of issues may arise during the process of obtaining informed consent that require careful scrutiny before determining whether voluntary informed consent can be obtained. These include, for example, determining when it is necessary to obtain written consent and when oral consent should be permitted; when, if ever, it is appropriate to withhold 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 for 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.

In light of the cultural variation that might arise in international clinical trials, 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 of dealing 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. Clearly, more research is needed in this area.

Recommendation 3.11: **U.S. research regulations should be amended to permit ethics review committees to waive the requirements for written and signed consent documents in accordance with local cultural norms. Ethics review committees should grant such waivers only if the research protocol specifies how the researchers and others could verify that research participants have given their voluntary informed consent.**

Recommendation 3.12: **The National Institutes of Health, the Centers for Disease Control and Prevention, and other U.S. departments and agencies should support research that addresses specifically the informed consent process in various cultural settings. In addition, those U.S. departments and agencies that conduct international research should sponsor workshops and conferences during which international researchers can share their knowledge of the informed consent process.**

Access to Post-Trial Benefits

Discussions of the ethics of research with human beings usually center on issues regarding research design and approval and how individuals' rights and welfare are protected when they are enrolled in research protocols. The same has been true of the U.S. regulations, which only tangentially address what happens after a research project has ended by requiring that research participants must be informed in advance about what compensation,

if any, will be provided if they are injured during the course of the research. Other questions about what should happen after a trial is completed are left unaddressed by U.S. guidelines.

Thus, central questions in the context of international research include the following: *What benefits (in the form of a proven, effective medical intervention) should be provided to research participants, and by whom, after their participation in a trial has ended, and what, if anything, should be made available to others in the host community or country?* Although these questions are relevant in terms of the ethical assessment of research—regardless of where the research is conducted—they are being posed with special force, especially regarding serious diseases that affect large numbers of people in developing countries. Therefore, the question of what benefits, if any, 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 who live in developing countries in which neither the government nor the vast majority of the citizenry can afford the intervention resulting from the research. Of course, this is especially germane when a drug is proven to be effective in a clinical trial.

An ethically relevant feature that distinguishes most developing from developed countries is the lack of access to adequate health care by a large majority of the population. Many developed countries have long provided universal access to primary health care through a national health service or government-based insurance system. However, 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. Access to health care is an important issue 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.

Recognizing that it is sometimes difficult to distinguish research from treatment when routine health care is inadequate or nonexistent, it cannot be denied that it may be difficult for participants, whose health status may be altered by their participation in a clinical trial, to distinguish between participating in research and receiving clinical care. Consequently, if all interventions by the research team cease at the end of a trial, participants may experience a loss and feel that the researchers in their clinical role have abandoned them. This sense of loss can take several forms, the starkest of which arises when participants are left worse off at the conclusion of the trial than they were before the clinical trial began. Being worse off does not mean that they were harmed by the research. It can simply mean that their medical condition has deteriorated because they were in what turned out to be the less advantageous arm of the protocol. Such an outcome—particularly when participants are worse off than they would have been had they received standard treatment or if they had been in the other arm of the trial—underlines the extent to which any research project can depart from the Hippocratic goal of "first, do no harm," despite the best intentions and efforts of all concerned. When such a result occurs, efforts to restore participants at least to their pre-trial status could be regarded as attempts to reverse a result that would otherwise be at odds with the ethical principles of nonmaleficence and beneficence.

Ironically, people who have benefited from an experimental intervention may also experience a loss if the intervention is discontinued when the project ends. It might be said that this is a risk the participant accepted by enrolling in the trial. But participants who are ill when they enter the research protocol may not be able to appreciate fully how they will feel when they face a deterioration in their medical condition (once the trial is completed) after having first experienced an improvement, even if the net result is a return to the status quo ante. One of the ways to mediate or reduce the burden of such an *existential loss* (the experience of loss as perceived by the research participant) and to sustain an appropriate level of trust between potential participants and the research enterprise is to continue to provide to research participants an intervention that has been shown to be efficacious in the clinical trial if they still need it once the trial is over.

Recommendation 4.1: **Researchers and sponsors in clinical trials should make reasonable, good faith efforts before the initiation of a trial to secure, at**

its conclusion, continued access for all participants to needed experimental interventions that have been proven effective for the participants. Although the details of the arrangements will depend on a number of factors (including but not limited to the results of a trial), research protocols should typically describe the duration, extent, and financing of such continued access. When no arrangements have been negotiated, the researcher should justify to the ethics review committee why this is the case.

Providing Benefits to Others

Once it is recognized that research projects should sometimes arrange to provide post-trial benefits to participants, a question arises about the justice of differentiating between former trial participants and others in the host community who need similar medical treatments. *Is the distinction between former research participants and those who were not merely arbitrary?* Applying a competing concept of justice, typically referred to as the principle of fairness—*treat like cases alike, and treat different cases differently*—to this situation requires a consideration of whether family members (or others) who suffer from the same illness as the participants should be treated as "like cases" with respect to receiving an effective treatment. Similarly, are the claims to treatment of people who were eligible for and willing to participate in a clinical trial but who for any number of reasons were not selected comparable to the claims of those who were selected? Or are such cases not sufficiently similar because participants undertook the risks and experienced the inconveniences of the research?

In NBAC's view, the relevant distinction between research participants and these other groups of individuals is that research participants are exposed to the risks and inconveniences of the study. Moreover, a special relationship exists between participants and researchers that does not exist for others. These are the ethical considerations that support the argument to provide effective interventions to research participants after a trial is completed.

On what basis then can one justify an ethical obligation to make otherwise unaffordable (or undeliverable) effective interventions available to members of the broader community or host country? Given that global inequities in wealth and resources are so vast, expecting governmental or industrial research sponsors to seek to redress this particular global inequity is unfair and unrealistic, especially when no such requirement exists in other spheres of international relationships. Typically, it is not the primary purpose of clinical trials to seek to redress these inequities.

Recommendation 4.2: **Research proposals submitted to ethics review committees should include an explanation of how new interventions that are proven to be effective from the research will become available to some or all of the host country population beyond the research participants themselves. Where applicable, the investigator should describe any pre-research negotiations among sponsors, host country officials, and other appropriate parties aimed at making such interventions available. In cases in which investigators do not believe that successful interventions will become available to the host country population, they should explain to the relevant ethics review committee(s) why the research is nonetheless responsive to the health needs of the country and presents a reasonable risk/benefit ratio.**

These concerns prompt the question of whether research sponsors should consider implementing arrangements, such as *prior agreements* (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), that would allow some of the fruits of research to be available in the host country when the research is over. Such arrangements would be responsive to the health needs of the host country. The parties to these agreements usually include some combination of producers, sponsors, and potential users of research products. 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.

Recommendation 4.3: **Whenever possible, preceding the start of research, agreements should be negotiated by the relevant parties to make the effective intervention or other research benefits available to the host country after the study is completed.**

Mechanisms to Ensure the Protection of Research Participants in International Clinical Trials

The two principal approaches used to ensure the protection of human participants in international clinical trials are 1) relying on assurance processes and reviews by U.S. Institutional Review Boards (IRBs) to supplement and enhance local measures for determining that a host country or host country institution has a system of protections in place that is at least equivalent to that of the United States and 2) helping host countries build the capacity to independently conduct clinical trials and to conduct their own scientific and ethical review. In addition, a regulatory provision permits the substitution of foreign procedures that afford protections to research participants that are "at least equivalent" to those provided in the Common Rule. Clarification of the scope and limits of these mechanisms and their use would increase public confidence that a valid system of protections is in place for participants in clinical trials conducted abroad.

Negotiating Assurances of Compliance

U.S. researchers or sponsors and their collaborators often encounter difficulties with some of the procedural and administrative aspects of the U.S. research regulations or their implementation and at times perceive U.S. regulations as unnecessarily rigid. Among the many concerns NBAC heard were those relating to the process of negotiating assurances. An assurance is a document that commits an 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.

In December 2000, the U.S. Office of Human Research Protections (OHRP) launched a new Federalwide Assurance (FWA) and IRB registration process. The process for filing institutional assurances with OHRP for protecting human research participants has been simplified by replacing Single, Multiple, and Cooperative Project Assurances with the FWA, one for domestic research and one for international research. Each legally separate institution must obtain its own FWA, and assurances approved under this process would cover all of the institution's federally supported human research. The proposed system eliminates the assurance documents now in place and replaces them with either a Federalwide Domestic Assurance or a Federalwide International Assurance, covering all federally supported human research.

NBAC was encouraged that OHRP is taking these steps to revise and simplify the current assurance process. It is not clear at this writing, however, whether the new FWA process will eliminate the problems and inconsistencies that exist among agencies such as the Department of Health and Human Services (DHHS), the Agency for International Development, and the Food and Drug Administration (FDA), or the difficulties expressed by researchers who are familiar with the previous assurance system. Moreover, it should be noted that the assurance process itself does not provide a failsafe system of protections. Because weaknesses in this system have been noted in failures at U.S. research institutions, care should be taken not to rely too heavily on this single mechanism to achieve protections abroad, especially when it is not clear that OHRP will provide a visible presence in the host country (through, for example, site visits). However, it will be important to evaluate the success of these new initiatives.

> ***Recommendation 5.1:*** **After a suitable period of time, an independent body should comprehensively evaluate the new assurance process being implemented by the Office for Human Research Protections.**

Ethics Review

It is now widely accepted that research involving human participants should be conducted only after an appropriate ethics review has occurred. 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 those 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. It is argued that committees that are familiar with the researchers, institutions, potential participants, and other

factors associated with a study are likely to provide a more careful and fully informed review than a committee or other group that is geographically displaced or distant and that only local committees can exercise the kind of balanced and reasoned judgment required to review research protocols. The concept of local review has been a cornerstone of the U.S. system for protecting human participants. Whether this standard can or should be applied to research sponsored or 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. 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 a local institution. Although several developing countries have instituted national research ethics guidelines, and in some countries, ethics review 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; the 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 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.

Ideally, equivalent (although not necessarily identical) systems for providing protections to research participants in developing countries would exist at both the national and institutional levels. In countries in which a system equivalent to the U.S. system exists at the national level, some institutions may be incapable of conducting research in accordance with that system. However, it is difficult to conceive of institutional systems being declared equivalent in the absence of an equivalent national system, although it may be possible in a few extremely rare cases. When multiple sponsors are participating in research, possibly all from developed countries, determining which ethics review committees (and how many) are required poses additional complexities. Because there may be legitimate reasons to question the capacity of host countries to support and conduct prior ethics review, NBAC believes that with respect to research sponsored and conducted by the United States, it will be necessary for an ethics review committee from the host country *and* a U.S. IRB to conduct a review. The FDA's regulatory provisions for accepting foreign studies not conducted under an investigational new drug application or an investigational device exemption do not address whether the foreign nation's system must meet U.S. ethical standards.

Recommendation 5.2: **The U.S. government should not sponsor or conduct clinical trials in developing countries unless such trials have received prior approval by an ethics review committee in the host country *and* by a U.S. Institutional Review Board. However, if the human participants protection system of the host country or a particular host country institution has been determined by the U.S. government to achieve all the substantive ethical protections outlined in Recommendation 1.1, then review by a host country ethics review committee alone is sufficient.**

Recommendation 5.3: **The Food and Drug Administration should not accept data from clinical trials conducted in developing countries unless those trials have been approved by a host country ethics review committee *and* a U.S. Institutional Review Board. However, if the human participants protection system of the host country or a particular host country institution has been determined by the U.S. government to achieve all the substantive ethical protections outlined in Recommendation 1.1, then review by a host country ethics review committee alone is sufficient.**

Lack of Resources as a Barrier to Ethics Review

Ethics review committees in developing countries may have difficulty complying with U.S. regulations because they lack the funds necessary to carry out their responsibilities. In previous reports, NBAC has recognized that there are costs to providing protection to human participants in research, and researchers and institutions should not be put in the position of having to choose between conducting research and protecting participants. Therefore, an additional means of enhancing international collaborative research is to make the necessary resources available for conducting ethics reviews.

Recommendation 5.4: **Federal agencies and others that sponsor international research in developing countries should provide financial support for the administrative and operational costs of host country compliance with requirements for oversight of research involving human participants.**

Equivalent Protections

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 determined that any guidelines or rules from other countries—even countries such as Australia and Canada, where research ethics requirements closely parallel (and to some extent exceed) those of the United States—afford protections equal to those provided by U.S. regulations. 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.

In June 2000, OHRP became the agency responsible for making determinations of equivalent protections for DHHS. However, to date, OHRP has not provided criteria for determining what constitutes equivalent protections or made any such determinations about other countries' guidelines. In lieu of having developed a process for making equivalent protections determinations, in the past OPRR relied on its usual process for negotiating assurances with foreign institutions to ensure the adequate protection of human participants.

Because the number of U.S.-sponsored studies 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. A way must be found 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.

Recommendation 5.5: **The U.S. government should identify procedural criteria and a process for determining whether the human participants protection system of a host country or a particular host country institution has achieved all the substantive ethical protections outlined in Recommendation 1.1.**

Building Host Country Capacity to Review and Conduct Clinical Trials

A unique feature of international collaborative research is the degree to which economically more prosperous countries can enhance and encourage further collaboration by leaving the host community or country better off as a result. The kinds of benefits that could be realized as a result of the collaboration would depend on local health conditions, the state of economic development, and the scientific capabilities of the particular host country. The provision of post-trial benefits to participants or others in the form of effective interventions is one option. The appropriateness of providing a benefit other than the intervention will depend on the nature of the benefit and on the economic and technological state of development of the host country. In most cases, offering assistance to help build local research capacity is another viable option. These two options are not, of course, mutually exclusive. But no matter what form the benefit takes, the ultimate goal of providing it is to improve the welfare of those in the host country.

Approaches to capacity building are related to, but not fully dependent on, the clarification and improvement of current U.S. procedures for ensuring the protection of research participants in international clinical trials. Progress can and should occur simultaneously in

both realms. Capacity building to conduct research could include activities undertaken by investigators or sponsors during a clinical trial to enhance the ability of host country researchers to conduct research (e.g., training and education) or to provide research infrastructure (e.g., equipment) so that future studies might proceed. Building capacity to conduct scientific and ethics review of studies, on the other hand, is primarily a matter of providing training and helping to establish systems designed to review proposed protocols and sustain mutually beneficial partnerships with other more experienced review bodies, including U.S. IRBs.

To enhance research collaborations between developing and developed nations, it is important to increase the capacity of resource-poor countries to become even more meaningful partners in international collaborative research. Making the necessary resources available for improving the technical capacity to conduct and sponsor research, as well as the ability to carry out prior ethics review, is one way to move forward in this effort.

Recommendation 5.6: **Where applicable, U.S. sponsors and researchers should develop and implement strategies that assist in building local capacity for designing, reviewing, and conducting clinical trials in developing countries. Projects should specify plans for including or identifying funds or other resources necessary for building such capacity.**

Recommendation 5.7: **Where applicable, U.S. sponsors and researchers should assist in building the capacity of ethics review committees in developing countries to conduct scientific and ethical review of international collaborative research.**

Conclusions

The ethical standards that NBAC is recommending for conducting research in other countries are minimum standards. Host countries might find it worthwhile to adopt human research participant protections that go beyond the protections that are currently provided under the U.S. system if these higher standards further promote the rights, dignity, and safety of research participants as well as the credibility of research results.

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 appropriate 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. 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.

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. However, even though 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.

The relationships and, ultimately, the level of trust established among individuals, institutions, communities, and countries are determined by complex and often contradictory social, cultural, political, economic, and historical factors. It is essential, therefore, that sponsors, the countries from which they come, and researchers work together to enhance these collaborations by creating an atmosphere that is based on trust and respect. Finally, because attention will continue to focus on the ethical and policy issues that arise in international research in general 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.

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 merely changing terminology cannot achieve the desired goal of true participation by individuals who volunteer for research, and NBAC 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 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.

3 In the United States, committees that review the ethics of human research protocols are referred to in regulation and practice as Institutional Review Boards (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.

4 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.

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.[1] 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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Chapter Two

Ethical Considerations in the Design and Conduct of International Clinical Trials

Introduction

As we stand poised on the frontiers of biomedical science, populations worldwide face a broad range of health concerns as well as many different issues related to the conduct of clinical trials in international health research. The multiple contexts within which biomedical research proceeds call for an array of research designs in order to forge scientific developments and advance clinical knowledge and treatment approaches. Any of a number of research designs may be appropriate for a clinical trial, depending on the context and circumstances of the research; however, every clinical trial must be scientifically sound and must incorporate important ethical principles regarding the treatment of research participants.

With respect to the ethical treatment of research participants, current U.S. regulations require that Institutional Review Boards (IRBs) determine that a research design is such that "risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result" (45 CFR 46.111(a)(2)). However, although the federal regulations do not require IRBs to review the scientific merit of a research design, research with a scientifically flawed methodology will not generate valid or reliable data or produce generalizable and beneficial knowledge. In such cases, it is the participants in the research who will incur the risks, inconveniences, or discomforts that might be involved. Because it would be wrong to put people at risk or even to inconvenience or discomfort them through participation in a poorly designed study, the scientific merit of research becomes an ethical issue (OPRR 1993). Therefore, the National Bioethics Advisory Commission (NBAC) believes that IRBs should assure themselves of both the ethical *and* scientific merits of the protocols they review. The Commission is not proposing that IRBs become responsible for conducting scientific peer review (as they may lack specific expertise, and in most instances the proposed studies of research sponsors must undergo independent scientific review)—but only that IRBs have confidence that a study has scientific merit.[1]

Even when a clinical trial uses a scientifically sound research design and addresses important questions, conducting the proposed research might be unethical if it would result in the violation of certain ethical principles. However, because determining the appropriate design for a clinical trial depends on various contextual considerations, what might be an ethically acceptable design in one situation could be problematic in another. For example, it might be unethical to conduct a clinical trial for a health condition in a country where that condition is unlikely to be found, but the same trial might be appropriately conducted where the results could be important to the local population. A more challenging question is whether a research design that could *not* be ethically implemented in the sponsoring country could be ethically justified in a host country when the health problem that the research is addressing is common to both countries.

It may be useful to classify international collaborative research projects in developed and developing countries on a continuum. At one end of the continuum is research that has no practical relevance to the health needs of the host country, but is important to the foreign sponsor or researcher. At the other end of the spectrum is research that is directly relevant to the health concerns of the host country, but not to sponsors or researchers. These two

extremes illustrate how situations can differ starkly, particularly regarding the potential for exploiting research participants in the host country. An assessment of the ethical appropriateness of a particular study's design should include an evaluation of where it lies along this continuum. It is worth noting that in an NBAC survey of U.S. researchers, 40 percent of those surveyed said that the research priorities of their funding agencies were incongruent with the top priorities of the developing country in which they were conducting research. Indeed, the relevance of the proposed research to the host country was questioned by U.S. IRBs in 30 percent of the cases reported and by host country ethics review committees in 23 percent of the cases. At the same time, a majority (73 percent) of U.S. researchers surveyed said that their interest in addressing global inequalities in health motivated them to work in a developing country.[2]

This chapter focuses on the ethical requirement of choosing a research design that minimizes the risk of harm to human participants in clinical trials and that does not exploit them (which raises the question of the obligations of sponsors and researchers to the research participants *during* the trial). Chapter 4 discusses the broader question of what obligation, if any, sponsors and researchers have to the participants and others in a host country *after* a research trial is completed. Following are some of the chief considerations with respect to both research design and ethical obligations owed to research participants:

- whether the research is responsive to the health needs of the host country;
- whether a study design is appropriate for answering the primary research question;
- whether an effective treatment already exists for the condition that is the focus of the study;
- whether the condition for which a new intervention is sought is severe or life threatening;
- the probability and magnitude of any harm that might come to participants in both the experimental and control arms of a given study;
- the probability and magnitude of benefits that may accrue to the study participants;
- the balance of the risks to the participants and the probable benefits to the participants and to others; and
- the future availability of the experimental intervention, if proven effective, to participants and others in the host country after the trial.

Because the choice of a study design for any particular trial depends on these and other factors, it would be inappropriate—indeed, wrong—to designate any one particular study design as ethical for all research situations. Nevertheless, under certain specified conditions, a particular design can be considered ethically preferable.

> ***Recommendation 2.1:*** **Researchers should provide ethics review committees with a thorough justification of the research design to be used, including the procedures to be used to minimize risks to participants.**

Ethical Issues in Clinical Trial Design

Important and distinct scientific and ethical issues and challenges can arise at different stages of drug development, during the development of other medical interventions, and in the use of various study designs used for clinical trials. The development of a new drug is a long and complex process that includes drug discovery, preclinical testing, and, finally, an ordered program of clinical trials. The development of other medical interventions—such as new vaccines, gene transfer technology, and medical devices—follows a similar process. Exhibit 2.1 summarizes the phases of drug development that typically form the basis of U.S. efforts. Exhibit 2.2 describes the principal types of trial designs used in testing clinical interventions.

Carefully designed and properly conducted clinical trials are recognized as the principal mechanism for testing new clinical interventions, and, given the rapid advance of biomedical science in recent years, the number of clinical trials is steadily increasing. The results of any clinical trial must be free of bias, which can be caused by flaws in the study design. Bias in clinical trials refers to the tendency of any aspect of the methodology or the interpretation of data to lead to conclusions about

Exhibit 2.1: Phases of Drug Development

The first step in the development process of a new drug, biologic (e.g., a vaccine, a gene transfer agent, a protein-based therapy), or medical device is called *discovery*. During the drug discovery process, chemical compounds are identified and/or synthesized and tested for biological activity. Of 5,000 to 10,000 chemical compounds tested for biological activity, approximately 250 eventually enter the next stage of drug development, called *preclinical testing* (PhRMA 1999).

Preclinical studies are experiments that are carried out in the laboratory and in animals to provide preliminary evidence that the experimental intervention will be safe and effective in humans. Safety information from preclinical testing is used to support a request to the Food and Drug Administration (FDA) to begin testing the experimental intervention in humans. Preclinical testing usually takes three to six years, and only 2 percent of compounds evaluated in preclinical testing are eventually tested in humans (Mann 1999; PhRMA 1999).

In the United States, an investigational new drug (IND) application or an investigational device exemption (IDE) must be submitted to the FDA before a drug, biologic, or device can be studied in humans. Once the FDA allows an IND or IDE to proceed, testing of an experimental intervention in a clinical trial can begin. For studies conducted outside the United States, an IND is not required, unless data from the study are intended to be used to support the licensing of a drug in the United States. Clinical trials usually are classified into the following four phases: *Phase I trials*, the earliest-stage clinical trials for studying an experimental intervention in humans, are small (typically fewer than 100 participants) and aim to determine the toxicity and maximum safe dose of a new drug. Phase I trials commonly are conducted with normal volunteers (rather than patients with the condition in question). However, Phase I trials that involve potent and potentially toxic chemicals (e.g., for cancer or HIV/AIDS) are often performed in participants with advanced disease who have not responded to all other standard treatments.

Phase II trials usually involve 100 to 300 participants and are designed to determine whether a drug produces any clinically significant effects in those with the targeted disease. If the results of these trials are promising, then a larger *Phase III trial*, aimed at establishing efficacy, may be conducted. Phase III trials are large, frequently multi-institution studies, and typically involve from a hundred to thousands of participants. Approximately 25 percent of all drugs tested in clinical trials successfully complete Phase III testing (Mann 1999).

Some Phase II and Phase III trials are designed to be *pivotal trials* (sometimes also called confirmatory trials). The goal of a pivotal trial is to eliminate systematic biases and increase statistical power and to establish the intervention's safety and efficacy. By providing firm evidence of safety and efficacy, pivotal trials are designed to produce data that will be accepted by the FDA as adequate for supporting a New Drug Application (NDA). On average, it takes almost seven years to complete the required clinical trials (Phases I through III) and to gather the data necessary to establish the safety and efficacy of an experimental intervention (PhRMA 1999).

Once sufficient evidence exists regarding the safety and efficacy of an experimental intervention from studies conducted inside and/or outside the United States, an NDA is submitted to the FDA for approval of a new drug; a Biologic License Application is submitted for approval of a new vaccine or other biologic; or a Product License Application is submitted for approval of a new device. Occasionally, the FDA requires *Phase IV trials*, which are usually performed after the intervention has been approved. Such post-marketing surveillance aims to obtain additional information about the risks, benefits, and optimal use of the intervention by observing the results of the intervention in a large number of patients. Phase IV trials enable the long-term effects of an intervention to be assessed and sometimes reveal rare, but serious, side effects.

the effects of an intervention that are systematically different from the truth (FDA 1999). Ensuring that the chosen study design avoids various forms of bias and generates data that can answer the scientific questions being asked can be difficult. Fortunately, a significant literature has been developed to address this challenge (Meinert and Tonascia 1986; Sackett 1983; Spilker 1991).

From the perspective of the protection of human participants in research, one of the most critical issues in clinical trial design concerns the use and treatment of control groups, which are often an essential component in methodologies used to guard against bias. The main purpose of a control group is to permit investigators to determine whether an observed effect truly is caused by the experimental intervention being tested or whether it

Exhibit 2.2: Clinical Trial Designs

Clinical trials are research studies that evaluate new ways to prevent, detect, diagnose, or treat disease in human beings. The key to clinical trial design is choosing an approach that addresses the scientific question being asked, the intervention being tested, and the group of participants involved, while at the same time considering the risks and benefits to the participants. Several commonly used research designs include the following:

Add-on design: A placebo-controlled trial of an experimental intervention is tested in people who are already receiving an established effective treatment.

Crossover design: Each participant is randomized to a sequence of two or more treatments and hence acts as his/her own control for treatment comparisons.

Equivalence trials: 1) compare the efficacy of an experimental treatment to that of an established effective treatment (also called noninferiority trials) and 2) compare bioequivalence (to show that two drugs have the same potency and tissue availability).

Factorial design: Two or more treatments are evaluated simultaneously in the same participant population through the use of varying combinations of the treatments (e.g., in a 2 x 2 factorial design, participants are randomly allocated to one of the four possible combinations of two treatments: A alone, B alone, both A and B, neither A nor B).

Group sequential design: Allows the trial to be monitored at specific time intervals so that a treatment arm, or the entire trial, may be stopped early if there is clear evidence of efficacy or of unacceptable adverse effects.

Parallel group design: Participants are randomized to one of two or more arms, and each arm is allocated a different treatment.

Randomized withdrawal design: Participants who respond positively to an experimental intervention are randomized either to continue receiving the intervention or to receive a placebo.

Superiority trials: Trials designed to determine whether an experimental intervention is more efficacious than an established effective treatment.

is caused by other factors, such as the natural progression of the disease, observer or participant expectations, differences in the baseline condition of subjects, or other treatment (FDA 1999). The experience of an appropriately selected control group lets the investigator know what would have happened to study participants had they not received the test intervention or what would have happened had they received a different treatment that is known to be effective (FDA 1999). (A description of and additional discussion regarding the use of control groups is provided below.)

This chapter will discuss the following ethical issues involved in evaluating any proposed clinical trial: equipoise; randomization; the nature and treatment of control groups; the distinction between efficacy and effectiveness studies; and the selection of the participant population and sample size.

Equipoise

Among the most important ethical and scientific justifications for beginning a clinical trial is the uncertainty about whether the experimental intervention is better than the status quo (which may be an existing treatment or no treatment at all). This state of uncertainty is known as *equipoise*, and it is a requirement for the ethical conduct of a clinical trial. Equipoise has been defined as the point at which a rational, informed person would have no preference between two (or more) available treatments (Lilford and Jackson 1995). It is a state in which honest professional disagreement exists among experts regarding whether the study intervention or the control is preferred. In the *clinical context*, the belief that one intervention is superior to others ethically compels the clinician to recommend the superior intervention. Clinicians are justified in recommending different treatments based on their assessment of what will be effective for a particular patient. Often, the preferences of a clinician regarding an intervention and those of the patient are similar in this regard. However, in the *research context*, individual preferences are replaced by the collective uncertainty of the clinical community. According to this concept of *clinical equipoise*, a trial is ethical if there is "genuine uncertainty within the expert medical community about the preferred treatment" (Freedman 1987).

It should be emphasized that often there is a considerable lack of clarity in the scientific community about the state of equipoise for a particular set of interventions. There may be no consensus about how many studies must be completed to show the efficacy of a new intervention or about how strong the evidence must be to change medical practice. In addition, there may be disagreement or concern about the applicability of research findings in, for example, different populations with different genetic backgrounds, different co-morbidities, or different environmental and social factors.[3] However, disagreements about these issues, although important, are distinct from those regarding equipoise. At the end of a clinical trial, if it is determined that an experimental intervention is superior—or inferior—to the control intervention, the state of clinical equipoise may have been eliminated or evidence may have been accumulated that could lead to such a conclusion. Therefore, although a clinical trial starts in a state of equipoise, investigators hope that the analysis of the data collected during the trial will remove or reduce the level of uncertainty.

Randomization

Randomization is the process by which participants in a clinical trial are assigned to different interventions in a study. Through randomization, each person has a specified chance of being assigned to one or another group. Randomization differs from systematic assignment, in which individuals are assigned to a particular arm of a study for a specific clinical, scientific, or perhaps demographic reason (e.g., medical history, presence of a genetic marker, age). Rather, it is a process used to minimize any inherent differences among participants in the various arms of a trial by distributing people with particular characteristics randomly to the intervention and control arms, and it is the only way to equalize all factors, known and unknown, between study groups (Fletcher et al. 1982). The consensus among clinical investigators is that nonrandomized controls can create severe bias and therefore may result in unreliable trial results. Along with the use of placebos (defined as an intervention that although physically resembling the intervention being tested is inert and not expected to have any pharmacological effect on the condition being treated) or other controls as well as double blinding (in which neither the investigator nor the participant knows which intervention, if any, the participant is receiving), randomization of a study is essential in evaluating new interventions. At times, however, randomized trials are not practical, such as when an insufficient number of participants is available to provide the statistical power needed for drawing conclusions.[4]

Types of Control Groups

The first documented example of a controlled clinical trial was James Lind's experiment in 1747 with 12 sailors with scurvy aboard the *H.M.S. Salisbury* (Lind 1753). Lind divided the sailors into six groups of two each and compared the effects of providing different nutritional supplements to each group. The two men who ate oranges and lemons recovered immediately. Lind concluded that something in the citrus fruit was counteracting the cause of the scurvy, so he gave citrus fruit to all the other men and observed that they too were cured of the disease. Lind's experiment laid the initial groundwork that established the controlled clinical trial as the best method for determining the effects of new therapies.

The FDA classifies clinical trial control groups into five types: placebo concurrent control, active treatment concurrent control, no treatment concurrent control, dose-comparison concurrent control, and external control (FDA 1999). Each type has strengths and weaknesses, depending on the scientific question being asked, the intervention being tested, and the group of participants involved. Therefore, because no one type of control group is ideal in all situations, researchers should choose the one that best answers the scientific question to be addressed and presents the least risk to the participants. Because of their importance, placebo concurrent control and active treatment concurrent control trials are described more fully below.

Placebo Concurrent Control

A placebo is an intervention that physically resembles the intervention being tested, but is inert and not expected to have any pharmacological effect on the condition being treated. Placebo-controlled trials control not only for the *placebo effect* (changes in a person's physical

or mental condition that result from his or her belief that the study is providing an active treatment), but also for changes that arise due to the natural course of the disease; participant or investigator expectations; the use of other therapies; and the subjective elements of a diagnosis or assessment (FDA 1999). By including a placebo group in a clinical trial, the action of the experimental intervention can be distinguished from other confounding factors and from changes that can be attributed purely to the physical or socioeconomic environment.

For some clinical trials, the decision regarding the appropriateness of using a placebo is not problematic. It is generally accepted that when no established intervention exists to treat or prevent the condition being studied, it is ethically acceptable to give the control group a placebo. This is because in such trials, there is no treatment against which to compare the experimental intervention. Another argument in favor of the use of placebo controls has been made in the context of research conducted in a developing country. Many researchers have contended that the research question must be defined differently in a setting in which health care resources are limited and participants do not have access to established effective treatments outside of the research context. Some have advocated that in these cases, the measurement of absolute efficacy of a new and potentially more affordable and available intervention is a more relevant research question for the host country than the comparison of a new intervention to an established effective treatment already available elsewhere (Levine 1999; Perinatal HIV Intervention Research in Developing Countries Workshop Participants 1999).

On the other hand, virtually all experts believe that a placebo-controlled trial would not be ethical if an established effective treatment that is known to prevent serious harm—such as death or irreversible injury—is available and can be provided. NBAC agrees with the consensus that it is not ethically acceptable to perform placebo-controlled clinical trials when established effective treatments exist (such as in the cases of new thrombolytics [blood clot-dissolving agents], beta blockers, aspirin, or angiotensin-converting enzyme inhibitors to improve survival after heart attacks, or new chemotherapeutics for leukemia or testicular cancer).[5] Even under these circumstances, however, exceptions may exist if an established effective treatment does not work in certain populations or has such serious side effects that some patients refuse treatment.

In the United States, there is substantial agreement in the research community that the use of placebos in studies involving severe or life-threatening illnesses when existing treatment could prevent them or delay their progression is ethically suspect.[6] The American Medical Association's (AMA's) guidance for the use of placebos states that "protocols that involve conditions causing death or irreversible damage cannot ethically employ a placebo control if alternative treatment would prevent or slow the illness progression....In general, the more severe the consequences and symptoms of the illness under study, the more difficult it will be to justify the use of a placebo control when alternative therapy exists" (AMA 1999). In contrast, most experts agree that the use of a placebo is acceptable if it does not harm the participants and only results in discomfort (Temple 1996). Similarly, guidance from the International Conference on Harmonisation (ICH) indicated that with informed consent and appropriate review by an IRB, research participants could be asked to participate in placebo-controlled trials, even if an existing treatment is available, when the only risk from not receiving treatment is discomfort (ICH 1996). In such cases, it is necessary to ensure that the setting is not coercive and that the participants are fully informed about other available therapies and the consequences of delaying treatment (FDA 1999).

Ethics review committees will rightfully exercise their judgment in assessing research designs that employ a placebo control. However, the Commission believes that there are some studies for which the presumption in favor of active controls simply cannot be overcome. Although NBAC did not review the protocol, it appears that a recently reported case may serve as example of such a study (see Exhibit 2.3). In addition, as reflected in the recommendations in this report, the study discussed in the exhibit would be unacceptable because it intends to use developing country citizens as research participants while its primary purpose is to develop a drug for market in the United States and other developed countries.

Exhibit 2.3: Placebo Versus Established Effective Treatment (Active Control)

In early 2001, a proposal was submitted to the FDA by a U.S. biotechnology company for approval of a three-arm study of a new surfactant drug in as many as four Latin American countries. In the study, a control group of premature newborn infants with Respiratory Distress Syndrome (RDS)—a potentially fatal condition—would be treated with placebos, rather than a life-saving and already FDA-approved surfactant drug (Flaherty and Stephens 2001; Lurie et al. 2001). The apparent justification for conducting these studies is to decrease the time needed to develop the drug, which is intended for market in the United States. The company also plans to conduct a similar study on newborns in Europe, where no placebo controls will be used. Instead, all newborns will receive either the experimental intervention or another already approved surfactant.

Concerns have been voiced about whether the proposed study is ethical, mainly because the study design involves the use of a placebo control when an established effective treatment exists (Flaherty and Stephens 2001; Lurie et al. 2001). Thus, approval is being sought to conduct research in a developing country that could not be ethically justified in a developed country. Indeed, internal FDA documents state that "conduct of a placebo controlled surfactant trial for premature infants with RDS is considered unethical in the USA" (Lurie et al. 2001). The company, however, contends that because infants in Latin America with RDS who do not have access to established drugs would not be left worse off by placebo treatment, the proposed study is ethically justifiable in the hospitals where surfactant drugs are not available (Flaherty and Stephens 2001; Lurie et al. 2001). It is widely accepted, though, that in cases such as RDS that involve a life-threatening condition, a placebo control should not be employed when an established effective treatment exists against which the experimental intervention can be tested.

The other ethical concern that has been raised about the proposed study is that poor Latin American newborns would be participating in testing an intervention, which, if proven effective, would be too expensive for their families or others in the host country (Flaherty and Stephens 2001; Lurie et al. 2001). The company has indicated that, to some extent, it will provide the drug at a reduced cost to the host countries if it is proven effective (Flaherty and Stephens 2001; Lurie et al. 2001). Nevertheless, the lack of care available in a developing country cannot provide the principal ethical justification for using such a research design, especially when the benefits of the study are intended primarily for the developed world.

In studies of this kind—in which the disease is life threatening, an established effective treatment is available, patients in developed countries will be the primary beneficiaries of the results of the clinical trial, and it is not clear that the clinical trial is responsive to the health needs of the host country—a placebo control would not be permissible under the rules recommended in this report.

Yet, there are some who criticize the use of placebo controls even in cases in which risks to participants are low. One argument against the use of placebos is often grounded in the *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*, which states that "[i]n any medical study 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 1989). Giving research participants a placebo in place of an established effective treatment deprives them of the "best proven diagnostic and therapeutic method" (WMA 1964, as amended in 1989). Moreover, some critics argue that 1) research participants should not face unnecessary pain or disease resulting from a medical experiment (Rothman and Michels 1994); 2) using a placebo instead of an established effective treatment knowingly breaches researchers' duty to minimize harm (Levine 1998); and 3) it is unethical for individual investigators to enroll patients in a study in which some participants are expected to do even slightly worse than others (Barinaga 1988).

Indeed, although the placebo-controlled, randomized, double-blind clinical trial is an authoritative and widely accepted standard for new drug evaluation, some have argued that it is not always ethical to use this trial design (Freedman et al. 1996). In situations in which the best scientific design is not ethically acceptable, it may be necessary to reconsider the primary research question and to choose one for which an ethically acceptable design can be proposed (Levine 1998), or it may be necessary to accept the fact that ethical constraints can create limitations to obtaining scientific knowledge.

The recent revision of the *Declaration of Helsinki* attempts to resolve the debate about placebos by recommending 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. 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). Certain criticisms about this provision remain—principally that it makes it very difficult, if not impossible, to conduct placebo-controlled trials when such trials may be the only method of addressing the health needs of a particular population (Enserink 2000).

Active Treatment Concurrent Control

Although placebos are a frequently used control for clinical trials, it is increasingly commonplace to compare an experimental intervention to an existing established effective treatment. These types of studies are called *active-control* (or positive control) *studies*, which can take two forms—*a superiority trial*, in which the question is whether the new drug will be superior to the active control, and an *equivalence* (noninferiority) *trial*, in which the question is whether the new drug will be equivalent to but not inferior to the active control (Hauck and Anderson 1999). Active-controlled trials are often extremely useful in cases in which it would be unethical to give participants a placebo because doing so would pose undue risk to their health or well-being.

In an active-control study, participants are randomly assigned to the experimental intervention or to an active-control treatment. Such trials are often double blinded, but this is not always possible. Many oncology studies are considered impossible to blind because of the variable regimens, different routes of administration, and range of toxicities involved. In a study in which an active control is used, it may be difficult to determine whether the active control or the experimental intervention had an effect unless the effects of the treatments are obvious or a placebo control is included. For example, because the natural history of depression varies from patient to patient and it is often difficult to prove that a standard treatment has had an effect, studies of anti-depressants usually include both an active control and a placebo control.[8]

Treatment of Control Groups

Within the context of active treatment concurrent controls, it is useful to consider whether, and if so under what circumstances, researchers and sponsors are obligated to provide an established effective treatment to the control group, even if that treatment is not available in the host country. In the survey conducted by Nancy Kass and Adnan Hyder, more than half (52 percent) of the surveyed U.S. researchers conducting studies with control groups in developing countries thought that the standard of care in the host country was lower than that in the funding country. This created ethical difficulties in establishing appropriate procedures for the control group. A strong majority (78 percent) of these researchers believed that the level of medical care provided to control groups should be decided on a case-by-case basis.[9]

One view pertinent to this dilemma was expressed to the Commission in the following way: It is unethical to provide members of a control group with an established effective treatment if that treatment is unavailable in the country where the research is conducted. This is because the opportunity to obtain this treatment would render the choice to enroll in the study irresistible, as those receiving the treatment are unlikely to be able to get it once the trial is over.[10] The Commission does not agree with this proposition, because cases exist in which trials using the established effective treatment as a control would generate valuable information that is responsive to the health needs of the host country.

Some might argue that researchers and sponsors are under no ethical obligation to provide members of a control group with an established effective treatment if that treatment is unavailable in the country in which the research is conducted. This position maintains that the researchers' and sponsors' obligations to participants do not go beyond providing treatments that are routinely available to the majority of people in the host country.

Still others might contend that researchers and sponsors have an obligation to provide members of a control group with an established effective treatment even if that treatment is unavailable in the host country. Supporters

of this view assert that a special relationship is created when sponsors and investigators from a developed country enter a developing country to conduct research. For many, these obligations arise regardless of the prevailing situation in a particular location or country.

A description of the obligations that arise from these situations can be found in the basic principles of research ethics presented in the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (National Commission 1979) and many other national and international guidelines. For example, the most straightforward interpretation of the principle of beneficence—to "maximize possible benefits and minimize possible harms"—is that sponsors and investigators should make an established effective treatment available whether or not it is routinely available, because providing the treatment to the control group would maximize possible benefits and minimize possible harms to that group. Therefore, assuming that the sponsoring agency or organization can provide an established effective treatment and that the host country's collaborators, ethics review committee, and ministry of health or other appropriate authority are willing to accept the established effective treatment as part of a randomized controlled trial, a presumption should exist to provide members of a control group with an established effective treatment whether or not that treatment is available in the host country.

A tension exists, however, between this version of the principle of beneficence and the need for a research design that is relevant to real health concerns facing the population of the host country. These concerns may not be the relative efficacy of the new intervention (compared to the established treatment available in the developed countries), but rather the absolute efficacy of the intervention compared with the absence of any treatment or the level of care routinely available. Researchers in the Kass/Hyder survey described the tension between researchers' desire to benefit the larger population of the host country and their concern for the well-being of study participants. One researcher described a dramatic example of a vaccine designed to prevent children from dying from a particular tropical disease. To determine if the experimental vaccine was effective—using mortality as an endpoint—the research design entailed administering either the vaccine or a placebo to groups of children and subsequently withholding a feasible effective treatment from sick children. The researcher who described this study thought that it was imperative to develop a vaccine for this illness, but was troubled by withholding treatment that could save lives.[11]

Resolving this tension is central to the assessment conducted by ethics review committees, whose responsibilities include evaluating the ethical appropriateness of study designs. Thus, for example, in assessing a given study design, ethics review committees should consider the potential harm that may occur to participants who do not receive an established effective treatment for their condition, the strength of the evidence that a new intervention will be useful and affordable to the host country, and the feasibility of implementing an existing established treatment during the course of the study. If researchers make an acceptable case to the ethics review committee that comparing the new intervention to an established effective intervention is not a relevant research question for the host country, then the control group may receive the best care available that enables the researcher to answer a useful question.

Determining the most useful and ethical research design depends on several factors particular to the circumstances, and one can expect a certain amount of disagreement in this area. Perhaps the best answer for now is to say that investigators must carefully explain and ethics review committees must carefully scrutinize the justification for the selection of the research design, including the level of care provided to the control group. If in a proposed clinical trial the control group will receive less care than would be available under ideal circumstances, the burden on the investigator to justify the design should be heavier. Furthermore, representatives of the host country, including scientists, public officials, and persons with the condition under study, should have a strong voice in determining whether a proposed trial is appropriate. This view is reflected in certain national and international guidelines (see Appendix B) and has been advocated by others as well (Benatar and Singer 2000).

Established Effective Treatment and Best Current Methods

Chapter 1 provided NBAC's rationale for adopting the term *an established effective treatment* and indicated that this phrase refers to a treatment or a group of treatments that has achieved widespread acceptance by the medical profession (established) and that is as successful as any in treating the disease or condition anywhere in the world (effective). The treatment is not limited to what is routinely available in the host country. The Commission concluded that the standard of an established effective treatment best conveys what is owed to research participants *during* a trial.

NBAC recognizes that although it can be difficult to determine whether an intervention constitutes an established effective treatment, this term has certain advantages. Among the difficulties noted, however, was the possible disagreement of some scientists about whether an intervention shown to be effective in one population is likely to be as effective in another population that differs in significant ways. By choosing the term *an established effective treatment* and avoiding the qualifier *best*, NBAC proposes, simply, that the selection of an established effective treatment in a clinical trial conducted in a developing country must be made on a case-by-case basis.

The Commission also believes that this approach would satisfy those who have criticized the *best proven method* standard, or the established effective treatment standard proposed here, by arguing that the use of complex and very expensive medical care (such as surgery or catheterization for cardiovascular disease) in a developing country often is not feasible, even within the context of most research studies, and that such care is not sustainable after the research is complete. These commentators allege that if complex and costly medical care is used as the control against which new interventions are measured, research studies will generate data that potentially will be irrelevant to the host country—an argument analogous to that used to defend placebo use.

As noted in the discussion of placebo use, three factors must be considered by researchers when designing a study and by ethics review committees when reviewing protocols if they are to assess the level of medical care that should be provided to participants: 1) the well-being of the study participants; 2) the relevance of the research question to the host country; and 3) the feasibility of implementing a given type of medical care in the host country setting. In the case of medical treatments that involve a huge medical infrastructure or that are extremely costly to implement, feasibility may be the determining factor. In addition to feasibility, the ethical assessment of what level of care to provide often will depend on balancing the concern for the well-being of study participants with concern for the relevance of the research question to the host country. NBAC believes that researchers and ethics committees must find a balance between these important ethical demands in each research project.

> ***Recommendation 2.2:*** **Researchers and sponsors should design clinical trials that provide members of any control group with an established effective treatment, whether or not such treatment is available in the host country. Any study that would not provide the control group with an established effective treatment should include a justification for using an alternative design. Ethics review committees must assess the justification provided, including the risks to participants, and the overall ethical acceptability of the research design.**

Distinguishing Between Efficacy and Effectiveness Studies

Efficacy clinical trials are sometimes considered *optimal care* studies in which the research question is whether the experimental treatment works under ideal conditions. In contrast, *effectiveness* clinical trials ask whether the experimental treatment works under ordinary circumstances. Often, there are legitimate differences of opinion regarding whether an efficacy trial or an effectiveness trial is more scientifically and ethically appropriate in a given situation. On the one hand, efficacy trials ignore problems of access to care, generalizability from a highly selective sample of patients and physicians, and adherence to regimens, for example. If an efficacy trial is negative, it is hard to imagine that an effectiveness trial would show a benefit; therefore, effectiveness trials might have limited usefulness in developing countries. If an efficacy trial is productive, the question regarding

whether the intervention will be effective when used by a broader range of doctors and patients, who may not find it affordable, accessible, or acceptable, is still open. On the other hand, a problem with effectiveness trials is that if they produce a negative result, it is unclear whether the experimental intervention would fail under any circumstances, or only because patients and doctors lacked access to it, or because the doctors were unskilled or the patients poorly adherent.

In an efficacy trial, the control group should receive the best established treatment. However, in an effectiveness trial, the research question cannot always be answered by giving the control group the best established treatment. No consensus has emerged that the research questions posed in efficacy trials would be as pertinent to the needs of a host country as would the research questions posed in effectiveness trials. To provide the best established treatment would be to ask a completely different research question, one that may not be relevant to the clinical needs of the population being studied.

Another consideration in the context of developing country research is that a new intervention's degree of effectiveness may be critically important in terms of allocating scarce resources. Although a new intervention may be shown to be significantly better than existing or no treatment, policymakers may want to determine exactly how much benefit can be derived from the new intervention before deciding to allocate funds to implement it, particularly when there are competing health priorities in the host country.[12]

Selection of the Participant Population and Sample Size

Another important study design issue is the selection of the population to be studied. In the early phases of drug development, for example, research participants are selected from a small subgroup of the patient population in which the drug eventually may be used (CPMP 1995). This is done to maximize the opportunity to observe specific clinical effects of interest. By the time the experimental intervention enters pivotal Phase III trials, the participants should more closely mirror the intended users. Therefore, in these trials the criteria for selecting participants usually are relaxed as much as possible, without jeopardizing the possibility of conducting a successful trial. However, even a Phase III clinical trial usually is not completely representative of future users, because of several factors, including the geographical location of the trial, when it is conducted, and the medical practices of the investigators and clinics involved (CPMP 1995). Multicenter trials help to reduce the influence of such factors; however, if a multicenter trial is not feasible, every effort should be made to reduce the variations that can be caused by these factors.

Determining the sample size is another important component of clinical trial planning. Appropriate sample size depends on the design of the trial and its primary objective. Many methods and statistical models have been developed to calculate appropriate sample size. However, the number of participants in a clinical trial always should be large enough (but no larger than necessary) to provide a reliable answer to the questions posed.

The issue of sample size has been raised in the debate over placebo-controlled trials and equivalence trials. Most equivalence trials require more participants than placebo-controlled trials, an argument that has been used against them. Because placebo-controlled trials involve fewer subjects, they tend to be completed more quickly, and any resulting treatment is made available sooner (Levine 1998). The sooner a new treatment is introduced, the more people stand to benefit from its use. Others argue that in a well-designed trial and with the use of appropriate statistical methods, the required sample sizes for equivalence trials are often similar to those needed for placebo-controlled trials.[13]

Each of these issues in the choice of research design—equipoise, randomization, the nature and treatment of control groups, the distinction between efficacy and effectiveness studies, and the selection of the participant population and sample size—involves scientific questions that have ethical relevance (Freedman 1987; Levine 1986; Sutherland et al. 1994) and are therefore properly the concern of ethics review committees. One additional issue, which has been identified recently as important in the design of clinical trials and which has particular relevance to international collaborative research, is the involvement of the community and study participants in the design of research.

Involvement of the Community and Study Participants in the Design of Research

Over the past three decades, researchers increasingly have deliberately involved communities in the design of research (Arole and Arole 1994; CDC 1997; Taylor 1970; Taylor 1983; Taylor 1984). In addition, research participants, health advocates, and other members of the communities from which participants are recruited have requested, and in some cases demanded, involvement in the design of clinical trials. These trends are noteworthy. By consulting with the community, researchers often gain insight about whether the research question is relevant and responsive to the health needs of the community involved. In addition, community consultation can improve the informed consent process and resolve problems that arise during this process because of the use of difficult or unfamiliar concepts. Such discussions can provide insight into whether the balance of benefits and harms in the study is considered acceptable and whether the interventions and follow-up procedures are satisfactory. Community consultation also can reveal the best methods for recruiting participants. (See Chapter 3 for a more extensive discussion of community involvement in the recruitment of participants and the informed consent process.)

The Joint United Nations Programme on HIV/AIDS (UNAIDS), for example, has since its inception in the mid-1990s promoted the involvement of local communities and prospective research participants in the design and implementation of research studies. UNAIDS has an Ethical Review Committee—the duties of which include the basic IRB function of ethical review of research protocols—and this committee's standard assessment form includes a section entitled "Community Involvement and Impact." The following questions are included in this section:

- Is there a process of community consensus-building prior to initiating the research, i.e., consultation/discussion of impact of study and its relevance to (a) potential beneficiaries, (b) participants' communities? If not, why?[14]

  and

- To the degree possible, are (a) potential participants; (b) beneficiaries; (c) other community members; (d) local researchers, involved in: (i) the design; (ii) evaluation; (iii) analysis; (iv) publication and/or dissemination of the proposal; (v) implementation of results? If not, why?[15]

Researchers submitting proposals to UNAIDS receive a copy of the assessment form used by the Ethical Review Committee and are made aware of the need to address the issue of community involvement in the preparation of a research proposal for submission to UNAIDS.

In anticipation of the initiation of an increasing number of HIV/AIDS preventive vaccine trials, UNAIDS issued a guidance document in February 2000, in which Guidance Point 5 recommends the following:

> To ensure the ethical and scientific quality of proposed research, its relevance to the affected community, and its acceptance by the affected community, community representatives should be involved in an early and sustained manner in the design, development, implementation, and distribution of results of HIV vaccine research (UNAIDS 2000, 19).

However, it is frequently difficult to define the relevant community of participants, no matter where the research is conducted. In cases in which no traditional community structure exists, local organizations or nongovernmental organizations often can assist in representing the interests of participants in the research process. A research project might involve participants from widely scattered communities—sometimes in several nations—and it might be logistically difficult to reach representatives of every location from which participants are drawn. In addition, in some communities social hierarchies or corrupt elements exist that might impede the consideration of research participants' interests; therefore, in each research setting, it is necessary to determine the most appropriate way to involve local representatives who can provide a voice for research participants.

> ***Recommendation 2.3:*** **Researchers and sponsors should involve representatives of the community of potential participants throughout the design and implementation of research projects. Researchers should describe in their proposed**

protocol how this will be done, and ethics review committees should review the appropriateness of this process. When community representatives will not be involved, the protocol presented to the ethics committee should justify why such involvement is not possible or relevant.

Other Issues in Research Design

Although this chapter has focused primarily on the ethical issues that arise in the design of clinical trials, two additional issues warrant mention—monitoring the interim results of a study and repeating a study.

Monitoring the Interim Results of a Study

Randomized clinical trials begin at a point of equipoise regarding the relative risks and benefits of the intervention being evaluated. As the study proceeds, however, cumulative data or recent findings from other research efforts may provide strong evidence in favor of one of the interventions being tested, thus overturning the equipoise and suggesting that the study should be stopped. Responsibility for the review of interim data is often given to an independent group, such as a Data and Safety Monitoring Board (DSMB), with expertise in the clinical problem, biostatistics, and bioethics. DSMBs have confidential access to interim results, which are not available to investigators or sponsors. Unblinding investigators and sponsors would introduce bias into the trial and undermine its integrity. The goal of interim analysis is to stop the trial early if the superiority or inferiority of the experimental intervention being tested has been clearly established, if it is evident that the experimental intervention has no efficacy, or if unacceptable adverse effects are occurring (CPMP 1995; DeMets et al. 1999).

In addition to examining the evolving results of the trial, groups that are conducting interim analysis should be aware of advances in the field and assess whether study designs remain ethically and scientifically valid. This is especially important for studies that involve diseases for which rapid progress in the development of effective therapies has occurred. For example, trials in which the control group receives an established effective treatment may be deemed unethical because a new treatment has been found that is clearly more effective. In addition, trials may no longer be considered ethical because they have no reasonable hope of leading to an unequivocal result, or they have already demonstrated a statistically definitive and clinically significant difference between the control group and the experimental arm. Trials that are deemed to be unethical should be terminated to protect the research participants, even if continuation of the research would be of interest to the medical and scientific communities. Because clinical trials often require several years to complete, it is important to monitor them regularly to safeguard the best interests of the participants.

Repeating a Study

A different situation arises when a treatment has been shown to be effective in a developed country and researchers propose to repeat the study in a developing country. What could justify repeating a study using the same research design? Several who provided comments to NBAC remarked that generally, an accumulation of evidence from many studies is needed in order to establish a new intervention as efficacious and to warrant changes in health policy or medical practice. Whether several studies of the same intervention constitute repetition or whether conditions or protocols among studies are different enough that genuinely new evidence is being collected may not be known until all of the data are examined. Dispute frequently occurs, even in the United States, about whether differences in study populations—such as race, sex, stage of disease, presence of other conditions, or environmental conditions—constitute scientific differences that necessitate further empirical research because they might have a material effect on the effectiveness of an intervention.[19] In principle, if there is no scientific reason to question the effectiveness of the new treatment in the developing country population, it would be ethically problematic to repeat the study. However, in practice, as mentioned above, it may be difficult to determine when valid reasons to repeat a study exist. In some cases, because different biological, social, and environmental conditions are found in different developing countries, new interventions must be studied in those countries to determine their effectiveness in those settings. In other cases it may be reasonable to presume that treatments that are recognized to be effective

based on data from the United States or other developed countries do not need to be studied in every country in which they are used.

Another possible reason to repeat a study is that policymakers in many countries will not accept the results of trials conducted elsewhere.[17] This reluctance can stem from legal or regulatory considerations or from the existence of a policy that requires a determination of the adequacy of other countries' scientific, technical, or ethical review procedures. However, a reluctance to accept data from studies conducted in other countries also may represent a political stance on the part of a ministry of health or legislative body—that is, a refusal to recognize the relevance of research results from other countries because of national pride or political rivalries or an unwillingness to accept the results of studies that are not conducted by local authorities. Although these reasons cannot alone serve as ethical justifications for conducting a study that has already been successfully conducted, the urgent health needs of a host country may lead developed country sponsors to decide that it would be unethical *not* to carry out the necessary research if the established effective treatment could not otherwise be made available to the population.

Conclusions

This chapter has focused on a specific set of ethical issues related to choosing research designs for clinical trials. The discussion of some alternative designs is intended to demonstrate that no single design is appropriate for answering all research questions. In addition, the very act of choosing a research question has ethical implications. NBAC does not try to draw a conclusion about the precise circumstances under which, for example, the use of a placebo is acceptable in a particular clinical trial. Rather, this chapter has identified a set of ethically and scientifically relevant considerations that must be taken into account from the earliest stages of research design and of which potential investigators, ethics review committees, research participants, and research sponsors must be aware.

NBAC recognizes that some will disagree with the position that, in general, researchers and sponsors should make every effort to design clinical trials that provide control group members with an established effective treatment. In taking this position NBAC seeks to apply the same ethical standard to research conducted in developing countries that is applied in countries where established effective treatments are available to the general population. To do otherwise would leave the door open to conducting research in a developing country that could not be conducted in a wealthier country, while still allowing the benefits to flow to the wealthier country. If one accepts the fundamental premise articulated in Chapter 1—that research should be responsive to the health needs of the host country—then the logical next step should be choosing an appropriate research design, one that does not exploit the populations of countries with few resources while permitting those countries to be the sites of research that could benefit their populations.

Notes

1 NBAC made recommendations in this area in two previous reports (NBAC 1998; NBAC 1999) that are just as relevant to the current discussion.

2 See Kass, N., and A. Hyder, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations," 49–50. This background paper was prepared for NBAC and is available in Volume II of this report.

3 Goodman, S., Public comment submitted to NBAC. November 13, 2000.

4 Dickersin, K., Testimony before NBAC. December 2, 1999. Baltimore, Maryland.

5 Temple, R., Testimony before NBAC. September 18, 1997. Bethesda, Maryland. Meeting transcript, 7–8.

6 AMA, Public comment submitted to NBAC. Received November 15, 2000; FDA, Public comment submitted to NBAC. Received November 9, 2000; Temple, R., Public comment submitted to NBAC. Received November 13, 2000.

7 Temple, R., Public comment submitted to NBAC. Received November 13, 2000.

8 Temple, R., Testimony before NBAC. September 18, 1997. Bethesda, Maryland.

9 See Kass and Hyder, 53.

10 Sommer, A., Testimony before NBAC. September 16, 1999. Arlington, Virginia. Meeting transcript, 189.

11 See Kass and Hyder, 53.

12 Goodman, S., Public comment submitted to NBAC. November 13, 2000.

13 Lurie, P., and S.M. Wolfe, Testimony before the Committee on Government Reform and Oversight. U.S. House of Representatives. April 22, 1998. Washington, D.C. Available at www.house.gov/reform/hearings/healthcare/fda498/index.htm. Last accessed January 9, 2001.

14 UNAIDS, Ethical Review Committee. Assessment Form for Committee Review. Question 9.

15 Ibid., Question 10.

16 Bennish, M., Public comment submitted to NBAC. Received November 12, 2000; Goodman, S., Public comment submitted to NBAC. Received November 13, 2000.

17 Sommer, A., Testimony before NBAC. September 16, 1999. Arlington, Virginia. Meeting transcript, 179–180, 188–189, 215–218.

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Chapter Three

Voluntary Informed Consent[1]

Introduction

The requirement to obtain voluntary informed consent from individuals before they are enrolled in a research trial is a fundamental principle of research ethics. This requirement is reflected in all published national and international codes, regulations, and guidelines pertaining to research ethics, including those in many developing countries, such as India, Thailand, and Uganda. It also appears in a major international human rights instrument—the International Covenant on Civil and Political Rights—to which the United States is a party. Article 7 of this covenant provides that "no one shall be subjected without his free consent to medical or scientific experimentation" (United Nations 1996).

The requirement for freely given and informed consent to participate in research reflects important substantive ethical principles, including respect for persons, human dignity, and autonomy. However, it is possible to respect persons and their dignity or autonomy and affirm the requirement to obtain voluntary informed consent and at the same time allow for the modification of the procedures that are involved in obtaining consent, such as those stipulated in the Federal Policy for the Protection of Human Subjects, known as the Common Rule (45 CFR 46.117(c)).[2]

Despite the ethical centrality of voluntary informed consent and its underlying principles, problems of interpretation and application exist for researchers and ethics review committees in both developed and developing countries. Some problems regarding informed consent are particularly difficult when the host country has little experience with clinical trials and has markedly different cultural values and ethical commitments than the United States. It is important, therefore, for U.S. sponsors of international research to address pressing issues concerning the application of U.S. research regulations for informed consent in settings with different cultures and customs.

This chapter addresses a number of related topics, including the following:

- whether cultural factors create a barrier to complying with the substantive ethical standard of informed consent and whether it is permissible to depart from that standard if the research could not otherwise be carried out;
- how investigators obtain voluntary informed consent in settings in which the belief system of potential research participants does not explain health and disease using the concepts and terms of modern medical science and technology;
- how voluntary participation can be ensured in settings in which community leaders may exert pressure on the entire community to enroll in a proposed clinical trial;
- how cultural differences can be addressed between the United States and other countries that make it difficult or impossible for other countries to adhere to U.S. federal regulations stipulating specific procedures for obtaining voluntary informed consent; and
- the means by which the United States could modify its informed consent regulations to adapt to various cultural circumstances in other countries without compromising the substantive ethical standard of informed consent.

Although individual voluntary informed consent by competent adults is a widely accepted standard in most research environments, it is not universally embraced.

Nonetheless, the National Bioethics Advisory Commission (NBAC) remains convinced that U.S. sponsors of research in developing countries should adhere to internationally agreed-upon ethical standards of voluntary informed consent for research, even in the face of cultural diversity. Obtaining adequately informed voluntary consent from individual research participants is a necessary requirement in preventing exploitation, and it should be possible to remain sensitive to cultural differences without departing from these standards.

The justification for the need for obtaining informed voluntary consent is simple: The use of human beings as a means to the ends of others without their knowledge and freely granted permission constitutes exploitation and is therefore unethical. NBAC recognizes, however, that disagreement still exists about this claim. One commentator has argued that "[i]t is 'ethical imperialism' at its worst to assume that the informed consent requirement, which does indeed serve one (only one) moral principle in the Western setting, is in itself such a universal ethical standard" (Newton 1990, 11). This same commentator contends that growing doubt surrounds the values of individualism and individual rights, so "the investigator might better stick to the research, and accept the local assessment as to adequate protection of individual rights" (Newton 1990, 11).

Two other commentators, Ijsselmuiden and Faden, take an opposing view: "Appeals to cultural sensitivity... are no substitute for careful moral analysis. We see no convincing arguments for a general policy of dispensing with, or substantially modifying, the researcher's obligation to obtain first-person consent in biomedical research conducted in Africa" (1992, 833). They add that defenders of such a policy "have relied on limited and often dated anthropologic literature that does not reflect the rapid cultural changes brought about by colonialism and independence, warfare, and urbanization" (1992, 833).

The recommendations developed in this chapter focus on three traditional elements of informed consent (Faden and Beauchamp 1986): 1) disclosing information to potential research participants (see Exhibit 3.1); 2) ascertaining their understanding of what has been disclosed; and 3) ensuring that their agreement to participate in research is voluntary. The basic elements of disclosure in the informed consent process as presented in the Federal Policy for the Protection of Human Subjects are listed in Exhibit 3.1. References in this chapter to the basic elements of disclosure in informed consent are to these eight requirements.

The Ethical Standard of Informed Consent

Various descriptions of the process and nature of informed consent can be found in the Common Rule (45 CFR 46.116 and 46.117), Food and Drug Administration (FDA) regulations (21 CFR 56), the Council for International Organizations of Medical Sciences (CIOMS) *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS 1993), the International Conference on Harmonisation (ICH) *ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice* (GCP) (ICH 1996), and the World Medical Association's (WMA) *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects* (WMA 1964, as amended in 1996 and again in 2000). Principle 9 of the 1996 revision of the *Declaration of Helsinki* states that "[i]n any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing" (WMA 1964, as amended in 1996). In the October 2000 revised *Declaration of Helsinki*, Principle 22 addresses the informed consent process, stating that:

> [I]n any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician

Exhibit 3.1: Disclosure Requirements in the U.S. Common Rule

The disclosure requirements found in the Federal Policy for the Protection of Human Subjects at 45 CFR 46.116(a), under the heading of "basic elements of informed consent," are as follows:

1) a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
2) a description of any reasonably foreseeable risks or discomforts to the subject;
3) a description of any benefits to the subject or to others which may reasonably be expected from the research;
4) a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
5) a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
6) for research involving more than minimal risk (as defined in 45 CFR 46.102(i)), an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
7) an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
8) a statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled (45 CFR 46.116(a)).

It should be noted that these requirements could be modified or waived by an Institutional Review Board (IRB) under certain circumstances. In addition to the basic information listed above, the U.S. regulations require that participants be given other information that may affect their participation in research, depending on the nature of the project itself. The U.S. regulations list six such additional disclosures (45 CFR 46.116(b)).

should then obtain the subject's freely given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed (WMA 1964, as amended in 2000).

Substantive changes between the 1996 and 2000 revisions of the *Declaration* include 1) informing each potential subject about any possible conflicts of interest and the institutional affiliations of the researcher; 2) ensuring that research participants have understood the information presented to them; and 3) requiring that if the consent cannot be obtained in writing, the nonwritten consent must be formally documented and witnessed.

For this report, NBAC adopts, as the clearest and most appropriate guides for discussion, the following definitions of informed consent and the substantive standard of informed consent: *Informed consent* is a *process* by which an individual voluntarily expresses his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the decision to participate. This definition is adopted from the ICH *Guideline for Good Clinical Practice*, GCP Guideline 1.28 (ICH 1996). An important feature of this definition is that it focuses on the *process* of obtaining consent rather than on the *documentation* of that process using, for example, a written, signed, and dated form.

In an ethically sound consent process, a member of the research team provides information to the potential participant, determines that the individual understands the information provided, and ensures that the individual voluntarily agrees to participate. Although consent traditionally has been documented by the signing of a consent form, other methods of documentation often are acceptable or even preferable, such as oral consent with a witness signature. In many settings, it is also required that the person obtaining the consent sign the consent form or other related documents and that a witness (or person designated by the participant) attests to the process. It is always essential to make a distinction between the consent *document* and the consent *process* and to not allow the document itself to constitute the process.

The phrase *substantive standard of informed consent* refers to the requirement to obtain voluntary informed consent and reflects the principle that competent individuals are entitled to choose freely whether to

participate in research. This definition was adopted from the CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Guideline 1, Commentary, para. 2 (CIOMS 1993, 13). In general, voluntary informed consent protects the individual's freedom of choice, respects his or her personhood, dignity, and autonomy, and reduces the chances of exploitation.

Objections to this substantive ethical standard are rarely, if ever, voiced, even in parts of the world in which less cultural emphasis is placed on individual rights and freedom of choice than is common in Western and most developed countries. However, various objections often arise about the need for certain procedures for obtaining and documenting informed consent, including those stipulated in U.S. research regulations and other documents, such as the ICH *Guideline for Good Clinical Practice*. As noted, it is important to distinguish *substantive ethical principles and standards* from the *procedures* that implement them. Although procedures are important, they often can be modified without compromising ethical principles or standards. Examples of procedural aspects of the informed consent process and its documentation include the following requirements: the informed consent documents should be in writing and signed by the research participant; the consent form should be signed by the person obtaining consent or by the principal investigator; and there should be a witness to the signing of consent forms. Other examples of procedures that are not always central to meeting the substantive ethical principles and standards of voluntary informed consent are involving family members in the consent process or obtaining a community leader's permission before approaching individuals in the community. Although it is necessary—and not always easy—to determine which procedural aspects are ethically required and which might be altered or waived altogether, procedural requirements should be viewed as less fundamental than matters of substantive ethical standards or principles.

Recommendation 3.1: **Research should not deviate from the substantive ethical standard of voluntary informed consent. Researchers should not propose, sponsors should not support, and ethics review committees should not approve research that deviates from this substantive ethical standard.**

Cultural Barriers Relating to Disclosure Requirements

Requirements for disclosing information in research settings usually exceed those for disclosing information in clinical contexts. In the United States, the requirements for disclosure of information to potential participants in research are specific and detailed. (See Exhibit 3.1.) The extent of medical information that is disclosed to patients in clinical settings differs among cultures and can influence judgments about the amount and kind of information that should be disclosed in research settings. Three principal types of disclosure are central to the process of informed consent in the research setting: 1) disclosure of diagnosis and risk; 2) disclosure of the use of placebos and randomization; and 3) disclosure of alternative treatments. In addition, NBAC considers a fourth type of disclosure—that of the possibility of access to any post-trial benefits—a central issue discussed in Chapter 4.

Disclosure of Diagnosis and Risk

In some parts of the world, it is still customary for physicians to withhold certain information from patients.[3] Clinicians often provide diagnoses (as well as prognoses) of cancer or other serious conditions to family members, but they withhold such information from patients. As a result, the patient's consent to certain procedures, if sought, may not be fully informed. Jeremy Sugarman and his colleagues noted in their report to NBAC that "[i]n one country, complete information about medical diagnoses and prognoses are withheld routinely from patients with certain diseases, such as cancer. Consequently, valid informed consent (for either treatment or research participation) can be difficult or impossible."[4]

Nancy Kass and Adnan Hyder describe a similar situation in their study for NBAC: "...in some developing country settings, a diagnosis of cancer would never be revealed directly to the patient but rather to members of the patient's family."[5] Although this observation was made in reference to clinical care, these cultural practices are relevant to research participants, who may have similar expectations. Similarly, different cultures have different attitudes toward the disclosure of risks in the *clinical context*,

and some researchers believe that it is not always appropriate to disclose to patients the full ramifications of their situation.

In another study conducted for NBAC, Nigerian researchers indicated that consent documents attached to certain research protocols included information that potential participants might find extraneous, irrelevant, or culturally inappropriate. These researchers called particular attention to the emphasis placed on explaining the potential risks to study participants, noting that in the United States, there is much greater interest in communicating the possibility of harm to research participants than there is in Nigeria. One physician noted that, given Nigerian cultural norms, disclosing all possible risks would unnecessarily alarm potential research participants associated with the research.[6] Based on such observations, some people believe that, at least in some cultures, it would be impossible to enroll research participants by adhering to the basic elements of disclosure as presented in 45 CFR 46.116(a).

NBAC believes that cultural standards regarding the inappropriateness of providing diagnoses and prognoses to patients or research participants do not justify deviation from the substantive ethical standard of informed consent in research. Even if the custom of routinely withholding complete information about diagnoses and prognoses from patients with certain diseases could be defended in ordinary medical practice, it poses a severe challenge to the need to adhere to the substantive ethical standard of disclosure required for research involving human participants. Those who lack information about their diagnosis and prognosis cannot be expected to understand the purpose of the research, any potential direct benefits, the risks of not participating, or the alternatives to participation. Similarly, potential participants cannot make an informed decision to participate without knowing that they may not receive a proven treatment that could be beneficial. Enrolling individuals in research who are not given the opportunity to understand such important information represents a deviation from the substantive ethical standard of disclosure required for adequate informed consent and should not be permitted. Diversity in the practice of disclosing information in the clinical context does not alter the requirements for such disclosure in the research context.

These matters must be studied in more detail to learn about how cultural variations affect the meaning and effectiveness of the consent process and the use of particular consent documents. It is critical that we find innovative and culturally responsive ways to disclose information to potential participants. NBAC heard testimony from U.S. and developing country researchers who have succeeded in adhering to this standard,[7] even though doing so often takes more time and effort than researchers typically expend in the informed consent process. Even in cultures in which a diagnosis of serious illness is not normally revealed in the treatment context, researchers often can find ways to overcome this barrier to disclosure in the research setting.

Disclosure About Control Interventions and Randomization

In some cultural contexts, questions also arise regarding the appropriateness of requiring information to be disclosed about the use of a placebo in one arm of a clinical trial, the randomization of participants, and any uncertainty that may exist regarding the efficacy of an experimental intervention. Sugarman and his colleagues reported on "local perceptions concerning cultural barriers to randomization and the use of placebos." Indeed, investigators sometimes struggled with these barriers, responding in different ways. For example, in one case, investigators who believed that it would be impossible to obtain valid informed consent for a randomized trial abandoned the use of randomization in their research. However, in another case, investigators used placebos, even though they did not believe that the research participants understood the implications of doing so.[8] Despite these barriers, cultural differences do not provide adequate justification for foregoing the requirement to disclose key elements of the nature of the clinical trial, such as the use of a placebo or the randomization of participants into different trial arms.

Disclosure of Alternative Therapies

An example from the literature illustrates a particular disclosure problem. Love and Fost (1997) describe a struggle that occurred in one U.S. IRB that reviewed a proposal for a randomized clinical trial of adjuvant treatment for breast cancer to be conducted in Vietnam. The

investigator "found himself uncertain about the application of American standards of informed consent in the Vietnamese setting." After consultation with experts on Vietnam and Vietnamese culture, he concluded that "American standards would not be acceptable to Vietnamese physicians, political leaders in Vietnam, or the vast majority of Vietnamese patients" (Love and Fost 1997, 424). The investigator argued that in medical practice in Vietnam, patients do not participate in their medical decisions. Thus, the researcher contended that participants in the clinical trial should not receive any information that would convey the treating doctor's uncertainty—specifically, information about alternative therapies and the use of randomization to determine the subject's proposed treatment (Love and Fost 1997).

Although the Commission recognizes the challenges raised by these cultural differences in practicing medicine and obtaining consent, it does not believe that these challenges provide adequate justification for foregoing the requirement to make disclosures about alternative therapies that are available to potential participants should they choose not to enter a clinical trial.

Recommendation 3.2: **Researchers should develop culturally appropriate ways to disclose information that is necessary for adherence to the substantive ethical standard of informed consent, with particular attention to disclosures relating to diagnosis and risk, research design, and possible post-trial benefits. Researchers should describe in their protocols and justify to the ethics review committee(s) the procedures they plan to use for disclosing such information to participants.**

Disclosure About Possible Post-Trial Benefits

The basic disclosure requirements for satisfying the informed consent provisions in U.S. research regulations (see Exhibit 3.1) focus on information needed by a potential participant to decide whether or not to participate in a study. Of the eight basic disclosure requirements, one focuses on potential benefits: "a description of any benefits to the subject or to others which may reasonably be expected from the research" (45 CFR 46.116(a)(1)). Traditionally, such a disclosure has been required to ensure that potential participants understand whether there is any possibility that the intervention itself might benefit them while they are enrolled in the study. There is, however, no specific mention of any *post-trial benefits*. In any case, those who may participate in studies should be informed of the potential benefits, if any, that they might receive by doing so. Because this information is relevant to participants' decisions to participate in the research, ethics review committees should require investigators to make these disclosures.

Recommendation 3.3: **Ethics review committees should require that researchers include in the informed consent process and consent documents information about what benefits, if any, will be available to research participants when their participation in the study in question has ended.**

Other Cultural Issues Relating to the Informed Consent Process

Additional issues in the informed consent process include the ability of potential participants to understand the scientific and technical aspects of research protocols—given the culture and belief systems within which they live—and the influence and involvement of others in the consent process.

Innovative Ways of Presenting Information to Participants

In some cultures, the belief system of potential research participants does not explain health and disease using the concepts and terms of modern medical science and technology. This is significant, because when people do not understand or accept scientific explanations of health and disease, the challenge of obtaining informed consent can be daunting.[9] Patricia Marshall's report to NBAC quotes one physician as follows: "...[W]hat I worry about is whether we are really informing them. We are talking to a society that does not believe in the germ theory of disease so it's difficult to explain." The researcher provided an example of the pervasive belief that a person's death is a result of sorcery rather than a lethal infection.[10] In noting that he had encountered a cultural belief that spirits cause epilepsy, Alfred Sommer, Dean of the Johns Hopkins University School of Hygiene

and Public Health, told NBAC that "we do not want to fight a belief system. We simply say we have this pill. We believe it is safe. We think it may reduce the recurrence of the following thing. We would like you to take it."[11]

Despite this potential barrier to adequate understanding, if they are willing to devote the time and effort to do so, researchers often are able to devise creative measures for overcoming these barriers. An example appears in the Kass/Hyder report for NBAC: "...the concept of immunology, an immune response, that there's something in your blood that's going to attack bacteria and viruses which you also don't have a concept for....[H]ow much can someone really focus on the consent form when they have this whole new idea that there's this battle going on in their bloodstream?...When we go and translate, we try to use, for example, immune cells, we talk about people who guard houses...it's a particular kind of watchman. So you have a particular kind of watchman in your blood...."[12] Even in countries with very low literacy rates (e.g., 30 percent for men and 10 percent for women in Senegal), one group found that "widespread illiteracy is not a barrier to comprehension, especially since informed consent is more an interactive process than one that depends on reading" (Preziosi et al. 1997, 372). However, the authors of this study concluded that understanding abstract scientific concepts, such as double blinding and randomization, could be difficult. To help explain these complex issues, researchers used terms and concepts that were understandable to the community involved: "To illustrate the principle of randomization and the possibility that one of the vaccines might fail, the presenters used a familiar agricultural example: the evaluation of fertilizers or of seed varieties on randomized plots, a procedure familiar to farmers in the area" (Preziosi et al. 1997, 370).

Another illustration emphasizes the importance of educating individuals and the community about the study and its specific purpose and procedures. Investigators and research assistants interviewed by Marshall noted that education should begin at the community level. "You approach some person as a contact person...you often start with the local governance...we need to obtain permission from them and we need their help to get to community leaders...they need to work with community leaders...we spend time discussing [the study]...you have to explain [it] fully."[13] Researchers may find, for example, that, in circumstances where they do not speak the local language, the use of intermediaries can be an effective means of ensuring adequate understanding among potential participants.

In some countries, a process of community education acts as a precursor to the process of obtaining individual consent. For example, one study reported that in Senegal, the field staff and physicians held meetings in each village to provide information about a study of a new pertussis vaccine and to obtain consensus about its use. A physician then provided additional information and sought individual informed consent at the monthly vaccination session. A clinical trial for vaccination against *Haemophilus influenzae* type b in The Gambia was preceded by an intensive publicity campaign involving radio, newspapers, and discussions with village leaders (Leach et al. 1999). When mothers attended the first child health clinic, they received an information sheet about the clinical trial to take home for discussion with their families. When a mother returned for the first vaccination, the trial worker explained the study again, and, if the mother gave oral consent, the trial worker signed the information sheet.

Translation and back translation of a written consent form may be one way of ensuring that information is correctly disclosed; however, this may not always be effective. Jean Pape, a researcher from Haiti, who is also on the Cornell University faculty, described the complexity of this process.[14] In preparing to begin HIV vaccine trials in Haiti, his research group needed approval from its own IRB in Haiti, as well as from the IRB at Vanderbilt University—one of the collaborators—and from the IRB at Cornell University Medical School. To be understandable to participants, the consent form had to be in the Creole language. Yet, the document also had to be in French, the language of the Haitian researchers. Because the consent form had to be reviewed by the Cornell IRB, a translation in English was also required. Pape said that the back translation of a consent form "does not guarantee that volunteers have really understood the objective of the study, the risks and advantages, and their voluntary participation,"[15] a difficulty reported in another study in Nigeria.[16]

NBAC also heard about the desirability of testing research participants to understand whether and how much they understood regarding the informed consent process.[17] Pape described the process he regularly undertakes to ensure understanding. This process includes a person who counsels potential participants about all aspects of the project, helps to develop a test questionnaire that all potential participants must pass before being given the actual consent form, and is available to address participants' concerns and questions. The period before obtaining ethical clearance from the various review committees is used to counsel and inform potential volunteers, who should pass this test of understanding before receiving a simpler informed consent form.[18] These mechanisms—the counseling sessions and test questionnaires—illustrate some of the ways in which informed consent can and should be a process that takes place over time and that is much more than the mere signing of a document that may be imperfectly comprehended. Despite the acknowledged difficulties of administering tests of understanding, NBAC supports the idea of incorporating these tests into research protocols.

Recommendation 3.4: **Researchers should develop procedures to ensure that potential participants do, in fact, understand the information provided in the consent process and should describe those procedures in their research protocols.**

Recommendation 3.5: **Researchers should consult with community representatives to develop innovative and effective means to communicate all necessary information in a manner that is understandable to potential participants. When community representatives will not be involved, the protocol presented to the ethics review committee should justify why such involvement is not possible or relevant.**

Involvement of Others in the Informed Consent Process

In some cultures, several barriers might arise to ensuring free and individual choice to participate in research. Among those identified by Kass and Hyder were deference to physician/health personnel; low economic status of potential participants; low level of awareness or education of potential participants; limited decisionmaking power for women; community leaders' disapproval; family disapproval; and cultural customs that prohibit "refusing a guest" (rules of traditional hospitality).[19] A subset of these barriers is discussed in this section—barriers that pertain to the involvement of community leaders and family members in the consent process.

Community Leaders

In some cultures, investigators must obtain permission from a community leader or village council before approaching potential research participants. Yet, it is important to distinguish between obtaining permission to enter a community for the purpose of conducting research and for obtaining individual informed consent. In their reports, NBAC consultants all noted that the role of community leaders or elders is an integral part of the process of recruiting research participants. Although these reports typically use the terminology of *consent* to refer to the community's permission or a leader's authorization for the researchers to approach individuals, NBAC will use this term to refer to the permission or authorization given by the individual being recruited as a research participant.

The need to obtain permission from a community leader before approaching individuals does not need to compromise the ethical standard requiring an individual's voluntary informed consent to participate in research. Gaining permission from a community leader is no different, in many circumstances, from the common requirement in this country of obtaining permission from a school principal before involving pupils in research, from a nursing home director before approaching individual residents, or from a workplace supervisor before initiating an experimental screening program. An ethical problem arises only when the community leader exerts pressure on the community in a way that compromises the voluntariness of individual consent. The reports commissioned by NBAC describe a number of situations in which community leaders have been involved in the informed consent process. (See Exhibit 3.2.)

Nevertheless, recruitment procedures in some cultures involve community leaders whose authority does not allow individual members of the community to refuse to participate in research for which the leader has

Exhibit 3.2: Involvement of Community Leaders in Informed Consent

During the course of its deliberations, NBAC sponsored a survey in which researchers who conducted international research were asked about the process of obtaining informed consent in different cultural settings.[20] The following excerpts highlight some of the issues raised when cultural practices require the involvement of community leadership in the informed consent process.

- "There are very positive informed consent stories where you would never go first to the individual. You can approach the individual after you have explained the research to the chief or local leader. Then they explain the informed consent process to their people without exerting the pressure. The best evidence of the effectiveness of this approach is when people refuse to participate. That's a good sign. They are able to refuse."[21]
- In contrast, in some settings, the head of the village or a group of elders makes a collective decision for the village. "If they make the decision in favor of participating in the trial, virtually everyone will participate. The people in the community are then extremely reluctant to withdraw from the trial because of the collective nature of community activities."[22]
- In other settings, there is authorization by a community leader that is compatible with individuals' right to refuse and authorization in a context in which the Chief's word is law. One physician described "two levels" of consent or permission: "One is community and the other is individual....When you leave [the Chief], the Chief is expected to open households so there is really another level of consent [in between]...the Chief and council, the household head, then the individual."[23] In answer to the question, "then how will the community respond?" the physician said that most of the time the members agree to participate. At the same time, there is some uncertainty on the part of the physicians interviewed about the extent to which individual agreement to participate is voluntary.[24]
- "Regarding whether the community leaders should be asked to approve the study depends on 1) whether you are working in a healthy community, and 2) the level of corruption of the community leaders. I have been conducting a study in an African city since 1987. There, we have 'laid low,' trying to avoid the gaze of the community leaders and state or national politics. Had we been noticed there, the tremendous corruption would have destroyed the study. However, working in an African village would be an entirely different matter. In that situation, a study could not be conducted without the approval and active support of the community leaders."[25]
- An American researcher conducting malaria studies in Mali and in Malawi noted the difference between the two settings. In Mali, the study was conducted in a remote rural area in which community leaders were heavily involved. In contrast, the Malawi study took place in a large city with an established health care system and a more educated population. In this latter setting, *community consent* at the national or institutional level is removed from individuals and the local community, and it seems likely that consent by community leaders would not have an undue impact on the decisions of individuals. In addition, in an urban context, it is more difficult to identify appropriate spokespersons for the larger community, especially as individuals in urban areas tend to associate themselves with many different kinds of communities.[26]

granted permission. Also, in some settings, authoritarian governments may limit autonomous decisionmaking by their citizens, which may affect their participation in research.[27] The question then arises regarding whether there are some countries in which U.S. researchers should not engage in international collaborative research. In NBAC's view, if a country's political system or a local situation makes it impossible for individuals' consent to be voluntary and that fact is known in advance, then, because U.S. researchers cannot adhere to the substantive ethical standard of informed consent, it would be inappropriate for them to choose such settings.

Recommendation 3.6: **Where culture or custom requires that permission of a community representative be granted before researchers may approach potential research participants, researchers should be sensitive to such local requirements. However, in no case may permission from a community representative or council replace the requirement of a competent individual's voluntary informed consent.**

Recommendation 3.7: **Researchers should strive to ensure that individuals agree to participate in research without coercion or undue inducements from community leaders or representatives.**

Family Members

It is customary although not required in some societies for other members of a potential research participant's family to be involved in the informed consent process. In most instances, the need to involve the family is not intended as a substitute for individual consent, but rather as an additional step in the process.[28] An example of a multistep process involving the family is described by Loue and colleagues (Loue and Okello 2000) in their report on a workshop in Uganda that addressed the problem of acquiescence by another family member in order for an individual to participate in research. (See Exhibit 3.3.)

Researchers in other countries also have reported on their efforts to involve the family in the informed consent process in ways that do not undermine the standard of individual consent. Marshall reported, for example, that in Nigeria in areas where traditional cultural norms are strong, the permission of a woman's husband might be required before she can enroll in research. A Nigerian physician involved in a breast cancer study noted that cancer patients often need the approval of their husbands to participate in research. However, the physician also emphasized that in such cases, the woman's individual consent is still essential. Indeed, most investigators have developed strategies that accommodate and encourage discussion regarding study participation with family members.[29]

NBAC recognizes that this situation does not apply in cases in which a family member lacks the capacity to give informed consent. Indeed, there is consensus that having the capacity to decide is an important precondition (or threshold element) for informed consent (Beauchamp and Childress 1994; NBAC 1998).

In many cases, family members may be approached before asking an individual directly to participate in a research project. However, seeking permission from family members without engaging the potential research participants at all clearly departs from the ethical standard of informed consent. On the other hand, potential participants might also choose to involve others, such as family members, in the consent process. Indeed, involving family or community members in the informed consent process need not diminish, and might even enhance, the

Exhibit 3.3: New Ugandan Guidelines for Informed Consent

Uganda has a new constitution that specifically recognizes the rights of women and minorities, which had not been recognized in that country.[30] A more specific development regarding research was the adoption of guidelines protecting the individual rights of research participants. In July 1997, the representatives of the National Consensus Conference on Bioethics and Health Research in Uganda voted unanimously to adopt the *Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda* (National Consensus Conference 1997). Participants in the consensus conference came from a wide range of governmental and nongovernmental agencies.

The Ugandan guidelines for research specifically prohibit an investigator from relying on the permission of a community leader for the participation of community members in research. The development and adoption of this requirement of individual consent necessitated a reexamination of various aspects of Ugandan customary laws, which traditionally have demanded the subordination of an individual's wishes to those of a specified family leader, usually the father or husband. An individual's wishes could be further subordinated to those of the community or the tribe. Although these guidelines clearly require individual consent, it is not known whether this provision is always adhered to in practice. The process that led to adoption of these guidelines was informed by Uganda's own recognition of its history, including its experience with tyranny, torture, and the elimination of targeted groups.

The Ugandan guidelines for research reflect efforts to achieve some balance between the older traditions and the ethical standard of voluntary and informed individual consent. The guidelines include a provision that allows potential participants sufficient and adequate time to confer with anyone else of their own choosing to discuss the particular features of the research and to minimize the possibility that they may be subjected to undue influence or coercion.[31]

individual's ability to make his or her choices and to give informed consent (or refusal).

These examples show that it is often possible to obtain individual informed consent, which may require and indeed benefit from the involvement of family or community members, while at the same time preserving cultural norms. Such involvement ranges from providing written information sheets for potential participants to take home and discuss with family members to holding community meetings during which information is presented about the research and community consensus is obtained. When the potential participant wishes to involve family members in the consent discussion, the researcher should take appropriate steps to accommodate this desire.

Recommendation 3.8: **When a potential research participant wishes to involve family members in the consent process, the researcher should take appropriate steps to accommodate this wish. In no case, however, may a family member's permission replace the requirement of a competent individual's voluntary informed consent.**

Consent by Women

Some cultures customarily require the permission of a woman's husband, if she is married, or her father, if she is unmarried, before she can enroll in a research protocol. A strict requirement that a husband must first grant permission before researchers may enroll his wife in research treats the woman as subordinate to her husband and as less than fully autonomous. If the requirement of spousal authorization, in addition to individual informed consent, were applied equally to enrollment of men and women as research participants, it would at least constitute gender equity. But in cultures in which spousal authorization for participation in research is customary, it appears always to be the woman who must obtain her husband's permission. If women wish to consult with their husbands or to seek voluntarily to obtain their husbands' permission before deciding to enroll in research, this is not only ethically permissible, but in some contexts highly desirable. However, a strict requirement of spousal authorization violates the substantive respect for persons principle, which mandates that equal respect be accorded to women as persons.

Much research is directed at conditions that affect both women and men. Yet, it is important not to neglect research on diseases or conditions that affect only women. In reality, without involving the husband in the consent procedures, it may be impossible to conduct some research on common and serious health problems that affect only women. In such cases, a likely consequence would be a lack of knowledge on which to base health care decisions for women in that country. The prospect of denying such a substantial benefit to all women in a particular culture or country calls for a narrow exception to the requirement that researchers use the same procedures in the consent process for women as for men, one that would allow for obtaining the permission of a man in addition to the woman's consent.

Recommendation 3.9: **Researchers should use the same procedures in the informed consent process for women and men. However, ethics review committees may accept a consent process in which a woman's individual consent to participate in research is supplemented by permission from a man if all of the following conditions are met:**

a) **it would be impossible to conduct the research without obtaining such supplemental permission; and**

b) **failure to conduct this research could deny its potential benefits to women in the host country; and**

c) **measures to respect the woman's autonomy to consent to research are undertaken to the greatest extent possible.**

In no case may a competent adult woman be enrolled in research solely upon the consent of another person; her individual consent is always required.

Voluntary Participation in Research

A fundamental principle of research ethics is the requirement that participation be voluntary—that is, "free of coercion and undue influence" (National Commission 1979). However, among the most difficult requirements to ensure is the voluntariness with which participants consent to enroll in a study. Pressure from a community

leader, the power and authority of the medical professionals who serve as investigators, and the fear of loss of health benefits that people would normally expect to receive may compromise individuals' freedom to refuse to participate in research. The provision of medical care and treatment during a study may constitute an incentive for individuals to enroll in a study, but it should not be construed as a coercive offer that would unduly compromise the voluntariness of participation.

Undue Inducement

It is likely to be difficult to decide when a study design constitutes an undue influence. One definition states that "undue influence...occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance" (National Commission 1979, 14). There are many circumstances that can cause undue inducements to participate in clinical trials, including offers of medical care not otherwise available or offers of money. Discussions in the literature traditionally have focused on monetary payments to research participants and address the question of whether any amount of money is an acceptable inducement, and, if so, at what point the acceptable inducement becomes undue (Dickert and Grady 1999; Macklin 1981; Macklin 1982).

Other aspects of research design that may pose a problem of undue influence have received considerably less attention. As the CIOMS *Guidelines* document acknowledges: "It may be difficult to distinguish between suitable recompense and undue influence to participate in research....Someone without access to medical care may be unduly influenced to participate in research simply to receive such care" (CIOMS 1993, 19). This situation is likely to exist in developing countries in which large numbers of people have little or no access to medical care and treatment even for ordinary illnesses, a concern expressed to NBAC in testimony.[32]

It is necessary, then, to answer the threshold question of whether the very offer to participate in research constitutes an undue inducement to citizens of developing countries who have little or no access to medical care and treatment (Bernstein 1999). Even a placebo-controlled trial offers such individuals a 50 percent likelihood (in a two-arm trial) of receiving an intervention that, although unproven, may be beneficial. If the solution to this fundamental problem is to forgo research entirely in such places, it might make those populations worse off than they would be if research goes forward. This consideration requires the review of the ethical consequences of *not* conducting research and the determination of whether those consequences outweigh the ethical problems alleged to exist in the conduct of the research. But the need to attempt such a balance can be avoided if a proper distinction can be made between acceptable inducements and those that constitute undue influence or coercion.

No hard-and-fast criterion can be stipulated for making this distinction. However, one approach would be to consider the possible motivations for participating in research, according to the following schema. People may, for example:

a) Act out of self-interest, when there is a potential benefit to them.
b) Act out of rational or enlightened self-interest, when there is potential benefit to others as well as to themselves, and some risk to themselves.
c) Act out of pure altruism, when they expect no benefit to themselves but expect benefit to others, and accept some risk to themselves.
d) Refuse to act because of perceived high risk or great inconvenience, only agreeing to undergo the risk when offered considerable material reward.
e) Act out of fear of the consequences of refusing to participate.

All of these situations apply to some extent in research. Situation (b) is the standard presupposition in Phase II or III clinical trials. Prospective participants weigh the risks and potential benefits, recognizing that there may be some risk to themselves but also some possible benefit and that the research as a whole may provide benefits to others. Situation (c) is the standard for research not designed to provide direct benefit to participants, but, for example, to determine the safety of drugs in Phase I studies, to discover basic physiological mechanisms, or to arrive at baseline data. Situation (d) captures the idea of undue inducement when people make a rational refusal based on perceived risk, but then agree to

accept the risk only when provided with a considerable material reward. Situation (e), by definition, is the paradigm of coercion: In hierarchical groups, in coercive settings, or under threat, individuals agree to participate in research because they fear the consequences of refusal. In this situation, their participation is coerced, not voluntary. Situation (e), therefore, is ethically prohibited.

In principle, there is no difference between the sort of motivation that prompts people anywhere to volunteer for research—situation (b)—and what may induce people in developing countries to agree to participate. The more difficult challenge lies in situation (d): Does the prospect of receiving medical care as a benefit during (or possibly after) the research prompt people in developing countries to undertake serious risks they would otherwise refuse to accept? There can be no general answer to this question, which can be determined only on a case-by-case basis. In studies with the usual range of risks, the provision of medical care may be an inducement to participate, but there is little reason to believe it is an undue inducement. Recalling the definition of undue influence cited earlier—"an excessive, unwarranted, inappropriate or improper reward"—it is reasonable to conclude that providing medical care to research participants is warranted, appropriate, and proper.

One might object that this definition is embedded in a document created in the United States—a wealthy, industrialized country—and therefore is irrelevant to resource-poor countries. The reply to this objection is twofold. First, poor people exist in every country, and participation in a clinical trial often is the only way that uninsured individuals in the United States can gain access to some medical care. Yet, no one could reasonably maintain that the poor or uninsured should be excluded from participation in research or that it would be ethically acceptable to deny them medical benefits that they could not otherwise obtain.

Second, the problem may not lie in the idea that an offer to possibly receive medical care is an inducement, but rather in the difficulty of determining when such an offer—admittedly an inducement—becomes *undue*. Those who argue that participation in research constitutes an undue inducement for poor people in developing countries would have to maintain that offering high-quality medical care and treatment that participants would not otherwise receive is unwarranted and inappropriate. However, the provision of medical care or treatment that would not otherwise be available to research participants should not, in principle, be construed as an undue influence to participate. This conclusion is supported by developing country researchers surveyed by Kass and Hyder: 64 percent stated that participants joined research projects in order to obtain benefits.[53] Many researchers interviewed in focus groups for this same study seemed to believe that this was acceptable, given the overall risk/benefit ratio of the research; some focus group respondents remarked that providing significant benefits essentially left potential participants with no reasonable choice except to participate, but they did not specifically refer to this as undue inducement.[54] NBAC concludes that although the potential benefits of participation in research may be an inducement for those in developing countries who lack access to medical care to participate in research, this does not sufficiently diminish the voluntariness of their decision in a way that would make their consent ethically invalid.

Somewhat more problematic are clinical trials studying a new intervention in which members of a control group receive an established effective treatment that is unavailable outside the trial. Does provision of the established effective treatment constitute an undue inducement to participate?

This situation can be cast in the form of a dilemma. If providing treatment otherwise unavailable to members of a control group is an undue inducement and hence ethically unacceptable, then the only ethically acceptable research design in such situations would be that of a placebo control or some other substandard treatment that is available. However, as discussed in Chapter 2, placebo-controlled trials may be ethically unacceptable in cases in which the disease is life threatening or permanently disabling and established effective treatments exist for the condition. The dilemma arises because of the tension between the potential loss of full voluntariness on the part of participants and the probability of harm befalling those in the control arm who receive the placebo instead of an established effective treatment.

As in any ethical dilemma, this one requires that moral considerations be weighed in order to determine which alternative is more acceptable. An appeal to certain ethical principles offers some insight. The well-accepted principle of nonmaleficence (Beauchamp and Childress 1994; National Commission 1979) requires that harm to participants be minimized;[35] however, it could never be used to justify coercion of research participants, which would entirely preclude their voluntary participation. NBAC concludes that in this situation, it is more acceptable to allow the possibility of somewhat diminished voluntariness of participation than to risk harm to participants in the control arm, who are denied an established effective treatment. This is a position consistent with other guidelines, such as those of the Medical Research Council of the United Kingdom (MRC-UK 1999).

Minimizing the Therapeutic Misconception

One barrier to understanding the relevant, important aspects of any proposed research is what has been called the *therapeutic misconception* (Appelbaum et al. 1982; Churchill et al. 1998; King 1995). This term refers to the belief that the purpose of a clinical trial is to benefit the individual patient rather than to gather data for the purpose of contributing to scientific knowledge. The trust that patients have in their physicians in the clinical setting depends on an important element of the physician-patient relationship—that physicians should choose the most appropriate treatment for their individual patients. To apply that same concept to the research setting is to fall prey to the therapeutic misconception, which surfaces even when participants have received complete information (ACHRE 1996). In short, the therapeutic misconception rests on confusion between the aims of research and those of individualized medical treatment.

The therapeutic misconception has been documented in a wide range of developing and developed countries. For example, in a study conducted in a clinic in Brazil, all of the women who were interviewed said that they entered the study because they "thought that the contraceptive being offered would be good for them" (Hardy et al. 1998). In some parts of the world, a different kind of complication arises from the language itself. One American respondent to the study conducted by Kass and Hyder stated the following: "In many African languages, there is no word for 'research' or 'science.' The word used is generally the same as the word for 'medicine.' There is no concept of an experiment, placebos, etc., and despite the best translation of the most simply worded consent form, many adult subjects still have no understanding of the difference between being a research subject and receiving medical treatment."[36] The researcher went on to say that "[t]his should not be a reason to exclude these people from research; in fact they are often the population who will benefit most from the research and the only population in whom the studies can be done, e.g., persons at risk of naturally acquired malaria or other tropical diseases."[37]

It is important to distinguish the confusion that arises from the therapeutic misconception from a related consideration. In the research setting, participants often receive beneficial clinical care. In some developing countries, the type and level of clinical care provided to research participants may not be available to those individuals outside the research context. It is not a misconception to believe that participants probably will receive good clinical care during research. But it is a misconception to believe that the purpose of clinical trials is to administer treatment rather than to conduct research. Researchers should make clear to research participants, in the initial consent process and throughout the study, which activities are elements of research and which are elements of clinical care.

> ***Recommendation 3.10:*** **Researchers working in developing countries should indicate in their research protocols how they would minimize the likelihood that potential participants will believe mistakenly that the purpose of the research is solely to administer treatment rather than to contribute to scientific knowledge (see also Recommendation 3.2).**

Documentation of Informed Consent

Distinguishing between the substantive need to obtain informed consent and the particular process by which consent is documented is critical. The U.S. requirements for documentation of informed consent (45 CFR 46.117) can pose unnecessary barriers to research that conforms

to the substantive ethical standard for informed consent. Problems arise, for example, from the need for written, signed consent forms and from the amount of information that is typically provided on U.S. consent forms for a complex clinical trial. In some developing countries, the requirement of documenting informed consent on a written form signed by the research participants is thought to be inappropriate. One obvious circumstance is that of illiterate participants, who may be able to understand information presented orally, but who find a written form on which they are required to make their mark useless. Moreover, in some cultures, people distrust any signing process. This distrust is common even in countries with a high literacy rate, such as Argentina and other Latin American countries, where people have lived under oppressive regimes and fear that signing a document could place them in jeopardy. Several examples that illustrate these situations are provided in Exhibit 3.4.

At the same time, there is some evidence that researchers can overcome many of the obstacles to participants' understanding of lengthy complicated consent forms by devoting more time and effort to the consent process. Several empirical studies of informed consent carried out in developed countries describe a fairly elaborate, multistage consent process aimed at overcoming these barriers. Studies conducted in Chile, the Netherlands, and Switzerland found that researchers could overcome these barriers with three separate

Exhibit 3.4: Examples of Documentation of Informed Consent Requirements

- Sugarman and colleagues provided two examples in which requiring a signed informed consent document was especially problematic: "...in one project involving many illiterate subjects, although thumbprints might be considered to be an appropriate means of documenting individual informed consent, local investigators did not use such an approach because it too closely related to past police tactics and [was] believed to frighten potential research participants. In another setting, where guerilla warfare was ongoing, the use of written informed consent posed a risk to participants because these documents linked them to particular institutions."[38]
- The Ugandan document *Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda* rejects a requirement for written informed consent. This rejection stems from Uganda's past experience of torture and persecution of individuals found to be associated with particular enterprises and recognizes the sensitivity to individuals' reluctance to sign a piece of paper that attaches their name to an enterprise. Individuals who do not wish to sign may put an "X" in place of a signature.[39] This is a good example of how procedural requirements can be made sufficiently flexible to reflect social and cultural sensitivities.
- Jean Pape, a Haitian researcher, discussed the complexity of the consent forms. He said that the forms are clearly too lengthy and that over the past 22 years, he has found them to be increasingly complicated. He stated that "[t]hey appear to be more concerned about legal implications for sponsor agencies than...with the welfare of the volunteers. We cannot read them to volunteers because the only time a volunteer had a document like this read to him was when he was in a court of law and had to sign some kind of papers. So this is changing the trust relationship that we have with our participants and, therefore, we have to explain it step by step."[40]
- Grace Malenga said of consent forms used in Malawi that providing too much information is likely to scare patients. "You start asking questions or telling them to sign...some papers and immediately...they will look at them, some of them have actually withdrawn." Some people were willing to participate until they were asked to sign a piece of paper.[41]
- Nigerian researchers pointed to the length and complexity of informed consent documents and the need for written consent as obstacles for those attempting to obtain consent from potential study participants.[42] In Marshall's study for NBAC, investigators agreed that individuals may have some anxiety about writing their signature or placing their thumbprint on a formal document because of uncertainties about whether the document could be used against them. One investigator noted the following: "Even if they use a thumbprint, they [can] get suspicious. They can't read so they wonder why [you need their thumbprint]. It's a big fear...the issue [has to do with] government documents. [It's threatening] because they don't know what they are signing or what they might be 'giving away.'"[43]

preparatory sessions conducted with potential participants (Rodenhuis et al. 1984; Sánchez et al. 1998; Tomamichel et al. 1995). For example, in approving protocols, IRBs may waive documentation of informed consent through a signature or a thumbprint, provided that the researchers provide adequate justification for the waiver and ensure adherence to the substantive ethical standard of informed consent. It is NBAC's view that in such cases, the justification, while important, also must pass public scrutiny, and we would encourage a process by which these waivers were audited by a competent body. Commentators to NBAC remarked that waivers of written consent documentation should include safeguards to ensure that individual consent is obtained. The FDA requires that clinical trial data entail some form of documentation of the consent process (21 CFR 312.62(b) and 21 CFR 812.140(a)(3)(i)), which means that an alternative form of documentation is needed for those trials submitted to the FDA that do not use individual signed consent forms. At the same time, more information is needed to determine the extent and magnitude of cultural differences in the informed consent process.

Recommendation 3.11: **U.S. research regulations should be amended to permit ethics review committees to waive the requirements for written and signed consent documents in accordance with local cultural norms. Ethics review committees should grant such waivers only if the research protocol specifies how the researchers and others could verify that research participants have given their voluntary informed consent.**

Recommendation 3.12: **The National Institutes of Health, the Centers for Disease Control and Prevention, and other U.S. departments and agencies should support research that addresses specifically the informed consent process in various cultural settings. In addition, those U.S. departments and agencies that conduct international research should sponsor workshops and conferences during which international researchers can share their knowledge of the informed consent process.**

Conclusions

In many countries, cultural barriers can prevent the informed consent process from being conducted in precisely the same way stipulated by U.S. research regulations. Investigators can, however, for the most part overcome these barriers without violating the substantive ethical standard that requires them to obtain individual and voluntary informed consent from competent research participants. One mechanism for addressing problems in a culturally sensitive way—without compromising ethical standards for obtaining voluntary informed consent—is to work collaboratively with the community in which the research will be carried out. Informing and educating the local community before the research begins can be helpful in recruiting volunteers and ensuring that this recruitment is noncoercive. Community education and consultation are important in protecting the rights of potential participants during recruitment, in promoting their understanding of the research, and in providing additional information about the study when relevant and necessary.

During the course of its deliberations, NBAC found that there is a great deal of support in developing countries for the requirement of voluntary, individual informed consent. The surveys conducted by Kass and Hyder lend considerable support to the view that both developed and developing country researchers view the requirement to obtain voluntary informed consent as a critical ethical standard. Adherence to this standard requires that researchers disclose relevant information, take steps to determine that potential participants understand what they have been told, and ensure that each individual's consent is voluntary. Nevertheless, for some customs and traditions, some of the specific procedures related to the process and documentation of informed consent as stipulated in the U.S. regulations must be modified. These procedures should be sufficiently flexible to be adapted for use in various developing countries. The requirements of written consent and the participant's signature, mark, or thumbprint on consent forms are procedures that ethics review committees should be allowed to waive when researchers provide adequate justification for such waivers.

Every competent adult should be able to decide freely whether to participate in research, a position adopted in previous NBAC reports (NBAC 1998; NBAC 1999). Those who wish to cede that decision to another should be able to do so, but the initial choice is still theirs. Often, personal and local circumstances complicate this choice, and many obstacles remain to achieving an ideal process. Nevertheless, adherence to a country's customs and traditions need not compromise the ethical standard of informed consent. In some circumstances, researchers should have greater flexibility in determining how they inform participants about the research and in the methods they use to document consent. In addition, potential participants may wish to involve family members in their decision to participate, and researchers may need to obtain a community leader's permission before approaching individuals in the recruitment process. NBAC believes that these recommendations represent only the first steps toward eventually reaching a point at which every competent individual, based on adequate information, can voluntarily make his or her own decision about participating in research.

Notes

1 The material in this chapter benefited from reports prepared by several NBAC consultants, articles published in the literature, and two unpublished studies provided to NBAC by researchers from South America (Hardy et al. 1998; Sánchez et al. 1998). The consultants' reports are as follows: 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.

2 We acknowledge that the principle of respect for persons also permits the foregoing of voluntary informed consent in certain situations, such as research involving those who lack the capacity to give consent, research involving only minimal risk, or emergency research. These areas pose their own unique issues, which will not be addressed in this report.

3 See Kass and Hyder; Marshall; and Sugarman et al.

4 See Sugarman et al., 10.

5 From data collected by Kass, N., and L. Dawson, 1999, *Preliminary Focus Group Report*, 9. For Kass, N., and A. Hyder, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations."

6 See Marshall, 18.

7 Plowe, C., Testimony before NBAC. February 29, 2000. Herndon, Virginia; Pape, J.P., Testimony before NBAC. February 29, 2000. Herndon, Virginia.

8 See Sugarman et al., 17.

9 See Kass and Hyder.

10 See Marshall, 34.

11 Sommer, A., Testimony before NBAC. September 16, 1999. Arlington, Virginia. Meeting transcript, 214.

12 See Kass and Hyder, 6.

13 See Marshall, 17.

14 Pape, J.P., Testimony before NBAC. February 29, 2000. Herndon, Virginia.

15 Ibid., 32.

16 See Marshall, 15.

17 Plowe, C., Testimony before NBAC. February 29, 2000. Herndon, Virginia. Meeting transcript, 151.

18 Pape, J.P., Testimony before NBAC. February 29, 2000. Herndon, Virginia.

19 See Kass and Hyder.

20 From data collected by Kass, N., and L. Dawson, 1999, *Preliminary Focus Group Report*. For Kass, N., and A. Hyder, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations."

21 See Kass and Hyder, 43.

22 From data collected by Kass, N., and L. Dawson, 1999, *Preliminary Focus Group Report*, 8. For Kass, N., and A. Hyder, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations."

23 See Marshall, 34.

24 Ibid., 22.

25 From data collected by Kass, N., and L. Dawson, 1999, *Preliminary Focus Group Report*, 1. For Kass, N., and A. Hyder, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations."

26 Plowe, C., Testimony before NBAC. February 29, 2000. Herndon, Virginia.

27 See Kass and Hyder, 43.

28 Sugarman and colleagues state that "investigators in one country repeatedly noted that patients who might be asked to enroll in a medical study would be skeptical of an investigator who did not involve the family in the decision making process." See Sugarman et al., 9.

29 See Marshall, 28.

30 The Constitution of the Republic of Uganda. Available at www.federo.com/Pages/Uganda_Constitution_1995.htm. Last accessed January 12, 2001.

31 Loue, S., Testimony before NBAC. October 21, 1999. Washington, D.C.

32 Plowe, C., Testimony before NBAC. February 29, 2000. Herndon, Virginia. Meeting transcript, 106.

33 See Kass and Hyder, 56.

34 Ibid., 57.

35 This same principle is implicit in 45 CFR 46.111(a)(1), stating that in reviewing research, IRBs must determine that risks to subjects are minimized.

36 See Kass and Hyder, 41.

37 Ibid.

38 See Sugarman et al., 11.

39 Loue, S., Testimony before NBAC. October 21, 1999. Washington, D.C. Meeting transcript, 28–29, 40.

40 Pape, J.P., Testimony before NBAC. February 29, 2000. Herndon, Virginia. Meeting transcript, 32.

41 Malenga, G., Testimony before NBAC. February 29, 2000. Herndon, Virginia. Meeting transcript, 61.

42 See Marshall, 24.

43 Ibid., 26.

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Chapter Four

When Research Is Concluded—Access to the Benefits of Research by Participants, Communities, and Countries

Introduction

Discussions of the ethics of research involving human beings usually center on issues regarding research design and approval and how individuals' rights and welfare are protected when they are enrolled in research protocols. The same has been true of the application of the Common Rule, which addresses only tangentially what happens after a research project has ended by requiring that research participants must be informed in advance about what benefits (in the form of a proven effective medical intervention), if any, will be provided if they are injured during the course of the research. (At the risk of creating semantic confusion, post-trial medical interventions are conventionally—and frequently in this report—described generically as "benefits.") Other questions about what should happen after a trial is completed are left unaddressed by U.S. guidelines. In the context of domestic research, this oversight is understandable. Although ethical issues certainly arise when many have no guarantee of access to an adequate level of health care services (which is true today for an estimated 44 million Americans, who lack public or private health insurance, to say nothing of the millions more whose insurance plans [including Medicare] do not adequately cover the cost of drugs and medical devices), these issues are usually related to access to health care services, not the ethics of health research.

In recent years, however, as research sponsored by government agencies, foundations, and private companies in developed countries increasingly has been conducted in developing countries, officials in some of these countries—as well as leaders of international bodies concerned with research ethics—have begun to insist that the ethics of research address what happens when a study ends. The questions raised—such as *what should be provided to research participants, and by whom, after their participation in a trial has ended, and what, if anything, should be made available to others in the host community or country?*—have obvious implications for domestic research as well, especially when such research is carried out among members of economically disadvantaged and/or socially or geographically isolated groups. But the questions of post-trial obligations have been raised first, and most urgently, in the context addressed by this report—that is, clinical trials conducted in developing countries by researchers and sponsors from the United States and other developed countries.

This concern springs from the stark reality that in many developing countries, a large portion of the population lives in poverty and cannot pay for needed health care services, and the government cannot provide for their health care needs. Consequently, the governments of and most people who live in the developing countries where new medical interventions have been tested cannot afford them. Indeed, a survey commissioned by the National Bioethics Advisory Commission (NBAC) of researchers from the United States and abroad conducted by Nancy Kass and Adnan Hyder revealed that 33 percent of the U.S. researchers and 48 percent of researchers abroad believe that the interventions being tested in their research are unlikely to be available to most host country residents in the foreseeable future.[1] Furthermore, data

provided by clinical trials in poor nations are sometimes important for the development and approval of new drugs, biologics, and devices in wealthy nations whose citizens therefore derive benefits that remain unavailable to those who live in the very nations where the trials were conducted. A researcher from a developing country who participated in an NBAC survey summarized the deeply problematic nature of this situation by saying that "[i]t should be made a requirement that [if developing country] research involving testing of drugs and other interventions [is] found efficacious, the participating populations should be among the first ones to benefit, at affordable costs."[2]

In addressing the topic of post-trial obligations, NBAC realizes that any changes in government policy should take into account a host of specific contextual factors, such as the following:

- Who is entitled to receive what benefits?
- What benefits should be provided to participants after the trial is completed—the intervention being tested, another intervention for the same condition, or some unrelated medical or nonmedical good that is relevant to a significant problem in the host country?
- How is what should be provided to participants affected by the outcome of the clinical trial? Specifically, is the obligation to provide post-trial benefits stronger when a pivotal clinical trial shows a statistically and clinically significant superiority of outcomes in the intervention group than when the evidence of benefit and safety is weaker?
- What is the cost of providing continued access to the intervention, and who is responsible for providing it?
- What mechanisms should be used to implement this responsibility, and how might these differ, depending on whether the research sponsor is an international pharmaceutical company eager to develop a new product for the world market, a government agency or nonprofit foundation responding to a request for funds from a group of investigators, the host country itself, or some combination of these or other sponsors?

Whether the concern is continuing a research intervention for participants after a trial has ended or making an intervention more widely available within the host country, certain issues must be addressed. For example, deciding when a particular trial has demonstrated a new intervention's effectiveness will seldom be a simple matter, and those who are trying to provide access to post-trial benefits must confront a number of economic and practical barriers in many developing countries. But in other respects, the issues regarding continuing benefits for research participants differ sufficiently from those regarding ensuring access for others in the host country that they require separate treatment.

Obligations to Research Participants

The obligations of sponsors and investigators to research participants have always been of central importance in research ethics. Over the years, these obligations—such as ensuring equitable selection of participants, minimizing risks and ensuring that they are reasonable in relation to potential benefits, and obtaining voluntary informed consent—have been formalized in government regulations and in international and professional guidelines. In a previous report, NBAC explored the issue of post-trial obligations to a particular group of patients involved in research studies and concluded that medical follow-up is warranted for research participants with mental disorders (NBAC 1998).

Should this position be generalized to other research participants, especially in developing countries? In recent years, a number of international organizations and national research regulators have moved in this direction. For example, in November 2000, the World Medical Association (WMA) adopted the latest revision of the *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*, which for the past three decades has been the most widely recognized statement of ethical principles for research involving human beings. For the first time, the *Declaration* contains a provision concerning the need for some benefits to accrue to research participants. Principle 30 states that "[a]t 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" (WMA 1964, as amended in 2000).

National guidelines on research have also recently begun to address the post-trial obligations of sponsors and researchers to participants. The requirements promulgated

thus far by developed nations have been modest, simply indicating that access issues should be dealt with before the start of research rather than imposing an affirmative obligation to make interventions available. In the United Kingdom, the Medical Research Council's (MRC's) *Interim Guidelines for Research Involving Human Participants in Developing Societies: Ethical Guidelines for MRC-Sponsored Studies* states that "[i]n anticipation of any beneficial results of therapeutic research, there should normally be discussion in advance with relevant parties in the developing society...about subsequent availability of the relevant product to local inhabitants" (MRC-UK 1999, Specific Consideration 9). Canada's *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* provides that the research ethics board should examine "the issue of continuing access after the trial" (MRC-CA, NSERC, and SSHRC 1998, Commentary to Article 7.2). Similarly, the guidelines issued by some nations that host research have begun to address such post-trial obligations. For example, South African guidelines refer directly to the availability of treatment to research participants after a trial is completed:

> The arrangements, *if any*, for continuing to supply the superior treatment, *if any*, after the end of the study should be known at the beginning of the study and declared to all potential participants. Any special arrangements should be honored. Participants do not have the right to claim ongoing treatment with a new unlicensed medicine unless special arrangements have been made at the time of the trial (MRC-SA 1993, Sect. 10).

Guidelines from other developing nations have taken the next step; they do not merely insist that the issue be addressed, but they impose affirmative obligations to provide effective interventions to research participants and in some cases to the general population as well. For example, the Ugandan document *Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda* obliges investigators to "make every effort to ensure its [an effective intervention, if available] provision, without charge, to participants in the trial following the conclusion of the trial" (National Consensus Conference 1997, Sect. V. Part D. 4). In Brazil, the National Health Council (NHC) approved a resolution that "research involving human subjects...must...ensure the research subjects the benefits resulting from the research project, in terms of social return, access to procedures, products or research agents" (NHC 1996, III.3(p)). The resolution also provides that "in case of research conducted abroad or with external cooperation" evidence "of commitments and advantages to the research subjects and to Brazil, which will result from the implementation of the research" must be submitted (NHC 1996). Another resolution states that "...access to the medicine being tested must be assured by the sponsor or by the institution, researcher, or promoter...in the event its superiority to the conventional treatment is proven" (NHC 1997, IV.1(m)).

In addition to the *Declaration of Helsinki*, other international documents make recommendations that would impose post-trial obligations. The Joint United Nations Programme on HIV/AIDS (UNAIDS) was the first organization to make recommendations that explicitly focus on resolving drug access problems as part of international collaborative research. Not only does the UNAIDS document *Ethical Considerations in HIV Preventive Vaccine Research* endorse the notion that planning for the availability of the proven intervention must begin before the start of the research, it also identifies in general terms the parties that should be part of that process and the issues that need to be addressed. Guidance Point 2 states that "[a]ny HIV preventive vaccine demonstrated to be safe and effective...should be made available as soon as possible to all participants in the trials in which it was tested....Plans should be developed at the initial stages of HIV vaccine development to ensure such availability." The document further explains that "[a]t a minimum, the parties directly concerned should begin this discussion before the trials commence" (UNAIDS 2000, 13–14).

What are some other reasons to recognize the obligation to care for research participants after a clinical trial has been completed? One source of support for doing so comes from researchers themselves. The Kass/Hyder survey revealed that a substantial percentage of the researchers surveyed had plans to distribute interventions that were proven effective to some participants at the conclusion of the research; 43 percent of U.S. researchers surveyed and 32 percent of developing country researchers surveyed planned to distribute the

intervention to the entire study population at the conclusion of the study. About a third of the researchers surveyed planned to provide the intervention to participants for two to five years, and another third for more than five years.[3] One U.S. researcher described plans made by the research team to provide medication to study participants:

> I would feel uncomfortable if I thought there was no chance what we were doing would be of benefit to that country. It doesn't have to be a benefit to that country the day the study ends. The day the study ends, though, I do think that all the participants in the trial should have the benefit of whatever was found to be the best therapy....We had made provisions for them not to just get [experimental treatment], but to get the [existing treatment] they were going to be placed on...indefinitely.[4]

Besides the examples of other nations and the beliefs of researchers, a number of reasons have been offered to justify the claim that participants should receive needed interventions that have been proven effective as a result of their research participation. Two prominent perspectives involve the nature of the special relationship that exists between researchers and research participants and the application of the concept of *justice as reciprocity*.

The Researcher-Participant Relationship

Ethicists have struggled to distinguish the researcher-participant relationship from the physician-patient relationship, because of concern regarding researchers' competing obligations to sponsors, institutions, and science that may affect the care they can offer participants. Indeed, such conflicts provide much of the rationale for the development of the federal regulations that are designed to protect human research participants. Furthermore, commentators have noted that problems arise when research participants in protocols that concern diseases or conditions that affect them directly think of themselves as the recipients of health care services rather than as research subjects. The trust that potential participants place in the medical profession undoubtedly affects their willingness to participate. Recognizing the resulting complications for the informed consent process, Chapter 3 of this report—and other work being undertaken by the Commission—suggests some mechanisms for minimizing the therapeutic misconception.

Although these efforts to distinguish research from treatment are appropriate, it is clear that participation in a clinical trial resembles treatment because the health status of participants may be altered by their participation. Consequently, if all intervention by the research team ends when the trial is over, participants may experience a loss and feel that the researchers in their clinical role have abandoned them. This sense of loss can take several forms. The starkest form arises when participants in a clinical trial are worse off at the conclusion of the trial than they were before it began. Being worse off does not mean that they were harmed by the research. It can simply mean that their medical condition has deteriorated because they were in the less advantageous arm of the protocol. Such an outcome—particularly when participants are worse off than they would have been had they received standard treatment or if they had been in the other arm of the trial—underlines the extent to which any research project can depart from the Hippocratic goal of "do no harm," despite the best intentions and efforts of all concerned. When such a result occurs, efforts to restore participants to at least their pretrial status could be regarded as attempts to reverse a result that would otherwise be at odds with the ethical principles of nonmaleficence and beneficence.

Ironically, people who have benefited from an experimental intervention may also experience a loss if the intervention is discontinued when the project ends. It might be said that this is a risk the participants accept by enrolling in the trial. But participants who are ill when they enter the research protocol may not be able to appreciate fully how they will feel when they face a deterioration in their medical condition (once the trial is completed) after having first experienced an improvement, even if the net result is a return to the status quo ante. One way to mediate or reduce the burden of such an *existential loss* (the experience of loss as perceived by the research participant) and to sustain an appropriate level of trust between potential participants and the research enterprise is to continue to provide to research participants an intervention that has been shown to be

efficacious in the clinical trial if they still need it when the trial is over.

Although the need to respond to the sorts of losses experienced by participants provides one justification for recognizing an obligation to continue to care for participants after a trial ends, many questions remain regarding the scope of the obligation as well as the circumstances in which it applies. For example, considerations of how effective an intervention is shown to be or the seriousness and clinical trajectory of the underlying condition clearly are pertinent factors. It seems reasonable to conclude that the greater and clearer the health benefit to participants, the stronger the obligation. Another issue is whether the relationship with the researcher, rather than the provision of the intervention, should continue. There is considerable evidence that a major benefit of being in a clinical trial derives from the quality of general care provided by the research team, not just the experimental intervention. Yet, it is doubtful that merely recognizing the value of the clinical activities that are inherent in the researcher-participant relationship is compelling enough to generate an open-ended obligation to provide all medical care—regardless of its relevance to the research—to participants indefinitely.

Justice as Reciprocity

Another perspective that is said to provide a justification for the provision of post-trial medical interventions to research participants arises from considerations of justice. Justice is a broad concept, encompassing several more specific concepts. Broadly, questions of justice ask, "What does this individual or group deserve?" One familiar conception of justice is *distributive justice*, which deals with the fair allocation of society's benefits and burdens. In the research context, distributive justice requires that no group or social class be disproportionately exposed to the risks and inconveniences of serving as participants in research that aims to develop medical interventions to benefit the entire population.

Justice as reciprocity, on the other hand, is concerned with what people deserve as a function of what they have contributed to an enterprise or to society. In the context of clinical trials, justice as reciprocity could mean that something is owed to research participants even after their participation in a trial has ended, because it is only through their acceptance of risk and inconvenience that researchers are able to generate findings necessary to advance knowledge and develop new medical interventions. Of course, the sense that they have made a contribution is especially strong at the completion of a successful trial—that is, one that establishes the efficacy and safety of an intervention. Yet, negative results also can be important in research, and the case for obligations of reciprocity may actually be stronger for those who participate in a trial in which the intervention has not been proven effective, because these participants are less likely to have benefited from their involvement.

Several problems are involved in the application of justice as reciprocity to clinical trials in developing countries. First, when post-trial treatment has not been promised to individuals, the fact that the trial has produced a success does not itself generate an obligation to go beyond the terms accepted by the participants when they enrolled. Although a sense of gratitude to participants under such circumstances would be understandable, this is not the same as an obligation to continue to provide the intervention when the study is over. Because the argument for reciprocity rests on the willingness of research participants to sacrifice their time (and even their well-being) to help advance knowledge, what is owed them can be no greater than what is owed those who made the same gift to a research project that may not have proved a particular medical innovation to be successful. Thus, if there is an argument in favor of "repaying" participants in a successful trial (one that resulted in an effective intervention) by continuing to provide the intervention after the trial is over, while not doing the same for participants in earlier trials, which, although unsuccessful, contributed to the eventual development of the effective intervention, it would appear to be a practical one. Difficulties in identifying participants in earlier unsuccessful trials and delivering the intervention to them, perhaps years after a trial is completed, might present obstacles that cannot reasonably be overcome.

A different problem would arise if applying the principle of reciprocity led to the inclusion of post-trial interventions in the initial design of the project. Indeed, great care must be exercised in this regard. On the one hand,

making a commitment to provide interventions to those who participated in establishing their value would overcome the argument that participants' initial consent negates the claim that they deserve a reciprocal gift from the researcher: If post-trial benefits are part of the inducement to participate, they would, of course, need to be provided. (Although this provision would in the first instance simply honor the contract between researcher and participant, in a deeper sense, including the post-trial benefit in the research plan could be said to reflect the need to reciprocate for what the participants are giving to the research.) On the other hand, the promise to continue to provide a successful intervention after the trial may exacerbate the therapeutic misconception and, in certain instances, even amount to an undue inducement to potential participants to enroll in the research. Indeed, in its examination of the general rules for research, NBAC has taken the position that in comparing the expected risks and benefits of research protocols, ethics review committees should exclude any potential post-trial interventions from the category of benefits.

If the cautions about the therapeutic misconception lead researchers to omit any mention of post-trial benefits from the informed consent process (which is not inconsistent with discussing the possibility of such benefits with research sponsors, the ethics review committee, and representatives of the host country), is there any room to apply the concept of justice as reciprocity when, in fact, a research project has established the value of an intervention? As with the effect of the researcher-participant relationship, where it seems reasonable to conclude that at the outset of research, participants cannot fully anticipate the loss they might experience when all interventions cease at the end of the trial, it also may be difficult in advance for either participants or researchers to fully appreciate the sense of injustice that would arise if participants were left in need while others (the researchers as well as patients who will receive the newly proven intervention) benefited from the success to which the participants had made such an essential contribution. In such circumstances, a narrow reading of the relevant obligations would surely be met with the question, "Don't they deserve better treatment than this?" That question is likely to become even more powerful in cases in which participants in a poor country already face many hardships and the beneficiaries of the research are patients, scientists, and companies in a wealthy country, such as the United States. It is unjust to deny them benefits based on the argument of justice as reciprocity. But it is also unjust because participants in these studies (especially studies that are shown to produce a benefit retrospectively) may be disadvantaged by the unequal relationship that exists between themselves and others (e.g., their own country's officials who approved the project, the foreign sponsors, the researchers).

Thus, although the strength of the obligation depends on the specific circumstances of a clinical trial, situations will arise in which a fair reading of justice as reciprocity would lead to the conclusion that participants are due some benefit at the end of the trial commensurate with what they have contributed. Yet, recognizing the justification for such an obligation is not the same as specifying the nature of the benefit itself. Some commentators have argued that it is particularly appropriate that the benefit should relate directly to the interventions studied in the research project. Making the benefit responsive to the health needs of the participants provides an additional way to ensure that research participants are not exploited. But given the considerable variations in local context, the presumption in favor of this form of compensation probably should not be mandatory and might be overridden if those who can speak with moral authority for the host community present good reasons why alternative forms of compensation would provide a more appropriate benefit. The notion that there should be some intrinsic connection between what people have contributed by participating in the research and what is returned to them opens the door to the provision, for example, of other health care services of comparable value to the newly proven intervention, while not allowing some other good—such as a new soccer stadium—to be regarded as appropriate.

The difference between justifying post-trial obligations to participants based on the moral nature of the researcher-participant relationship and justifying such obligations based on justice as reciprocity is illuminated by comparing what is owed to participants in a control group who did not receive the experimental intervention and what is owed to those who did receive the intervention. Although justice as reciprocity would lead to treating

the two groups similarly because both suffer from the illness and undertook the risks of research, what is owed the two groups from the perspective of the researcher-participant relationship could differ. This is because only the participants who actually benefited would experience a loss if the intervention were discontinued. Of course, if the experimental intervention turns out to be ineffective, and a control group in the study received an established effective treatment, then those in the control group would experience loss at the end of the trial. This leads to the question of whether those in the experimental group should be provided with the established effective treatment that benefited the control group. Responding to these dilemmas—for which there are no easy solutions—depends on the context of each research project. At the very least, it would be highly desirable if collaborating parties in international research negotiated and reached agreements in advance on this and similar issues. Because potential participants are most affected by the research and its aftermath, researchers should consider including representatives from the community being studied in these negotiations and agreements.

What Should Be Provided to Communities and Countries?

Once it is recognized that research projects should sometimes arrange to provide post-trial benefits to participants, a question arises about the justice of differentiating between former trial participants and others in the host community who need similar medical treatments. A competing concept of justice—typically referred to as the principle of fairness—is to *treat like cases alike, and treat different cases differently*. To implement this concept, the equivalence of persons or situations must be determined. For example, should family members (or others) who suffer from the same illness as participants be treated as like cases with respect to receiving an effective treatment? Similarly, are the claims to treatment of people who were eligible for and willing to participant in a clinical trial but who for any number of reasons were not selected comparable to the claims of those who were selected? Or are such cases not sufficiently similar because participants undertook the risks and experienced the inconveniences of the research?

In NBAC's view, the relevant distinction between research participants and these other groups of individuals is that research participants are exposed to the risks and inconveniences of the study. Moreover, a relationship grounded in trust and care exists between participants and researchers that does not exist for others. The concept of justice as reciprocity addresses what people deserve as a function of what they have contributed to an enterprise or to society and the related risks that they undertook. These ethical considerations support the argument for providing effective interventions to research participants after a trial is completed.

On what basis then can one justify an ethical obligation to make otherwise unaffordable (or undeliverable) effective interventions available to members of the broader community or host country? Given that global inequities in wealth and resources are so vast, expecting governmental or industrial research sponsors to seek to redress this particular global inequity is unfair and unrealistic, especially when no such requirement exists in other spheres of international relationships. Typically, it is not the primary purpose of clinical trials to seek to redress these inequities.

Some have urged, however, that those who sponsor and conduct research are obligated to provide effective interventions after a study is completed to the population from which the research participants were drawn. One group of commentators offers the following rationale for this position:

> Research is, by definition, designed to create generalizable knowledge, and is legitimate in a developing country only if its purpose is to create generalizable knowledge that will benefit the citizens of that country. If the research only has the potential to benefit the limited number of individuals who participate in the study, it cannot offer the benefit to the underdeveloped country that legitimizes the use of its citizens as research subjects. It should be emphasized that research whose goal is to prevent or treat large populations is fundamentally public health research, and public health research makes no sense (and thus should not be done) if its benefits are limited to the small population of research subjects (Glantz et al. 1998, 41).

Grace Malenga, a researcher from Malawi, testified before NBAC about clinical trials conducted in her country in which mefloquine was found to be more effective against malaria than either quinine or chloroquine; however, 20 years after the study was completed, mefloquine has yet to be used there.[5] Christopher Plowe, a malaria researcher from the United States, expressed a similar view. When asked if he thought whether there is an ethical obligation to provide some benefit to the country in which the research is conducted, Plowe testified that he would have questions about conducting a mefloquine study in Malawi, knowing that it would remain very expensive and thus inaccessible in that country.[6] In contrast, a more cost-effective and efficacious anti-malarial study involving sulfadoxine-pyrimethamine was completed in Malawi in early 1992. This study regimen has been implemented as national policy by the Malawi Ministry of Health (Schultz et al. 1996).

A number of international and national guidelines recognize post-trial obligations to host communities and countries. The commentaries under the Council for International Organizations of Medical Sciences (CIOMS) *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Guideline 8, "Research Involving Subjects in Underdeveloped Communities," and Guideline 15, "Obligations of Sponsoring and Host Countries," provide support for the obligation of sponsors to make the products of research available. The language used in the two commentaries is similar. Although they both provide that, as a general rule, effective interventions developed through research should be made "reasonably available," the guidelines are inconsistent in specifying who should be the recipients of such products. Commentary from Guideline 8 refers to "inhabitants of the underdeveloped community in which the research was carried out" (CIOMS 1993, 26), while Guideline 15 refers to "the inhabitants of the host community or country" (CIOMS 1993, 45). Both guidelines also indicate that the agreement to provide effective interventions after completion of the study (or to make exceptions to the general rule) should be reached in advance of the research (CIOMS 1993). Later, this chapter will address in more detail the issue of prior agreements. Regarding the "reasonable availability" clause, although considerable discussion has occurred about its meaning and how it should be applied, to date no consensus has been reached.

Another international document, the World Health Organization's (WHO's) *Operational Guidelines for Ethics Committees That Review Biomedical Research*, refers to the consideration of the availability of successful interventions in the host community in the ethics review process. The document states that "a description of the availability and affordability of any successful study product to the concerned communities following the research" should be considered as part of the ethical review process (WHO 2000, para. 6.2.6.6). The UNAIDS *Guidance Document* provides that effective HIV vaccines should be made available not only to research participants, but also "to other populations at high risk of HIV infection" (UNAIDS 2000, 12).

Finally, the recently revised *Declaration of Helsinki* contains a new provision concerning the need for the accrual of some potential benefit to the population in which the research is conducted. Principle 19 states that "[m]edical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research" as well (WMA 1964, as amended in 2000).

As noted earlier, the document *Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda* makes a distinction between the post-trial obligations owed by investigators to research participants and to the host community. In contrast to the investigator's charge to make "every effort to ensure its provision" to participants following the conclusion of the trial, in the case of the local community in which the research occurred, "the investigator shall make a reasonable effort to secure the product's availability" (National Consensus Conference 1997, Sect. V. Part D.4).

Several provisions from Brazil addressing access to benefits by participants and others were discussed earlier in this chapter. However, there is another provision in the 1996 resolution that states that research should "guarantee the individuals and communities where the research was undertaken a return on the benefits obtained in the research" (NHC 1996, III.3 (n)).

This discussion about documents that support the idea of post-trial obligations to the host community or country also should include the *Belmont Report: Ethical*

Principles and Guidelines for the Protection of Human Subjects of Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission 1979) and the *Statement on Benefit Sharing* of the Ethics Committee of the Human Genome Organisation (HUGO 2000) (the international organization of scientists involved in the Human Genome Project—the global initiative to map and sequence the human genome). Chapter 1 of the *Belmont Report* sets forth the "responsive-to-needs" requirement as a manifestation of the core ethical principles of beneficence and respect for persons. The justification for requiring that research be responsive to the health needs of the population involved in it also rests on a concept of justice that was articulated by the National Commission as the third basic tenet of research ethics. In conjunction with its discussion of justice and the distribution of the benefits and burdens of research, the *Belmont Report* touches indirectly on the issue of making effective interventions available to those populations upon which they were tested:

> [W]henever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research (National Commission 1979, 10).

The *Belmont Report's* concept of justice encompasses the prospect of making effective interventions available to a population that is larger than that of the research participants, whether the population is a poor group within a wealthy society or one that lives in a developing country and is participating in a study sponsored and/or conducted by a developed country.

The Ethics Committee of HUGO in April 2000 issued a *Statement on Benefit Sharing*, which recommends that "all humanity," not just research participants, share in the benefits of genetic research. The statement resulted from the recognition that "expenditures by private industry for genetic research now exceed the contributions of governments" (HUGO 2000, Section A). The Ethics Committee recommended prior discussion with individuals and communities about benefit sharing, including "consideration of affordability and accessibility of eventual therapy, and preventive and diagnostic products of research" (HUGO 2000, Section G). It further recommended that for-profit entities engaging in genetic research donate a percentage of their annual net profit "to the health care infrastructure or for vaccines, tests, drugs, and treatments, or to local, national, and international humanitarian efforts" (HUGO 2000, Section G).

NBAC believes that an ethical obligation to make effective interventions available to the developing host country arises from the concept of distributive justice, which refers to a fair and equitable distribution of social benefits and burdens. In the research context, distributive justice demands that no one group or class of persons assumes the risks and inconveniences of research if that group or class is unlikely to benefit from the fruits of that research. When research is conducted in the developing world, the huge power disparity between rich and poor nations manifests itself in two ways. In most cases, the developed world sets the research agenda and carries out the research. The involvement of developing countries in these activities is generally still limited (although it is gradually changing), and in only a few instances do they function as full and equal partners in either respect. Moreover, although it assumes very few of the burdens of research, the developed world receives the great majority—and in some cases, all—of its benefits because it can afford to buy the interventions that are proven to be effective. The burdens of research, in contrast, are borne by developing countries whose poorest inhabitants serve as research participants, but these countries rarely share the benefits, because many interventions are beyond the economic reach of both the research participants and their governments. Under these circumstances, the concept of distributive justice supports a fair and equitable distribution of research benefits to the host community or country. However, crafting practical and economically feasible solutions that support distributive justice in research conducted in the developing world is one of the most difficult challenges in international research.

Data suggest that in international research, post-trial benefits are being provided to developing countries. In

the Kass/Hyder survey of U.S. and developing country researchers, 29 percent of U.S. and 22 percent of developing country respondents stated that the intervention being tested in their study would be available to the entire host country at the conclusion of the research.[7] Researchers listed a variety of parties to these agreements for making the interventions available as well as different sources of funds, including those from U.S. and international funding agencies as well as host country governments. Clearly, in some cases, plans for providing effective interventions to host countries can be negotiated before the research ends; however, further work in this area is needed to implement and expand successful strategies.

Who Should Provide Post-Trial Benefits?

Determining *who* should be responsible for providing post-trial benefits to research participants and host communities or countries is an especially difficult problem. This report has referred generally to the obligations of researchers or sponsors. But it is evident that these categories cover a diverse set of individuals and entities, with different resources, roles, and responsibilities in the research process. These differences will influence the nature of the obligations that each party should shoulder.

Obligations of Researchers

Although individual researchers do not usually have either the resources or the authority to directly provide post-trial benefits to participants or host countries, they can play an important role in helping to ensure that such arrangements are in place. As described earlier, the researcher-participant relationship gives rise to certain obligations regarding how participants are treated before and during a clinical trial, but these obligations generally do not extend to the post-trial distribution of resources and the economic, social, and health policy implications of such activities.

In NBAC's view, however, the post-trial obligations of researchers do extend to some kind of an advocacy role. The researcher's basic and generally accepted responsibility is to respect the participants (and the community they represent) by informing them about the research and their role in it, obtaining meaningful consent, enrolling participants in clinical trials only when there is a reasonable balance between risk and potential benefits, and designing the study in such a way that it addresses a pressing health problem.

Researchers can further fulfill their ethical obligation to participants and host countries by ensuring that the issue of access to effective interventions and other post-trial benefits is considered at each stage of the research process, especially the planning and design stages. This means discussing with relevant parties the potential for making effective interventions available and serving as an advocate, assuming that the trial results are positive. This does not mean that researchers must negotiate directly with host country governments or international agencies, although they may make recommendations and serve as consultants. This advocacy role follows from the researcher's specialized knowledge and expertise about the diseases being studied, his or her understanding of who might benefit from or be harmed by particular interventions, and his or her commitment to the participants and to the research process. Consideration, therefore, should be given to including researchers as parties in the process of negotiating post-trial benefits.

Obligations of Public and Private Research Sponsors and Others

Given that most researchers are not able themselves to ensure that research participants and others in the host community obtain post-trial benefits, consideration should be given to whether that burden would fall most appropriately on research sponsors. There are many types of research sponsors—ministries of health in the host country, federal research agencies, nonprofit organizations, and private corporations—each of which supports research in different ways and for different reasons. Thus, it is important to consider what motivates sponsors. Government sponsors are accountable to their citizens for the use of public funds for research. Often they are motivated by a desire to advance and promote the public's health. In addition, they may wish to assist other countries in addressing their health concerns. Their ability to commit support for future benefits may be

constrained, however, by their annual cycle of legislative appropriations or other factors. Charities and philanthropies also are motivated by a desire to advance and protect the public's health, but these organizations may not wish to or be able to assume future obligations to provide post-trial benefits. Private sponsors, and industry in particular, are driven by an interest in maximizing benefits to their shareholders, customers, or clients, and these organizations may not feel any obligation or be able to provide post-trial benefits. In addition, the types and numbers of sponsors vary greatly across clinical trials. Many trials involve multiple sponsors—some U.S. government sponsors and others private companies. Still other studies involve multiple sponsors from different countries, in which the distinction between public and private sponsors is not made in the same way as it is in the United States. In still other clinical trials, the sponsor's involvement is limited to providing funds directly to the project rather than to an institution.

Despite these variations, general support exists for the proposition that the obligation should be placed on the sponsors and/or researchers to make effective interventions available to a host country or community after a study is completed. If one accepts NBAC's justification for conducting research in developing countries—that the research will offer some prospect of direct benefit to the population from which research participants will be drawn—then that justification provides a strong basis for also accepting the claim that researchers and sponsors should play a significant role in making arrangements to provide post-trial benefits to the host country.

International researchers participating in focus groups conducted for NBAC expressed a strong belief that effective interventions should be implemented in the host countries and that U.S. or other foreign sponsors have an obligation to give something back to their host countries. Yet, U.S. researchers surveyed for this report worried that, over time, an absolute requirement to provide effective interventions to host countries would act as an impediment to finding sponsors that are willing to support research and thus might harm developing countries by delaying or preventing beneficial research.[8] One U.S. researcher suggested that an assessment should always be made about the economic feasibility of implementing a particular intervention:

> There is the issue of scope, in both place and time—for how long should the intervention be implemented with outside assistance? Should it cover the original study population, the whole country, or what? I feel strongly that only interventions which have a hope of being replicable in the prevailing conditions should be tried in the first place—that's where the economic work should come in, and at the very beginning, not as an add-on. No research funding agency would accept funding with a blank check for implementation of the intervention at the end.[9]

It has been pointed out that expecting industrial sponsors to provide expensive drugs free of charge after a trial is over might curtail interest among companies in developing interventions specifically for diseases prevalent in developing countries (Nuffield Council on Bioethics 1999, 19). If companies do not anticipate a fair return on their investment, either from the market or from government subsidies, they might be less likely to embark on such research.

The obligation of researchers and sponsors to provide post-trial benefits cannot be absolute. This is because the availability of effective interventions will depend on many factors that are often beyond the control of researchers and sponsors, who, under these circumstances, should make good faith efforts to secure the continued benefit of effective interventions by ensuring that the issue of their availability is discussed during trial planning. The result of these negotiations should be included in the protocol submitted for Institutional Review Board (IRB) review, and potential participants in the trial should be told during the consent process what arrangements have been made for making effective interventions available after the trial is completed and that availability of the intervention will cease when it becomes available as standard care in the host country. In some situations, researchers and others involved in negotiating post-trial benefits may conclude that there is no plausible scenario in which an effective intervention would become available to the participants in the trial or to the population from which potential participants are drawn. Under these circumstances, the parties need to reconsider whether the study should be carried out at all.

Prior Agreements

The discussion regarding post-trial benefits leads to the following questions: *What is the process that should be used for determining what benefits, if any, should be made available following completion of research, and who should shoulder this obligation?* Although there are no single or simple answers to these questions, ethically appropriate conclusions can be reached through negotiations on a case-by-case basis, supported by a principled justification.

Kass and Hyder recommend a number of innovative mechanisms for encouraging researchers to engage donors, aid agencies, or health care delivery organizations in discussions about realistic strategies before a study is initiated:

> Possible mechanisms might include: requiring discussion in a grant proposal about prospects for future implementation; including a professional from a donor agency on study sections for international health research; encouraging IRBs to incorporate questions related to future access in their review; or offering continuation grants for implementation and infrastructure creation to support research interventions shown to be successful. This does not mean that studies cannot go forward without guarantees of future access; however, it does mean that studies cannot go forward where researchers have given no thought to how realistic future implementation is. While researchers do not need to shoulder this responsibility alone, it is still not appropriate for funders to support research where no one is taking responsibility for holding discussions about the feasibility of future access to effective health interventions.[10]

In recent years, efforts have been made to define the arrangements for making proven interventions available when a successful clinical trial has ended. These arrangements are generally referred to as *prior agreements*. The parties to these agreements usually include some combination of producers, sponsors, and potential users of research interventions. Industry, academia, and various other organizations are frequently producers and sponsors in these arrangements, while developing country governments and not-for-profit health organizations are most likely to be users. The use of the term *agreement* generally is not meant to have any legal connotation in the international research context, and, although some of these agreements will be legally binding instruments, others will not.

Furthermore, only a limited number of prior agreements are in place in international collaborative research today. Four entities that have used prior agreements are WHO, the world's leading international health organization; the International Aids Vaccine Initiative (IAVI), an international scientific nonprofit organization founded in 1996; VaxGen, a small California-based biotechnology company; and UNAIDS. WHO collaborates with industry to promote the development of health-related products and technologies pursuant to agreements designed to ensure that final therapeutic interventions will be made widely available at low cost to developing countries. Likewise, IAVI has secured unique pricing and intellectual property agreements with its industrial partners aimed at increasing global access to AIDS vaccines developed with IAVI support. VaxGen is working directly with the government of Thailand to test an AIDS vaccine it developed for use in that country. As part of this collaboration, the company has agreed to help build research capacity in Thailand by transferring knowledge and technology. It has also provided a letter of intent to assist the Thai government in producing the vaccine for use in Thailand, should it prove effective. In two instances, UNAIDS and product manufacturers have entered into preferential pricing agreements for developing countries prior to the commencement of research. (See Appendix C.)

Prior agreements also can be used in a number of ways to provide the benefits of the proposed research to the population from which the research participants are drawn. One way is to design prior agreements so that the experimental intervention that is being tested will be made available to research participants and their communities at a cost the developing country can afford. This could be accomplished, for example, by continuing to provide a proven intervention to the class of individuals represented by the participants in a clinical trial for a specified period and at a specified cost. Exactly what this would mean in a given situation would depend on a number of factors, particularly the health problem that

the intervention is intended to address. Or, if a country's need for a particular drug can be adequately quantified and the shelf life of a drug and other factors made it appropriate to do so, the country could make bulk purchases of the drug, perhaps at a subsidized price.

Prior agreements also can be designed to provide a benefit derived from research other than the research intervention itself. An example of such a benefit is technology transfer. In such a case, a pharmaceutical company could agree to grant to a developing country government a free or low-cost license to manufacture a drug in exchange for a commitment from that government to manufacture the drug and distribute it to its population. Another potential benefit of this type, discussed in Chapter 5, is helping to build research capacity in the host country.

The kind of benefit that is negotiated will depend on the conditions in and the capabilities of the host country. The suitability of providing a benefit other than the research intervention will depend on the nature of the benefit and the economic and technological state of development of the host country. Technology transfer may be an especially useful benefit for countries in the process of developing strong local pharmaceutical industries. On the other hand, assistance in building research capacity is applicable to most, if not all, developing countries involved in international research.

Some have argued that, in order to be ethically acceptable, research sponsored by developed countries and conducted in developing countries must "offer the potential of actual benefit to the inhabitants" (Glantz et al. 1998, 39) of that country by providing affordable access to the intervention to those communities where the intervention has been tested. Even if the intervention being tested is provided to the participants in a trial, without a guarantee of affordable access to the intervention by the population from which the participants are drawn, the developing country receives little benefit. If the knowledge gained from the research is used primarily for the benefit of the developed world, the research may be rightly characterized as exploitative and therefore unethical (del Rio 1998; Glantz et al. 1998).

Some observers believe this argument can be taken even further. Glantz and his co-authors write that, ethically, it is not enough to make a proven intervention available to a developing country by removing the financial barrier to access if there is no means of getting the intervention to the population that needs it. A realistic plan for distribution must be provided as part of the study review process in order to determine that there will be sufficient potential benefit to justify conducting the research. "Where the infrastructure is so undeveloped that it would be impossible to deliver the intervention even if it were free, research would be unjustified in the absence of a plan to improve the country's health care delivery capabilities" (Glantz et al. 1998, 41).

Some Critiques (and Responses) Concerning Prior Agreements

Most stakeholders in the research enterprise probably would agree that, at least in principle, prior agreements are an ethically desirable idea and that their use should be encouraged in international collaborative research. When research is to be conducted expressly for the purpose of responding to public health needs in developing countries, prior agreements can assist researchers, sponsors, ethics review committees, developing country governments, and other involved parties to focus on whether the proposed research will truly benefit those countries. Plans that are devised for the funding, distribution, and use of successful interventions before research begins can help to overcome some of the major barriers to making interventions widely available in the countries in which they are tested. An agreed-upon plan for funding may help solve the problem of affordability, to which poverty and high prices contribute, while a plan for distribution can help address obstacles to availability and inappropriate drug use, such as a weak health care infrastructure or overprescription of drugs by providers.

However, others believe that it is not feasible to use prior agreements that are negotiated as a condition of research approval to ensure the availability of a proven intervention or other health benefit. Following are some of the criticisms that have been made of requiring the use of prior agreements in international collaborative research. They appear in order of NBAC's determination of the most to the least valid:

- Prior agreements would serve only to delay or prevent new drug research in developing countries.

- Prior agreements are substantively, procedurally, and logistically problematic.
- The use of prior agreements is not the prevailing international standard.
- The use of prior agreements would go far beyond the influence one can reasonably expect sponsors or researchers to have concerning changes in a country's health policy.
- The use of prior agreements would create a double standard.
- Prior agreements can always be breached.

Delay or Prevention of Research

One criticism of imposing a requirement to negotiate prior agreements as a condition of research approval is that it will serve only to delay or prevent new drug research in developing countries (Glantz et al. 1998; Lie 2000). Others respond that, even if this is true, the population has lost nothing, because the benefits of the research would not be available to them anyway (Glantz et al. 1998). Furthermore, the fact that the research is not conducted serves to protect the country's inhabitants against exploitation as participants in research from which only developed countries are likely to benefit.

NBAC has already expressed the view that any obligation to provide effective interventions to host countries would be borne principally by research sponsors rather than by, for example, researchers. However, as several public commentators have noted, for a variety of reasons, research sponsors may be reluctant to make financial commitments to provide effective interventions as part of the prior agreement process, which, in turn, might ultimately affect their willingness to sponsor research in developing countries. Nonetheless, the use of prior agreements and the advancement of research that is beneficial to developing countries are not mutually exclusive goals.

First, it is erroneous to assume that all, or even most, effective interventions simply will be distributed to developing countries free of charge. Although in many cases effective interventions will be purchased by developing countries, the ability to do so will vary greatly. Some countries cannot afford to buy interventions, even at a reduced cost, while many others are able to buy them as long as they are not expected to do so at developed-world prices. Still others can be licensed to produce the intervention themselves. Over time, interventions should become more accessible to developing countries as their economic and technological capabilities improve.

Second, although in many situations research sponsors will play a primary role in providing effective interventions, this will not always be the case. Public agencies that sponsor research are often too constrained financially to provide post-trial interventions. When such an obligation arises, the public agency becomes responsible for locating another funding source for the intervention (such as an organization involved with promoting health or development). Similar creative funding arrangements also may be needed for private industry in order to provide incentives for undertaking research on neglected diseases that occur primarily in the developing world. Thus, the actual or perceived barrier to research imposed by prior agreements might be removed (or at least lowered) through the use of creative partnerships and arrangements designed to more widely distribute any financial burdens of fulfilling the obligation to provide effective interventions to developing countries. Much-needed research can move forward while, at the same time, these countries are protected from exploitation through arrangements designed to ensure that they receive the benefits of research.

Substantive, Procedural, and Logistical Problems

A second criticism of requiring the use of prior agreements in international collaborative research is that in practice, many substantive, procedural, and logistical aspects of prior agreements can be extremely problematic. Affordability, availability, and appropriate product use must all be considered before the research is conducted. The UNAIDS *Guidance Document* identifies specific issues that need to be addressed in order to ensure product availability, including "payments, royalties, subsidies, technology and intellectual property, as well as distribution costs, channels and modalities, including vaccination strategies, target populations, and number of doses." The text surrounding Guidance Point 2 expressly states that it is necessary for these discussions to "consider financial assistance regarding making vaccines available"

and to "help build the capacity of host governments and communities to negotiate for and implement distribution plans" (UNAIDS 2000, 14).

It is easy for some to dismiss the use of prior agreements because of problems that arise for which there are, as yet, no solutions. However, resolving critical health problems always requires grappling with complex and challenging issues, and collaborators in international research acknowledge that the concerted efforts and talents of multiple partners from diverse environments and disciplines are needed. Collaborative efforts are routinely employed to address problems arising from the funding or distribution of drugs in developing countries in a nonresearch context, including situations involving purchases made by nongovernmental organizations (NGOs) or donations made by pharmaceutical companies. In both cases, decisions must be made about to whom drugs will be distributed and how. If drugs are purchased by an NGO, a determination must be made regarding whether the proven intervention will be distributed free of charge or the developing country will be responsible for paying a minimal charge. Thus, there is no good reason to believe that these same kinds of problems in international collaborative research cannot be resolved in a similar fashion.

The process of negotiating a prior agreement requires focusing on the expected benefits of the proposed research by developing a detailed and concrete plan for funding and distributing the proven intervention. There may be cases in which, at the time the protocol is being reviewed, it is known (or should be known) that the proposed intervention will not be widely available in the host country after the trial. The process of developing a funding and distribution plan would make this apparent and help the parties focus on and deal with the issue of availability. Or, it may become apparent in the course of developing this plan that availability cannot realistically be addressed. This situation may call for re-evaluating the ethics of conducting the research. One commentator encouraged

> ...the creation of a multidisciplinary partnership for a given study, or for a program of research, consisting of investigators, study sponsors, host country authorities, international assistance organizations, representatives of the prospective research participants' communities, and other relevant parties. This group would assume the responsibility for post-trial implementation and develop approaches to negotiating that would remain responsive to changes over time as the study data mature, and as other related evidence unfolds. This group would begin work at the earliest possible stages of planning and design of the study and would remain in place to address any developments, research-related or otherwise, as they arose through the course of the study and for post-trial implementation. To the extent possible in any given context, its proceedings would be open to general scrutiny.[11]

If these issues are not addressed, the new proven intervention may not be made available to the host country. For example, if a drug that requires refrigeration is being developed for use in a country that cannot provide refrigeration, a plan for ensuring that the drug will be properly stored must be devised. There is no reason to believe that such issues cannot be addressed effectively before the research begins or that it is somehow easier to address them after the study is completed. Ultimately, the parties involved must reach an understanding about how the country will benefit from the proposed research before it begins. This does not mean that the entire population must benefit immediately, but rather that the parties involved should be convinced that sufficient numbers will benefit over a reasonable period, demonstrating that a meaningful contribution to the country's overall welfare will occur.

Finally, the debate concerning the definition of reasonable availability has continued, and arriving at a definition that would satisfy all parties remains a formidable challenge. However, developing an internationally acceptable standard is a highly desirable goal that should continue to be the subject of discussion. Meanwhile, the use of prior agreements might enable effective interventions to be made available to communities and countries on a case-by-case basis without the need to first reach a consensus on this difficult and divisive issue. The use of prior agreements may even facilitate this process by providing specific examples of the effectiveness or ineffectiveness of various types of arrangements for making effective interventions available.

Not the Prevailing International Standard

A third criticism of requiring prior agreements in international collaborative research is that an ethical obligation to make proven interventions available to communities or countries where research is conducted is not the prevailing international standard. It is far from being universally accepted by researchers, ethicists, public health officials, politicians, industry, and other stakeholders in new drug development, and there is little support for such an obligation in existing ethical guidelines.

Many believe strongly that a plan to make interventions available should be adopted based on the premise that the host community or country, and not just the research participants, should benefit from the research if it is to be ethically sound and not exploitative. Even though it is not the prevailing international standard, support for making interventions available after the research has ended is found in a number of important documents, including the CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS 1993); the WHO *Operational Guidelines for Ethics Committees That Review Biomedical Research* (WHO 2000); the guidelines of a few industrialized and developing countries, including the United Kingdom (MRC-UK 1999), Canada (MRC-CA, NHERC, and SSHRC 1998), Uganda (National Consensus Conference 1997), and Brazil (NHC 1996; NHC 1997); the UNAIDS *Guidance Document* (UNAIDS 2000); the Human Genome Organisation Ethics Committee *Statement on Benefit Sharing* (HUGO 2000); and the most recent revision of the *Declaration of Helsinki* (WMA 1964, as amended in 2000). Such support has manifested itself in two ways. First, all of these documents encompass the notion that the ethical acceptability of the proposed research, including issues related to product availability, should be determined before it is under way. Second, a more limited number of them (CIOMS 1993; National Consensus Conference 1997; NHC 1996; NHC 1997; UNAIDS 2000; WHO 2000; WMA 1964, as amended in 2000) impose an affirmative obligation to provide successful interventions to research participants and to the host community.

To consider as part of the protocol review whether a proven intervention will be made available after the trial forces researchers and their sponsors to be realistic about the reasons they want to conduct the research. Is the proposed research to be conducted in a developing country for the express purpose of addressing a particular health need of that country? What is the likelihood of implementing the proven intervention in the host country, and how will implementation occur?

Even though making effective interventions available to the host country after a trial is over is not the prevailing international practice, it is still a standard to which ethical researchers and sponsors should aspire. Little attention has been given in international research ethics to the question of what should be provided to communities and countries in which research is conducted. As these issues begin to receive the benefit of public debate and scholarly discourse, our collective ethical conscience will be raised and our ways of thinking about obligations will change accordingly. One might reasonably expect to see increasing numbers of international and national ethical guidelines address these considerations in the future. NBAC welcomes and encourages this development.

Unrealistic Influence on Health Policy

A fourth criticism of requiring prior agreements in international collaborative research is that it "would go far beyond the influence one can reasonably expect researchers to have concerning changes in a country's health policy" (Lie 2000). In other words, a question arises regarding the likelihood that government policy in a developing country will change as a result of conducting a study so that those who need an intervention will receive it.[12] Researchers contend that they are powerless to ensure that interventions will actually be made available once a study is over, even when the interventions are supplied to developing countries.

The problem, in most instances, is not that researchers cannot influence national health policy or that developing countries are being told that they must accept unwanted prior agreements. Rather, it is that access to successful interventions, which goes far beyond affordability, is an issue that researchers, sponsors, IRBs, and/or developing countries have either failed to address altogether or have simply neglected to address in sufficiently explicit and realistic terms. As one public commentator noted, there is a need to "integrate the new

intervention into the priorities and complex politics of an existing health care system"[13] in developing countries with limited funds. It is important that issues, such as health care financing and delivery, infrastructure development, and appropriate use of products, are considered during pretrial negotiations regarding making products reasonably available. Also, product availability cannot be the sole province of researchers. It is crucial to involve sponsors, host country governments, the community, international aid agencies, and other interested parties in this process.

There may be circumstances under which one or more of these parties is not willing to make a firm commitment to making a particular product available until after the conclusion of a pivotal clinical trial that clarifies the probability and magnitude of beneficial effect, safety, and the effectiveness of alternatives. As one international health researcher testified, "...in a vaccine study in another African country...the Health Ministry resented the requirement that some commitment be made up front feeling that that was a patronizing requirement and that they would be able to make a commitment when they saw the results of the study and could do an appropriate analysis of cost and benefit. And that gets to some of the perceived paternalism and rigidity of the current guidelines."[14] Moreover, the results of the trial may strengthen the position of the host country in negotiating with sponsors, manufacturers, and private philanthropies.

In the complex and uncertain environment in which research products are to be made reasonably available, a commitment to a continuing process of discussion and negotiation about post-trial benefits undertaken by the parties before research begins is the first step. During their initial discussions about proposed research, developing country governments should make known to researchers their positions concerning the availability of the intervention once the research is completed. Assuming that the host country wants to move toward ensuring that a proven intervention will be made available to its population after the research is completed, the use of a prior agreement can assist in this effort through the development of an implementation plan.

Creation of a Double Standard

A fifth criticism of prior agreements is that adopting a requirement for negotiating prior agreements in conjunction with research conducted in developing countries when it does not currently exist for research conducted in the United States creates a double standard. It has been suggested that without prior agreements, the benefits of successful research will not be generally available in developing countries (as it would be in the United States): "The reality in the United States is that regardless of the very significant gaps in insurance and Medicaid coverage and the health care discrepancies between the rich and poor, medical interventions are relatively widely available, especially when compared to developing countries" (Glantz et al. 1998, 41).

However, others disagree. Evidence suggests that access to proven interventions is an issue for some people in this country. For example, one study concluded that food, housing, and other subsistence needs of HIV-infected individuals in the United States are just as important to quality of life as access to health care (Cunningham et al. 1999). Some would respond that, even so, in contrast to developing country research, government-sponsored research in the United States would never be considered ethical if only the poor were recruited as research participants and the resulting intervention would not be made generally available to them (Glantz et al. 1998).

NBAC does not seek to determine whether a double standard would, in fact, be created if prior agreements were required for research conducted in developing countries. However, the fact that the use of prior agreements is not the current ethical standard for research conducted in the United States does not justify the lack of adherence to such a standard elsewhere. Perhaps we should set the goal of reaching agreements before research starts in this country to ensure that effective interventions are made available to those who need them here.

From a number of ethical perspectives, NBAC believes that those enrolled in clinical trials should have access to treatments that a trial proves effective. This report focuses on trials conducted in developing countries, where the discrepancies in access are greatest.

However, it is also ethically unacceptable if those enrolled in clinical trials in the United States have little likelihood of gaining access to the treatments studied after the trial ends. Whenever researchers carry out clinical trials in populations with poor access to health care, they should consider in advance the question of access to treatments that are proven effective after the trial and should seek prior agreements in order to make treatments accessible.

Potential for Breach of Obligations

A final criticism of prior agreements is that researchers, sponsors, and others (such as host country governments, agencies that provide aid, and NGOs) might breach their prior agreement obligations to make proven interventions available (Glantz et al. 1998). Because most of these agreements are not legally binding, developing countries are left without a reliable remedy, and they might be reluctant to enter into such agreements. However, although a party's failure to honor an agreement is always a possibility, this does not provide sufficient justification for rejecting the use of prior agreements. A suitable analogy can be made to promise keeping. People make promises and then break them. In doing so, a moral rather than a legal wrong is committed, one for which there is no remedy. However, this is not a reason to forego the institution of promise keeping as a means of establishing legitimate expectations in a given situation. Furthermore, the threat of debarment from future research and ostracism by the international research community would in many cases serve as effective deterrents to an unjustified breach of a prior agreement (Glantz et al. 1998). Finally, depending on whether there is general compliance with nonbinding prior agreements, parties may in the future insist on legally binding documents with enforceable remedies.

Economic globalization and the AIDS epidemic have made the developed world more acutely aware of the magnitude of health problems in developing countries and the imbalances in the global burden of disease. These factors have impressed upon us the need for moral progress and reforms to liberate countries from poor health and poverty and have led to a new awareness that unique and untested approaches must be considered for narrowing the gap between the developed and the developing worlds. In 2000, substantial commitments made by President Clinton, the U.S. Congress, private industry, foundations, and NGOs to combat AIDS indicate an increasing recognition by the developed world that developing countries may be unable to successfully address their health needs without its help. (See Exhibit 4.1.)

Exhibit 4.1: Vaccine Initiatives Timeline 2000–2001

January 24, 2000: Representative Jim Leach introduces H.R. 3519, the World Bank AIDS Prevention Trust Fund Act. Senator John Kerry introduces companion legislation, S. 2033, on February 3. The legislation requires that the Secretary of the Treasury negotiate with the World Bank to create a trust fund to address the AIDS epidemic in eligible countries.

January 27, 2000: In his State of the Union address, President Clinton proposes the Millennium Vaccine Initiative. The initiative includes a $50 million contribution to the Global Alliance for Vaccines and Immunization, an increase in federal funding for basic research on diseases that affect developing nations, and a tax credit for sales of vaccines for infectious diseases to accelerate invention and production.

March 1, 2000: Senator Kerry and Representative Nancy Pelosi introduce S. 2132/H.R. 3812, Vaccines for the New Millennium Act of 2000. The legislation includes a tax credit for medical research and a sales credit for vaccine purchases by foreign governments and nonprofit organizations for distribution in developing countries. The bills authorize contributions to the Global Alliance for Vaccines and Immunization and the IAVI. The bills also establish a vaccine purchase fund, through which the Secretary of the Treasury is authorized to purchase vaccines for distribution to developing countries. In addition, the President is authorized to negotiate with foreign governments and other parties to establish a similar international vaccine purchase fund.

March 2, 2000: In a White House event, President Clinton meets with leaders of pharmaceutical and biotechnology companies, who endorse the Millennium Vaccine Initiative and pledge to donate more than $150 million in vaccines to developing countries. Merck pledges to donate doses of its hepatitis B vaccine and commits to developing

Exhibit 4.1 continued

vaccines for worldwide HIV strains, American Home Products pledges to donate doses of its *Haemophilus influenza* type b (Hib) vaccine, Glaxo SmithKline Beecham pledges to expand its malaria vaccine program and donate funds to eliminate elephantiasis, and Aventis Pharma pledges to donate doses of polio vaccine to Africa.

May 15, 2000: H.R. 3519 passes the U.S. House of Representatives. On July 26, the legislation passes the U.S. Senate. On August 19, President Clinton signs the Global AIDS and Tuberculosis Relief Act of 2000, Public Law 106-264. In its final form, the act provides for a World Bank AIDS Trust Fund for prevention and treatment of individuals with HIV/AIDS and health care and education for AIDS orphans. The law also authorizes appropriations to the Global Alliance for Vaccines and Immunizations and the IAVI.

September 2000: The Presidential Advisory Council on HIV/AIDS recommends the creation of a global plan for HIV vaccine development. The council recommends that the administration boost research funding, create tax credits for vaccine research and development, and establish international purchase funds.

November 6, 2000: The FY 2001 Foreign Operations Appropriations, Public Law 106-429, is signed into law. The law allows for up to a $50 million contribution to the Global Fund for Children's Vaccines of the Global Alliance for Vaccines and Immunization, up to $10 million to the IAVI, and up to $20 million for the World Bank AIDS Trust Fund. The statute also appropriates up to $435 million for Heavily Indebted Poor Countries debt relief.

HIV/AIDS Drug Cost Reduction Initiatives

May 10, 2000: President Clinton issues Executive Order (EO) 13155, Access to HIV/AIDS Pharmaceuticals and Medical Technologies. The EO is designed to make HIV/AIDS drugs available at lower costs in sub-Saharan Africa. It declares that the United States will not seek revocation or revision of intellectual property law or policy in sub-Saharan African nations that promotes access to HIV/AIDS drugs or technologies, as long as the law or policy is consistent with the Agreement on Trade-Related Aspects of Intellectual Property Rights. This allows countries to license local companies to manufacture generic versions of drugs or to import the drugs from other countries where they are available at a lower cost. The EO also notes that the United States shall encourage "policies that provide an incentive for public and private research on, and development of, vaccines and other medical innovations that will combat the HIV/AIDS epidemic in Africa."

May 11, 2000: Five pharmaceutical companies announce that they will reduce the cost of HIV/AIDS drugs for African and other developing nations. Merck, Glaxo Wellcome, Boehringer Ingelheim, Bristol-Myers Squibb, and Roche announce that they will work with UNAIDS, WHO, the World Bank, the United Nations Children's Fund, and the United Nations Population Fund to improve access to HIV/AIDS care and treatment.

Bill and Melinda Gates Foundation Research Initiatives

July 10, 2000: Together with Merck, the Bill and Melinda Gates Foundation announces a donation of $50 million to Botswana for HIV/AIDS prevention, health care access, patient management, and treatment of HIV. The Gates Foundation will focus on improving the health care system, and Merck will handle the management and delivery of pharmaceuticals.

July 12, 2000: The Gates Foundation announces a $15 million grant to the Elizabeth Glaser Pediatric AIDS Foundation. The gift will support the Glaser Foundation's Call to Action project in Africa and Thailand, which provides for community training, HIV testing and counseling, treatment, and education to prevent mother-to-child transmission.

July 30, 2000: The Gates Foundation awards a $40 million grant to the London School of Hygiene and Tropical Medicine to strengthen the public health infrastructure and research capacity for nations heavily affected by malaria. The work is in collaboration with WHO, Wellcome Trust Research Laboratories, and the National Institute for Medical Research in Tanzania. The program involves developing centers of excellence in Africa, which could eventually receive money directly from the Gates Foundation.

December 18, 2000: The Gates Foundation awards a $15.1 million grant to an international consortium of researchers to develop new drugs to fight African sleeping sickness and leishmaniasis. The team will be led by a researcher at the University of North Carolina at Chapel Hill and includes the Kenya Trypanosomiasis Research Institute and Immtech International, Inc., an Illinois-based company.

January 27, 2001: IAVI receives a $100 million challenge grant from the Bill and Melinda Gates Foundation to mobilize global support toward the development and delivery of a preventive AIDS vaccine.

Increasingly, efforts are being undertaken before research begins to make proven interventions and other research benefits widely available in host communities and countries. Two organizations have successfully used prior agreements to make proven interventions available to developing countries, while other initiatives are newly developed and untested.

Many opportunities and challenges remain in pursuing the use of prior agreements in international collaborative research. Some agreements, such as those employed by WHO and UNAIDS, have proved successful. Agreements forged by other entities, such as IAVI and VaxGen (see Appendix C), remain untested, and whether their experimental interventions will actually be made available to the developing countries in which they are studied is not yet known. Nevertheless, the use of prior agreements in international collaborative research shows great promise as a means of helping to ensure that proven interventions and other research benefits will be made widely available to the developing countries in which they are tested and thereby prevent the exploitation of those countries and the individuals who serve as research participants.

The prior agreements described in Appendix C all have been negotiated with the aim of making successful interventions available to host communities and countries. In addition, international documents such as the CIOMS *Guidelines*, the UNAIDS *Guidance Document*, and the revised *Declaration of Helsinki* urge that successful products should be made available not just to the research participants themselves, but also to a wider segment of the population.

Conclusions and Recommendations

This chapter has considered the question of what benefits, if any, sponsors and researchers should provide to participants after their participation in a trial has ended, and what benefits, if any, should be made available to others (i.e., nonparticipants) in the host country at the conclusion of a study. NBAC concludes that at the end of a clinical trial that results in an effective intervention, research participants should be provided with this intervention. In addition, NBAC concludes that before initiating a research project, researchers or sponsors should consider how they might make benefits, if any, available to others in the host country, with the understanding that appropriate host country decisionmakers must be meaningful and essential participants in making such arrangements.

Recommendation 4.1: **Researchers and sponsors in clinical trials should make reasonable, good faith efforts before the initiation of a trial to secure, at its conclusion, continued access for all participants to needed experimental interventions that have been proven effective for the participants. Although the details of the arrangements will depend on a number of factors (including but not limited to the results of a trial), research protocols should typically describe the duration, extent, and financing of such continued access. When no arrangements have been negotiated, the researcher should justify to the ethics review committee why this is the case.**

Recommendation 4.2: **Research proposals submitted to ethics review committees should include an explanation of how new interventions that are proven to be effective from the research will become available to some or all of the host country population beyond the research participants themselves. Where applicable, the investigator should describe any pre-research negotiations among sponsors, host country officials, and other appropriate parties aimed at making such interventions available. In cases in which investigators do not believe that successful interventions will become available to the host country population, they should explain to the relevant ethics review committee(s) why the research is nonetheless responsive to the health needs of the country and presents a reasonable risk/benefit ratio.**

Recommendation 4.3: **Whenever possible, preceding the start of research, agreements should be negotiated by the relevant parties to make the effective intervention or other research benefits available to the host country after the study is completed.**

Notes

1 See Kass, N., and A. Hyder, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations," 141. This background paper was prepared for NBAC and is available in Volume II of this report.

2 Ibid., 98.

3 Ibid., 39–40.

4 Ibid., 43.

5 Malenga, G., Testimony before NBAC. February 29, 2000. Herndon, Virginia.

6 Plowe, C., Testimony before NBAC. February 29, 2000. Herndon, Virginia.

7 See Kass and Hyder, 39–40.

8 Ibid., 40–41.

9 Ibid., 41.

10 Ibid., 155.

11 National Institutes of Health (NIH), Public comment submitted to NBAC. Received November 13, 2000.

12 Sommer, A., Testimony before NBAC. September 16, 1999. Arlington, Virginia.

13 NIH, Public comment submitted to NBAC. Received November 13, 2000.

14 Killen, J., Testimony before NBAC. September 16, 1999. Arlington, Virginia. Meeting transcript, 120.

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Chapter Five

Ensuring the Protection of Research Participants in International Clinical Trials

Introduction

In previous chapters of this report, the National Bioethics Advisory Commission (NBAC) has made recommendations regarding the ethical design and conduct of clinical trials sponsored by U.S. organizations and subject to U.S. regulations that are carried out in developing countries. For the most part, these recommendations have focused on issues that arise *during* and *after* the trials themselves. The Commission has expressed the view not only that research participants should be left no worse off as a result of their participation in clinical trials conducted in a developing country, but that there is an ethical obligation to provide participants (and perhaps others) with the benefits that follow from a successful trial once it has ended. In the most general terms, it is important that sponsors or investigators from developed nations who are conducting clinical trials in developing countries take steps to ensure that participants are not exploited. Likewise, because there is always a possibility that exploitation might occur when a large disparity in power and wealth exists between the parties involved, it is important to ensure that the host country itself is not exploited and that the rich and powerful do not appropriate an unfair share of the fruits of the research. In addition, when the disparity between the resources of the sponsoring and host countries is large, the sponsoring country has an ethical obligation to ensure that the host country receives an adequate share of the research benefits.

It is important to consider the overall nature of the ethical obligation, if any, of richer nations to transfer resources to poorer nations (known as *distributive justice*). For some observers, such an ethical obligation arises either out of a desire to relieve poverty and distress or because of a belief that the wealth of the richer countries is unearned and, therefore, undeserved. This report does not address issues, as important as they are, related to the general obligations of rich nations in the context of international distributive justice. However, NBAC acknowledges these issues in order to ensure that in considering the ethical concerns that accompany the interactions of nations engaged in biomedical research, discussions are not complicated by conflating more general ethical obligations to improve the well-being of poorer countries with the ethical obligations that arise specifically within the context of biomedical research.

A unique feature of international collaborative research is the degree to which economically more prosperous countries can enhance and encourage further collaboration by leaving the host community or country better off as a result. The kinds of benefits that could be realized as a result of the collaboration would depend on local health conditions, the state of economic development, and the scientific capabilities of the particular host country. As discussed in Chapter 4, the provision of post-trial benefits to participants or others in the form of effective interventions is one option. The appropriateness of providing a benefit other than the intervention will depend on the nature of the benefit and on the economic and technological state of development of the host country. In most cases, offering assistance to help build local research capacity is another viable option. These two options are not, of course, mutually exclusive. But no matter what form the benefit takes, the ultimate goal of providing it is to improve the welfare of those in the host country.

Although NBAC has not been persuaded that there is an absolute obligation to provide a proven intervention to all citizens of a country who need it (as opposed to those who participated in the clinical trial), the Commission believes that serious efforts should be made to ensure that some post-trial benefits flow to the host community or country and that negotiations and the use of prior agreements should be considered as vehicles for such efforts. (See below and Appendix C.) Additional opportunities to provide long-lasting benefits to communities and countries may be available by taking steps that would enhance future or ongoing international research collaboration.

This chapter discusses measures to enhance the ethical soundness of collaborative international research by focusing on the following issues: 1) clarification of the substantive and procedural requirements for ensuring the protection of those who participate in research and 2) assistance in building host country capacity to conduct clinical trials and undertake the necessary scientific and ethical review of these studies.

In considering these topics, NBAC attempts to clarify the current U.S. regulatory procedures regarding research conducted or sponsored by U.S. interests in developing countries, and, when appropriate, make suggestions for revisions. Currently, there is some uncertainty about the scope of existing U.S. regulations, particularly with respect to the determination of whether other countries (and their research institutions) have systems to ensure that the substantive ethical protections the Commission described in Chapter 1 are achieved. Other considerations include the role of U.S. Institutional Review Boards (IRBs) in the review of research conducted abroad and the process used by the U.S. government for issuing assurances of compliance to institutions located abroad.

Approaches to capacity building are related to, but do not fully depend on, the clarification and improvement of current U.S. procedures for ensuring the protection of research participants in international clinical trials. Progress can and should occur simultaneously in both realms. Capacity building to conduct research could include activities undertaken by investigators or sponsors during a clinical trial to enhance the ability of host country researchers to conduct research (e.g., training and education), or to provide research infrastructure (e.g., example, equipment) so that future studies might proceed. Building capacity to conduct scientific and ethics review of studies, on the other hand, is primarily a matter of providing training and helping to establish systems designed to review proposed protocols and sustain mutually beneficial partnerships with other more experienced review bodies, including U.S. IRBs.

U.S. Procedures for Ensuring the Protection of Human Participants

Two principal regulatory mechanisms are used under the U.S. system for ensuring the protection of human participants in research: assurances and ethics review. In addition, a regulatory provision permits the substitution of foreign procedures that afford protections to research participants that are "at least equivalent" to those provided in the Federal Policy for the Protection of Human Subjects (45 CFR 46, Subpart A), also known as the Common Rule. Clarification of the scope and limits of these mechanisms and their use would increase public confidence that a valid system of protections is in place for participants in clinical trials conducted abroad.

Assurances

An assurance is "[a] legally binding written document that commits a public or private entity to compliance with applicable federal minimum standards for the protection of human subjects prior to engagement in department or agency conducted or supported research."[1] The assurance document can be described as a pledge or commitment by the institution to conduct research ethically and in accordance with the Common Rule. An approved assurance is a prerequisite to research conducted or sponsored by federal agencies that are signatories to the Common Rule. It is important to note that assurances are required regardless of the type of federal sponsorship.[2] For example, if a federal employee collaborates in research, even though no federal funds are provided, this constitutes agency support sufficient to bring the institution under the agency's jurisdiction, which in some cases renders it subject to the Common Rule. In cooperative research projects, each institution engaged in

research, whether domestic or foreign, must have a valid assurance.

The current assurance practice of the Office for Human Research Protections (OHRP) applies to institutions conducting research with human participants that is subject to the Common Rule, whether the research site is in the United States or abroad. Institutions engaged in research may be any public or private entity or any federal or state agency (45 CFR 46.102(b)). Under this definition, for example, the U.S. Centers for Disease Control and Prevention, a drug company, or a non-governmental organization may constitute an institution. Each institution involved in a cooperative research project (a project involving more than one institution) is responsible for safeguarding the rights and welfare of human participants and for complying with the Common Rule (45 CFR 46.114).

Until recently, OHRP has used two main types of assurances: Multiple Project Assurances (MPAs) and Single Project Assurances (SPAs). A third type of assurance, the Cooperative Project Assurance (CPA), also was used for research conducted under the Cooperative Protocol Research Program, which involves multiple sites and multiple protocols where the studies are similar (e.g., oncology trials) and under joint institutional sponsorship. A variation of the CPA, the International Cooperative Project Assurance, often was used for research conducted in other countries. Finally, the regulations authorized the Department of Health and Human Services (DHHS) to approve an institution's assurance for use across federal agencies. When DHHS approved such an assurance, all other Common Rule signatory agencies had to accept the assurance if it is "appropriate for the research in question" (45 CFR 46.103(a)). If another department accepted the DHHS assurance for such use, the institution had to provide any reports required under the regulations to the former Office for Protection from Research Risks (OPRR) and the supporting agency.

Criticisms of the SPA Process

Many researchers working in developing countries have found the SPA process to be burdensome, irrational in its structure, and of questionable merit in achieving the goal of protecting research participants.[3] One concern is that because separate assurances are required for each source of funds involved in a research protocol rather than for the individual research protocol itself, researchers may need to obtain several SPAs for a single protocol with multiple funding sources. Moreover, when a funding source changes for the same protocol, researchers must obtain a new SPA, which imposes what may be the unnecessary burden of multiple reviews on the U.S. researchers and their collaborators in other countries, who often question the need to review a study more than once.[4]

Some have criticized OPRR/OHRP's assurance process, principally because it requires foreign institutions to rigidly abide by U.S. procedures. For example, according to a 1997 survey of international researchers using SPAs, "there needs to be an increased acceptance by OPRR of ethical guidance and standards of practice in other countries" (Wichman et al. 1997, 5). Other comments from researchers about how to improve the current process for protecting research participants in international collaborative research almost uniformly suggest the need for greater flexibility by the United States in the application of its regulations. One individual urged that other countries' institutions should choose the composition of the IRB. Another asked, "Why is it that the country's or institution's IRB must be approved on every occasion? It is stupid and embarrassing to have to demand this. Approve the Board and let them get on with the job" (Wichman et al. 1997, 4). Still another researcher said, "My single experience has been very negative—to the point where my collaborators almost pulled out" (Wichman et al. 1997, 4). Wichman and her colleagues observed that:

> [i]n requiring conformity by foreign sites with all U.S. regulatory requirements, the current process may not be the best way to promote the ethical principles underlying the obligation to protect human research subjects. If...the assurance process is based on trust, then a major goal should be to assure that the rights and welfare of human subjects will be protected in accordance with commonly held ethical principles and standards of practice, not necessarily those of the United States (Wichman et al. 1997, 6).

In addition, in their study prepared for NBAC, Nancy Kass and Adnan Hyder reported that 77 percent of U.S. and 85 percent of developing country researchers surveyed recommended the use of international guidelines instead of U.S. regulations to cover joint projects.[5]

An alternative mechanism proposed to NBAC would allow for the certification of foreign ethics review committees. Under this mechanism, once a foreign ethics review mechanism achieves certification, it would be allowed to review and approve protocols in the same manner as institutions that have received an MPA.[6]

A particular feature of the SPA process is the requirement by OHRP that foreign research ethics committees be constituted in precisely the way stipulated by the U.S. regulations. Several researchers commented that this procedural requirement is unduly rigid. In the Kass/Hyder report, 83 percent of U.S. researchers and 92 percent of international researchers surveyed commented that U.S. regulations should not dictate the composition of host country ethics review committees.[7]

OHRP's Proposed Revisions to the Assurance System

In December 2000, OHRP launched a new Federalwide Assurance (FWA) and IRB registration process. The process for filing institutional assurances with OHRP for protecting human research participants has been simplified by replacing SPAs, MPAs, and CPAs with the FWA, one for domestic research and one for international research. Each legally separate institution must obtain its own FWA, and assurances approved under this process would cover all of the institution's federally supported human research. The proposed system eliminates the assurance documents now in place and replaces them with either a Federalwide Domestic Assurance or a Federalwide International Assurance, covering all federally supported human research.

Other features of the new assurance system would permit a U.S. institution to keep or establish its own IRB(s), rely on the IRB of another institution, or use an independent IRB. Foreign institutions would be permitted to abide by the ethical principles of the World Medical Association's *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research's *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (1979), or other relevant international research guidelines as an alternative to the U.S. research regulations. Under all assurances, institutional personnel (assurance signatory official, senior IRB/ethics review committee administrator or contact person, IRB/ethics review committee chairperson and members, and research investigators) are required to complete training on guidelines or regulations pertaining to the protection of human research participants. OHRP will provide a basic education module through its website to facilitate such training. To ensure that institutions are in compliance with the assurance, OHRP plans to expand educational activities, review institutional procedures for protecting human participants, increase the number of announced and unannounced site visits, and develop a website and a telephone information service.

NBAC is encouraged that OHRP is taking these steps to revise and simplify the current assurance process. It is not clear at this time, however, whether the new FWA process will eliminate the problems and inconsistencies that exist among agencies such as DHHS, the Agency for International Development (USAID), and the Food and Drug Administration (FDA) or the difficulties expressed by researchers who are familiar with the previous assurance system. Moreover, it should be noted that the assurance process itself does not provide a failsafe system of protections. Because weaknesses in this system have been noted in failures at U.S. research institutions, care should be taken not to rely too heavily on this single mechanism to achieve protections abroad, especially when it is not clear that OHRP will provide a visible presence in the host country (through, for example, site visits). However, it will be important to evaluate the success of these new initiatives.

Recommendation 5.1: **After a suitable period of time, an independent body should comprehensively evaluate the new assurance process being implemented by the Office for Human Research Protections.**

Ethics Review

NBAC has argued that individuals enrolled as research participants in clinical trials in developing countries should be guaranteed the substantive ethical protections outlined in Recommendation 1.1 and based on the ethical standards currently embodied in the U.S. system for the protection of human participants. Nevertheless, it is appropriate to allow for procedural variations in order to accommodate circumstances that are common in some developing countries. NBAC also has argued that in the absence of these protections, clinical trials in developing countries should not be conducted or sponsored by the U.S. government and that federal regulatory agencies should not approve drugs, devices, or biologics for sale in the United States based on such trials. (See Chapter 1, Recommendation 1.2.) As stated in Recommendation 1.1, prior review by ethics review committees is one of the most important ethical and procedural requirements for research.

Ethics review and the assurance process are closely connected. Each institution provides an assurance to DHHS that research involving human participants will be reviewed, approved, and provided continuing review by the IRB identified in its assurance (45 CFR 46.103(b)). The Common Rule establishes detailed requirements regarding the form and substance of IRBs, including membership (45 CFR 46.107), functions and operations (45 CFR 46.108), requirements for review of research (45 CFR 46.109), criteria for approval of research (45 CFR 46.111), authority to suspend or terminate research (45 CFR 46.113), record-keeping obligations (45 CFR 46.115), and the authority of the institution within which an IRB resides to approve or disapprove research (45 CFR 112). This means that all foreign institutions engaged in DHHS-sponsored research must comply with these requirements.

The FDA, although an agency of DHHS, operates under separate human participant protection regulations (21 CFR Parts 50 and 56) promulgated pursuant to the Federal Food, Drug, and Cosmetic Act[8] and the Public Health Service Act.[9] The FDA regulates all human research involving human drugs, biologics, and medical devices that is submitted in support of U.S. marketing approval for such products (21 CFR Parts 312 and 812). All of the limited amount of research involving human participants that the FDA sponsors and conducts is subject to the DHHS regulations. In addition, DHHS-funded research studying FDA-regulated products is subject to both DHHS and FDA regulations.

Like DHHS, USAID is a federal agency that subscribes to the Common Rule. However, its interpretation and implementation of the Common Rule differ markedly from those of DHHS in several respects and can be problematic for both U.S. researchers and their host country collaborators. USAID sponsors research in the United States and in other countries, but the agency does not conduct any research of its own. It has codified the Common Rule to set standards for USAID-supported research conducted in the United States or in other countries (22 CFR 225). The regulations are oriented primarily toward biomedical research, but they cover other types of research in which the principal issue generally "is protection of privacy rather than direct physical harm" (USAID 1996, 6(a)).

Safeguarding the rights and welfare of human research participants is the primary responsibility of the organizations to which USAID provides support. Its regulations and procedures emphasize "practicality, flexibility, and common sense" (USAID 1996). USAID recognizes three essential "pillars of protection": 1) review by a properly constituted ethics review committee or IRB; 2) a meaningful assessment of risk/benefit by the IRB or ethics review committee; and 3) a meaningful informed consent procedure. USAID "recognizes that foreign countries may often present special situations" (USAID 1996, 2(c)).

Multicenter cooperative research projects present special problems for ethics review because the ethics review committee of each participating institution must review the same research protocol. In addition to duplication of effort, time, and resources (which are particularly scarce in many developing countries), multiple reviews always present the possibility of different review outcomes. Although the DHHS regulations provide that, with the approval of the department or agency head, an institution participating in a cooperative research project may enter into a joint review arrangement and rely on the review of another qualified IRB or "make similar arrangements for avoiding duplication of effort" (45 CFR 46.114), NBAC is

not aware that this provision has been used in conjunction with cooperative research projects.[10]

In contrast, in a situation in which USAID provides support to a U.S.-based institution conducting research in another country, only the U.S. institution is required to review the research. The foreign institution is encouraged to review the research as well, but USAID does not require it. The FDA regulation also differs slightly from the DHHS regulation in that the FDA does not require approval of institutional agreements regarding whether one or multiple IRBs meeting regulatory requirements will review the research (21 CFR 56.114). NBAC also recognizes that the FDA clinical investigation and product approval regulations are not congruent with the Common Rule regarding IRB review of foreign clinical studies. The FDA expressly requires review by an IRB when an investigational new drug (IND) application or an investigational device exemption (IDE) has been filed (312.23 (a)(1)(iv), 812.42). In cases in which a foreign clinical study of a drug or biologic is not conducted under an IND, the FDA requires that "[f]oreign clinical research is required to have been conducted in accordance with the ethical principles stated in the 'Declaration of Helsinki' or the laws and regulations of the country in which the research was conducted, whichever represents the greater protection of the individual" (312.120(c)(1)). Similar language is used in the medical device approval regulations (21 CFR 814.15(b)).

Current Challenges to Host Country Ethics Review

The concept of local review—that is, review conducted by committees located in the community or institution in which the research will occur—enjoys considerable support in the international research ethics community and is one of the cornerstones of the U.S. system for protecting human participants. It is argued that committees that are familiar with the particular researchers, institutions, potential participants, and other factors associated with a study are likely to provide a more careful and considered review than a committee or other group that is geographically displaced or distant. According to this perspective, only local committees can exercise the kind of balanced and reasoned judgment required for reviewing protocols, and review cannot be accomplished from a distance.

Although ethics review committees are widely used throughout the international research community to ensure the protection of human participants, differences still remain in the level and quality of review. Data from the Kass/Hyder study provide some insight into the review and oversight of research in developing countries. For example, nearly all (91 to 96 percent) of the studies described by U.S. respondents were reviewed by a U.S. IRB, and these respondents reported that 87 percent of studies also were reviewed by an ethics review committee in the host country. In 29 percent of studies reported by U.S. researchers, the host country ethics review committee was established because of U.S. regulations.[11] In general, however, ethics review committees in developing countries were less likely to raise either procedural or substantive issues for a given study, compared to U.S. boards.[12] Survey respondents also remarked that host country ethics boards may be likely to have conflicts of interest regarding study approval, because research generates desperately needed resources that often provide an incentive to host country governments, ethics committees, and local researchers to accept such projects.[13] These findings provide a useful reminder of the difference between the existence of an ethics review committee and the capacity of the committee to conduct ethics reviews. Nevertheless, most respondents (85 percent of the host country researchers and 77 percent of U.S. researchers surveyed) believed that local review should be required for all studies conducted in developing countries.[14]

The Need for Multiple Ethics Reviews

Any research project in which a U.S. institution receives federal funds from an agency or department that is a signatory to the Common Rule (regardless of the number and location of other sponsors or research sites) must be submitted to and approved by a U.S. IRB of an institution with which the researcher is affiliated. Some commentators view this requirement as an imposition by the United States on other countries. Despite the fact that some countries—such as Australia, Canada, Denmark, India, the United Kingdom, and New Zealand—have well-established systems of oversight (with detailed guidelines and policies), NBAC believes it is essential to our system of oversight that studies conducted with funds from U.S. interests also comply with U.S. regulations.

For these countries, a different type of problem exists: Institutions in those countries must find ways to comply with their own guidelines as well as with those of the United States. Institutions in these countries would be unlikely to delegate ethics approval of studies to U.S. IRBs, even though local review processes and principles are similar to those under the U.S. regulations.[15]

As a result, some researchers surveyed for this report expressed a preference for using guidelines from the host countries rather than those of the United States:

> National guidelines in developing countries should take precedence over U.S. regulations when the study is initiated by researchers in the developing country and the role of U.S. researchers is merely to provide technical assistance and expertise as in the collection and analyses of samples....Alternatively, international guidelines should be instituted based on international consensus. Having international guidelines would expedite the IRB approval process since researchers in all countries would be operating under the same set of rules.[16]

In contrast, expert testimony provided to NBAC, as well as data collected by Kass and Hyder from researchers from both the U.S. and developing countries, indicated that host country ethics committees are not always well equipped to address substantive ethical issues. One researcher working in a developing country told Kass and Hyder that "[i]n [African country] there was no ethics or research committee by the time I got there and...there were a lot of researchers coming from abroad and calling themselves researchers who just came to the country and they did what they wanted to do and left. It took awhile for us to push the government to the point [of addressing the situation]."[17]

Similar sentiments were expressed to Kass and Hyder by U.S. researchers. One said, "Some of the [developing country IRBs] do really quite a decent job, just as you would want them to be. And there are others that are completely rubber stamps, and nothing else....Yes, there's an IRB, [but] I don't have any faith that there was any real review."[18] Another U.S. researcher added, "In some cases, the developing country ethical review is actually a process of seeking permission to conduct research, and no ethical questions are raised at all. Developing country review boards are often more concerned about the financial aspects of the study than about ethics."[19] Efforts are needed, therefore, to enable the systems for protecting human research participants—including their ethics review committees—of some other countries to become more fully committed to the ethical standards outlined in Chapter 1.

Ideally, equivalent (although not necessarily identical) systems for providing protections to research participants in developing countries would exist at both the national and institutional levels. In countries where a system equivalent to the U.S. system exists at the national level, some institutions may be incapable of conducting research in accordance with that system. However, it is difficult to conceive of institutional systems being declared equivalent in the absence of an equivalent national system, although it may be possible in a few extremely rare cases. When multiple sponsors are participating in the research, possibly all from developed countries, determining which ethics review committees (and how many) are required poses additional complexities. Because there are legitimate reasons to question the capacity of host countries to support and conduct prior ethics review, NBAC believes that with respect to research sponsored and conducted by the United States, it will be necessary for an ethics review committee from the host country *and* a U.S. IRB to conduct a review. The FDA's regulatory provisions for accepting foreign studies that are not conducted under an IND or IDE do not address whether a foreign nation's system must meet U.S. ethical standards.

Recommendation 5.2: **The U.S. government should not sponsor or conduct clinical trials in developing countries unless such trials have received prior approval by an ethics review committee in the host country *and* by a U.S. Institutional Review Board. However, if the human participants protection system of the host country or a particular host country institution has been determined by the U.S. government to achieve all the substantive ethical protections outlined in Recommendation 1.1, then review by a host country ethics review committee alone is sufficient.**

Recommendation 5.3: **The Food and Drug Administration should not accept data from clinical trials conducted in developing countries unless those trials have been approved by a host country ethics review committee *and* a U.S. Institutional Review Board. However, if the human participants protection system of the host country or a particular host country institution has been determined by the U.S. government to achieve all the substantive ethical protections outlined in Recommendation 1.1, then review by a host country ethics review committee alone is sufficient.**

Challenges of Multiple Review

Some U.S. researchers who work in other countries and their host country collaborators have expressed concern about the excessive rigidity of certain U.S. regulations and the perceived inflexibility with which the former OPRR had interpreted and implemented these regulations.[20] These researchers noted inordinate delays in being able to start their work and requirements that are procedurally burdensome, sometimes either financially or administratively impossible for many developing countries to fulfill, and, in any case, ethically unnecessary.

It may be problematic for ethics review committees in other sponsoring or collaborating countries to conform to U.S. regulations. Patricia Marshall's report to NBAC cites the comments of a physician-researcher from Lagos, Nigeria. In addition to having to "fight with Washington" to change the consent form, this investigator was frustrated with the administrative aspects of the process, including paperwork and committee negotiations.[21] After making the required changes in consent forms, several physicians expressed concerns about the possibility of overlooking some of the suggested modifications for consent forms because of the need to route them back and forth between U.S. and host researchers and their ethics review committees, as well as to the U.S. funding agency.

Haitian researcher Jean Pape testified about the complexity of the IRB process, which he noted as the area where collaboration has been the most difficult. He described the barriers he has faced:

> ...for any given project there are multiple IRB clearances. Each IRB meets once a month at different times. Each IRB uses different presentations and consent forms. Each IRB has a different set of rules. Some accept oral consent. Others written consent. Others written consent with witnesses, without witnesses. And depending on who the witnesses are, each IRB responds with different comments that must be addressed, a different time period for approval and, therefore, different time for yearly renewal.[22]

The need to seek approval of a protocol and informed consent documents from multiple ethics review committees raises the question of what should be done when ethics review committees disagree. Currently, some argue, there is no mechanism for resolving such conflicts and no understanding on the part of one ethics review committee of how the other committee operates.[23] Ethics review committees' lack of familiarity with the situations in host countries was noted by many researchers, who stated that U.S. IRBs essentially have no experience with the conditions and realities of life, medical care, and research in developing countries.[24]

Regardless of these concerns, it is clear to the Commission that ethics review in the *host* country is important, because the host country is best able to represent the interests of prospective participants. Although some developing countries currently may not have mechanisms in place to conduct ethics review, they should be encouraged to engage in this process as a step toward full collaboration with the visiting research team. NBAC heard a number of useful suggestions for addressing these issues, both from researchers who provided testimony and from respondents to NBAC-commissioned surveys. These suggestions included the following:

- Seek ways to increase communication among multiple ethics review committees responsible for review of U.S.-sponsored research conducted in other countries, perhaps through an annual meeting between the chairs of the ethics review committees/IRBs from collaborating countries or through visits between the chairs of each ethics review committee/IRB.
- Develop a system of coordination among investigators and local IRBs/ethics review committees.
- Seek input from host country ethics review committees or community members in the host country in designing the consent process before review by a U.S. IRB. The U.S. IRB should be flexible and receptive to such proposals.

- Have local investigators design consent forms in the host country, followed by approval by the local ethics review committee, rather than having the documents and their approval come from the United States.
- On U.S. IRBs that review developing country protocols, include members who have experience working or living in developing countries.

These suggestions for reducing the burden of multiple ethics reviews have not yet been assessed comprehensively, but they are worth pursuing. Clearly, in cases in which clinical trials are supported by multiple sponsors (including several sponsors from the United States or other countries), ethics review may be conducted in accordance with the guidelines and procedures already established in those settings. In such cases, coordination and communication between and among review committees as described above should be fostered. This is particularly important when more than one U.S. sponsor or institution is involved, in which case it might be important to designate a lead U.S. IRB in order to achieve timely review.

Lack of Resources as a Barrier to Ethics Review

Ethics review committees in developing countries may have difficulty complying with U.S. regulations because they lack the funds necessary to carry out their responsibilities. In some cases, local IRBs have requested overhead or operational costs for studies conducted in collaboration with U.S. researchers. Some investigators interviewed by Marshall suggested that U.S. regulatory agencies should make a greater investment in the ethics review committees of host countries through training members and providing materials and resources.[25] This suggestion raises concerns about the intermingling of ethics and finances, a situation that can be problematic, because protocols could be delayed for financial reasons rather than as a result of ethical concerns. Because the National Institutes of Health (NIH) does not provide financial support to subcontracting institutions in other countries, and the World Health Organization (WHO) pays no overhead, "what you end up doing is trying to bargain by offering to train personnel, provide equipment, provide services, or trying to somehow imbed the equivalent of overhead in your budget and deal with it that way."[26]

One researcher noted that ethics review committees in developing countries have no budget and asked why these committees should use their time to meet U.S. regulations when no funds are provided for salary, secretarial assistance, courier service, office maintenance, or other necessities.[27] Indeed, 20 percent of U.S. researchers surveyed by Kass and Hyder mentioned that host country ethics board members had complained of lack of resources, and 70 percent believed that U.S. funding agencies should help to support the work of these committees.[28] Two researchers commented that support for host country ethics review should come in the form of a percentage of each research grant, which would be donated to host country ethics systems. This would help avoid a situation in which an individual research grant pays to convene a specific IRB.[29]

NBAC is persuaded that funding issues are often problematic for researchers and ethics review committees in other countries. Indeed, in previous reports (NBAC 1998; NBAC 1999a; NBAC 1999b), the Commission has recognized that there are costs to providing protection to human participants in research and that researchers and institutions should not be placed in the position of having to choose between conducting research and protecting participants. Therefore, an additional means of enhancing international collaborative research would be to make the necessary resources available for conducting ethics reviews.

> ***Recommendation 5.4:*** **Federal agencies and others that sponsor international research in developing countries should provide financial support for the administrative and operational costs of host country compliance with requirements for oversight of research involving human participants.**

Equivalent Protections

DHHS and its lead agency, NIH, conduct or sponsor more research involving human participants in the United States and abroad than any other federal agency. OHRP is responsible for interpreting and implementing the DHHS regulations that provide protections for human research participants. The cornerstone of the DHHS regulatory framework is the Common Rule, which "applies...to federally funded [human participants]

research that is supported or conducted by a signatory agency or department, either internally by its own staff and in its own facilities, or externally through grants and contracts with investigators at universities or other research facilities." It includes such research "conducted, supported, or otherwise subject to regulation by the Federal Government outside the United States" (45 CFR 46.101(a)).

The same regulations that apply to research conducted in the United States apply to U.S.-sponsored research conducted in foreign countries. The only provision in the DHHS regulations unique to research conducted in foreign countries is one that permits the substitution of foreign procedures that afford protections to research participants that are "at least equivalent" to those provided in the Common Rule (45 CFR 46.101(h)). This means that instead of adhering to the particular procedures of the Common Rule, the regulations allow foreign researchers to follow procedures adopted by their own country *if* these procedures provide protections for research participants that are "at least equivalent" to those protections provided in the U.S. regulations. For purposes of international research, the "equivalent protections" provision is one of the most important provisions of the Common Rule, because if another ethics review system were to be declared equivalent to those procedures in the Common Rule, a foreign institution following that system would not be required to negotiate an assurance with a U.S. agency.

Earlier in this chapter, NBAC examined some of the difficulties that U.S. and foreign researchers who must adhere to the provisions of the Common Rule encounter when participating in DHHS-conducted or sponsored research in developing countries. These requirements can be problematic in two respects. First, they may present unnecessary difficulties for the foreign researchers and developing country researchers in particular who must implement them. For example, as noted above, the regulations that govern the assurance process and ethics review are viewed by some as tedious and often require researchers in other countries to duplicate their efforts and spend scarce resources on administrative requirements that have little to do with the actual protection of human research participants. Second, by "exporting" its regulations to foreign countries as a way of ensuring that human research participants involved in U.S.-sponsored research in those countries are sufficiently protected, the United States may appear to be exhibiting a lack of respect for the countries and their researchers and research institutions. For example, some researchers expressed the view that there is a perception that U.S. regulations are being "imposed" on other countries. A U.S. researcher who participated in the Kass/Hyder survey for NBAC invoked the distinction between ethical principles and specific procedures with the following comment: "The principles of U.S. ethical review should be applied overseas but not the specifics."[30] Others expressed a preference for using international guidelines instead of U.S. rules. One U.S. researcher said that "[I]t would be good to have international standards that at least match the extent of the U.S. requirements, since these would be more appropriate to the international setting."[31]

The regulations themselves may provide the framework for a possible solution to these problems. As mentioned earlier, a provision in the regulations permits a foreign institution to deviate from the specific procedures for protecting human participants delineated in 45 CFR 46 as long as the procedures with which it agrees to comply provide "at least equivalent" protections (45 CFR 46.101(h)). That provision states that:

> When research covered by this policy takes place in foreign countries, procedures normally followed in foreign countries to protect human subjects may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration...issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a Department or Agency head determines that the procedures prescribed by the institutions afford protections that are at least equivalent to those provided in this policy, the Department or Agency head might approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy.

Starting in June 2000, OHRP became the agency responsible for making determinations of equivalent protections for DHHS. However, to date, OHRP has not provided criteria for determining what constitutes equivalent protections or made any such determinations about other countries' guidelines. In lieu of having developed a process for making equivalent protections determinations, OPRR in the past relied on its usual process for negotiating assurances with foreign institutions to ensure that human participants are adequately protected. In response to questions from NBAC, an OPRR official wrote that "[t]here is no established process by which requests for 'equivalent protections' determinations are made. Requests to OPRR to accept an institution's procedures for protecting human subjects are generally made by investigators which, in turn, are invariably addressed in the process of negotiating an assurance."[12] The same official testified before NBAC that "[t]ypically what happens is that we very delicately negotiate an assurance that spells out those protections without actually citing the U.S. regulations. In other words, what we have done is negotiate an assurance on a case-by-case basis that incorporates those national protections without a formal declaration of equivalence."[13]

OHRP, however, has taken steps in the direction of recognizing the protections described in three guidelines: the Canadian *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (1998), the recently issued *Ethical Guidelines on Biomedical Research Involving Human Subjects* of the Indian Council of Medical Research (2000), and the International Conference on Harmonisation (ICH) *ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice* (1996). The FDA is a signatory to the ICH and has adopted the ICH document as FDA guidance. In doing so, OHRP has permitted institutions in Canada and India to follow their own guidelines as part of negotiating assurances under the new FWA, which permits investigators to follow ethical codes with which they are more familiar and comfortable. OHRP has not, however, declared these guidelines to provide equivalent protections pursuant to 45 CFR 46.101(h). To do so would obviate the need for assurances, and, as a result, OHRP would have to relinquish its oversight authority.

USAID, a signatory to the Common Rule, also has the authority to make determinations of equivalent protections. USAID will accept foreign procedural systems as long as they are determined to provide protection to human participants "at least equivalent" to its policy (USAID 1996). Substantive application of the three essential pillars of protection described earlier in the chapter—ethics committee review, risk/benefit assessment, and meaningful informed consent—will generally satisfy this requirement. "At least equivalent" determinations can be made by USAID in two ways. First, the agency has determined that "research supported through or adhering to the standards established by United Nations agencies" is considered to afford "at least equivalent" protections (USAID 1996, 4(a)). In theory, this mechanism is based on USAID's familiarity with the United Nations' agency standards and review processes and its trust in those agencies to protect human research participants.

In addition to its authority as a signatory to the Common Rule, USAID has developed a procedure for making its own "at least equivalent" protections determinations through its recognition of the three essential pillars of protection, which generally satisfies the "at least equivalent" protections requirement. USAID procedural guidelines state that "[i]n assessing equivalency, the general concept should be whether protection under the system is for all practical purposes the same when viewed *in toto* [meaning under all the circumstances or when viewed in totality] and not whether any specific component (e.g., the precise make-up of the IRB equivalent) is identical." A justification memorandum must be prepared that describes how the alternative system provides the three pillars of protection (USAID 1996). The *in toto* standard used by USAID differs significantly from what OHRP generally would require under the same circumstances (i.e., full compliance with U.S. regulations). Although the *in toto* standard has never been invoked by USAID, the USAID standards provide a solid foundation on which to build, and NBAC encourages USAID to adopt the substantive ethical standards described in this report in determining equivalency.

The FDA regulations do not contain the equivalent protections provisions set forth in the DHHS and USAID

regulations. The FDA does not specify the location of the IRB or ethics review committee conducting the assessment and does not require institutions to negotiate assurances. However, in requiring that research be conducted in accordance with international ethical principles (such as the *Declaration of Helsinki*), which mandate ethics review, and in its adoption of the standards of the ICH, the FDA regulations do address many of the central issues involved in determining equivalent protections. NBAC recognizes that, from the perspective of researchers in other countries who wish to collaborate with U.S. colleagues, the potential exists for confusion regarding the different sets of U.S. regulatory requirements—those of the FDA and those of the Common Rule agencies (which may differ as well). A step toward reducing this confusion would be for the FDA to amend its regulations to conform with the recommendations in this report regarding equivalent protections and review by multiple ethics committees when studies involve multiple countries.

It appears that U.S. agencies that sponsor or conduct research in other countries have the authority to determine whether foreign laws, regulations, or guidelines provide protections to human participants equivalent to those provided in the U.S. regulations; however, no criteria exist for agencies to implement this authority, nor does there appear to be any incentive to do so. Indeed, as Bernard Dickens observed in a paper commissioned by NBAC for this report:

> Accordingly, it may be an act of faith for a Department or Agency head to determine that institutional procedures in some foreign countries 'afford protections that are at least equivalent to those provided in this policy' as required by 45 CFR 46.101(h). Ultimately, confidence may have to be placed in foreign institutions' conformity with substantive rules of ethical conduct for protection of human subjects of research, and not on the procedures that they use.[34]

Given the breadth of experience within U.S. agencies—particularly DHHS and USAID—this situation could be remedied quickly. It is appropriate for OHRP to both coordinate this activity and be responsible for developing further guidance in conjunction with FDA, USAID, and other U.S. agencies.

The Need for Uniformity in Application

As noted above, the equivalent protections provision of the DHHS regulations has never been explicitly used by OHRP (or OPRR), nor has OHRP developed any criteria by which to make such determinations. The regulations do not specify what is meant by equivalent protections, and, furthermore, the language of 45 CFR 46.101(h) is confusing. For example, it speaks of "procedures normally followed in the foreign countries to protect human subjects" and "a foreign institution which complies with guidelines consistent with the...Declaration of Helsinki," but also of "procedures prescribed by the institution [that] afford protections that are at least equivalent to those provided in this policy." Just how the language of this section should be interpreted is unclear. Dickens addresses this issue as follows:

> This intention to accommodate studies the policy covers that are conducted in a foreign country therefore depends on a determination that 'the procedures prescribed by the institution' afford human subjects at least equivalent protections to those provided in the policy. The reference to 'procedures' repeats the policy's recognition that 'procedures normally followed' in foreign countries 'may differ from those set forth in this policy.' This raises the issue of whether equivalent protection is focused only on matters of institutional review procedures, where the equivalent structure and functioning of an IRB are required, or whether equivalence must extend beyond the process of review to include the substance of the proposal to be reviewed....[35]

The issue Dickens raises is significant and supports the distinction emphasized earlier in this report that substantive ethical principles or standards are more fundamental and, therefore, much less subject to negotiation than are matters of procedure. Any given set of substantive ethical standards and principles may give rise to more than one set of appropriate procedures to implement these standards. As long as a particular procedure (e.g., obtaining informed consent without documenting signatures) is consistent with the ethical standard, it should be seen as less consequential. In contrast, disagreements or tensions regarding a substantive ethical principle or standard can cause problems for which no mere procedural solution would be adequate.

Assuming that a host country's substantive guidelines are determined to provide equivalent protections, how do we ensure that a particular ethics review committee in that country is able to comply with those guidelines? In the United States, OHRP assures that local institutions comply with federal regulations. Similarly, ethics review committees in another country, whether they exist at the national, regional, local, or institutional level, would be established by the appropriate authorities in that country and would be equivalent in stature to a U.S. IRB. Such a process would have the same effect as the committee having obtained an MPA or an FWA from a U.S. agency.

NBAC believes that equivalent protections should mean that a process should be established to determine whether the system of protection of human participants in another country meets the three basic ethical principles of respect for persons, beneficence, and justice, and has adopted the substantive ethical standards outlined in Recommendation 1.1. Developed and developing countries might aspire to go even further to promote the rights, dignity, and safety of research participants in other ways.

Consistent with the substantive ethical standards and procedural requirements set forth above, OHRP should take affirmative steps, in conjunction with other U.S. agencies, to develop uniform and detailed criteria for determining whether the system of protection of human participants in a host country and/or host institution is fully equivalent to the U.S. system. Once these criteria are developed, OHRP should begin to use them to identify those countries whose guidelines are deemed to provide equivalent protections. Although it has never been invoked in this way, the approach that has been adopted by USAID in setting standards for equivalent protections determinations under the Common Rule is useful. This approach is to ask whether the protection afforded to human research participants under the system being assessed, for all practical purposes, is the same when viewed *in toto*, and it stands in sharp contrast to the approach of asking whether the individual components of that system are identical (e.g., the precise make-up of the ethics review committee or what constitutes a quorum).

Recommendation 5.5: **The U.S. government should identify procedural criteria and a process for determining whether the human participants protection system of a host country or a particular host country institution has achieved all the substantive ethical protections outlined in Recommendation 1.1.**

At the same time, the move toward equivalent protections is one that needs to be made carefully and with much thought regarding substantive criteria and process. NBAC recognizes that this recommendation may be an aspiration that will only be attained after efforts are made that will take a great deal of time. The Commission hopes that in the near future at least some, if not many, of the difficulties and frustrations currently experienced by U.S. and foreign researchers conducting research in developing countries will be alleviated through determinations that the laws, regulations, or guidelines of those countries provide equivalent protections. Such a process would also accord to those countries, their researchers, and research institutions an appropriate level of respect for their research systems and capabilities. Nevertheless, it appears that at least some of the problems associated with the assurance process described above could be avoided if determinations of equivalent protections were, in fact, made by DHHS and other agencies.

Building Host Country Capacity to Review and Conduct Clinical Trials

NBAC heard repeated testimony about the need to build capacity in international research. For example, one expert noted that training and capacity building help to provide mechanisms for strengthening relationships with local collaborators as well as for leaving behind lasting benefits in the host communities.[36] Researchers suggested various approaches to building capacity, including training local personnel who will remain at the end of a trial in clinical areas and research methodology; involving host country scientists in writing grants as well as in analyzing data and preparing manuscripts; and at the conclusion of a trial, leaving behind equipment that can continue to serve local needs. Similarly, scientists who responded to the Kass/Hyder survey agreed that capacity building should be an integral part of any study. Kass and

Hyder characterized this sentiment as follows: "Researchers should conceive of their role as facilitating host countries' capacity to eventually conduct most of their research independently, and should aim for such capacity development to be one of the most significant benefits a study can provide."[37]

In addition, many survey respondents remarked that the participation of local researchers was essential to conducting well-designed studies in developing countries and provided examples of long-term collaborations between U.S. and host country research institutions.[38] Developing country scientists commented that effective collaboration entails involving host country researchers in the early stages of research design and including them as partners throughout the research process. Such collaboration results in additional benefits that flow in two directions: The host country researchers may gain from the expertise and material resources of the U.S. team, and the U.S. researchers benefit from the knowledge and experiences of the local team, whose input into the research process often is essential to reaching the most appropriate and relevant research design.

The guidelines and other policy statements of several national and international bodies emphasize capacity building. These documents include provisions that pertain to the responsibilities of developed country research sponsors in developing countries, including providing assistance in building local and national capacity for designing and conducting trials, and for their scientific and ethical review, and for implementing the results of the research following a trial. The provisions of some developing countries' guidelines directly address these issues. For example, Section III.3.s of Brazil's *Resolution No. 196/96 on Research Involving Human Subjects* states that "...[s]tudies sponsored by external organizations must also respond to training needs in Brazil" (NHC 1996). The South African *Guidelines on Ethics for Medical Research* states that "[w]hile studies are in progress...the opportunity should be taken to train local health workers in skills and techniques that can be used to improve health services....When the study team departs it leaves something of value, such as the ability to monitor diseases or mortality rates" (MRC-SA 1993, Sec. 18). In addition, both the 1993 CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS 1993) and the UNAIDS *Guidance Document for Preventive HIV/AIDS Vaccine Trials* (UNAIDS 2000) address this topic.

In a departure from the way research in developing countries has been conducted in the past, a consensus has emerged that a fuller and more genuine partnership should be forged, rather than an approach in which developed country sponsors dictate the terms of the research. For example, UNAIDS has developed a list of mechanisms for capacity building in the context of HIV vaccine research that may be adapted to other areas of international research, including the following:

- scientific exchange and knowledge and skills transfer between sponsor countries and institutions, host countries, and communities;
- capacity-building programs in the science and ethics of vaccine development;
- development of national and local ethics review capacity;
- information and education program support to affected communities from which research participants are drawn; and
- early involvement of affected communities in the design and implementation of research protocols (UNAIDS 2000, 16).

A number of organizations are involved in the type of capacity-building activities suggested by UNAIDS (see Exhibit 5.1).

As acknowledged in Chapter 4, a potential problem exists in maintaining the quality of health care that has been established during the course of a clinical trial. This point has been made by other entities, such as the Nuffield Council on Bioethics, whose discussion paper notes that "[o]ften, large-scale trials of interventions in developing countries are associated with improvements in community healthcare during the period of the trial due to better staffing and facilities. The support required for the improvement will not ordinarily continue after the trial is over" (Nuffield Council on Bioethics 1999, 5). Although sponsors should not be expected—once the trial is over—to continue to provide staffing and equipment indefinitely, they could nevertheless undertake efforts to train personnel in the host country in providing

Exhibit 5.1: Examples of Building Research Capacity

- The Fogarty International Center (FIC) at NIH sponsors international research and training programs aimed at building research capacity in the poorest nations of the world where the need is the greatest. These grants allow institutions in the United States to work in partnership with colleagues in the developing world to conduct research and, in the process, build a cadre of young foreign investigators positioned to address the scientific challenges in the most crucial areas, including HIV/AIDS, emerging infectious diseases, bioethics, medical informatics, population and health, environmental and occupational health, maternal and child health, and others.[39] The center's activities follow from the many activities of "international cooperation" described in the U.S. Public Health Service Act (Sec. 307 [242] (a)). Recently, the FIC announced the funding of five initial awards and three planning grants to institutions in developing countries under the new International Bioethics Education and Career Development Award Program. Support for the program will total $1.4 million over three years.[40]
- The International AIDS Vaccine Initiative (IAVI) has formed several wide-ranging partnerships to accelerate the development and testing of preventive AIDS vaccines that would be appropriate for use in various parts of the developing world. (See also Appendix C.) One of these partnerships is with the Ugandan Ministry of Health. Ugandan scientists will be collaborating with IAVI on the development and testing of an orally administered AIDS vaccine under development at the University of Maryland Biotechnology Institute. The vaccine's development is being funded by IAVI. The Ministry of Health in Uganda and IAVI also intend to work together to support ongoing efforts in Uganda to build clinical trial infrastructure and prepare sites for trials of a range of preventive AIDS vaccines. Both organizations also are committed to strengthening the capacity of Ugandan scientists to play an active role in vaccine research and development and to collaborate with other U.S. and European groups working on vaccine development in Uganda.
- The Rockefeller Foundation created the International Clinical Epidemiology Network (INCLEN) in 1980 to improve the health of populations by bringing the science of public health epidemiology to bear on the practice of medicine. INCLEN identifies medical schools in the developing world to train mid-level faculty in the disciplines of clinical epidemiology, biostatistics, health social science, and clinical economics and supports those faculty members (and the Clinical Epidemiology Units [CEUs] that they formed) through mentorship, continuing education, logistical support, and ongoing linkages with colleagues around their regions and the world. INCLEN helps those who have been trained establish themselves as productive and influential teachers and researchers, as well as clinicians, administrators, and policymakers. INCLEN has trained nearly 500 faculty members at the master's level since 1980, and 83 percent remain affiliated with 56 CEUs, located in 24 countries.[41]

adequate medical care and maintaining equipment and facilities. The goal of capacity building is to enable host country researchers to develop fuller partnerships with developed country researchers or sponsors. However, the particular needs that capacity-building activities could address may depend on the local circumstances.

Recommendation 5.6: **Where applicable, U.S. sponsors and researchers should develop and implement strategies that assist in building local capacity for designing, reviewing, and conducting clinical trials in developing countries. Projects should specify plans for including or identifying funds or other resources necessary for building such capacity.**

Of particular importance to the concerns addressed in this report is the adequacy of procedures in host countries for conducting prior scientific and ethical review of clinical trials. Ultimately, increased capacity for conducting these reviews contributes to more effective collaborations in international research. Chapters 2, 3, and 4 offer recommendations that address specific aspects of ethics review that are relevant to the assessment and approval of clinical trial protocols. This chapter focuses on enhancing the capacity of developing countries to conduct scientific and ethical reviews independently.

Variation in National and International Guidelines

In developing recommendations for enhancing international collaborative research and to more fully understand what provisions currently exist regarding international collaborative research, NBAC has prepared a detailed comparison of 25 documents that contain the international laws, regulations, and guidelines from 15 countries and 7 international organizations. (A summary of the analysis appears in Appendix B, and the complete analysis is available in Volume II of this report.)

The seven documents developed by international organizations describe general principles and guidelines for the ethical conduct of research, while the national documents set forth the laws, regulations, or guidelines specific to particular countries. These documents were selected from developed and developing countries and represent a breadth of geographical and cultural diversity. The analysis focused on identifying features of U.S. research regulations that might be absent from other national and international documents, and conversely, determining whether issues that are dealt with in certain international documents are not found in the U.S. regulations. Exhibit 5.2 lists the 25 documents.

It is evident that although the importance of prior scientific and ethical review is well established in many developed countries and agencies that sponsor international collaborative research, the associated procedures necessary to effectively implement the relevant principles are at different stages of evolution. In addition, many developing countries have not yet promulgated national ethics guidelines related to the protection of human participants, including those necessary to support and implement review and monitoring of research. In certain countries where international collaborative research is conducted, ethics review committees are not well established. At the very least, these differences begin to explain why researchers who are from different countries collaborating on the same research project may encounter misunderstandings regarding which ethical standards and procedures must be satisfied. At worst, it may indicate that if the lack of consistency among guidelines and practices is not addressed, the implementation of a coherent and sufficient set of guidelines may pose serious and unnecessary difficulties in international research, possibly preventing important and ethically sound research from going forward.

Although researchers sometimes complained about delays of more than two years, which undermined effective collaboration with local scientists,[42] good reasons for delays in the review process may exist, including, most obviously, some countries'—and the research institutions within them—lack of capacity to establish and maintain a system of ethical review. This is why, for example, the *UNAIDS Guidance Document* (2000) and the WHO *Operational Guidelines for Ethics Committees That Review Biomedical Research* (2000) recommend that collaboration between sponsors and host countries and among other international organizations and experts can enhance the capacity for developing countries to provide independent and competent review.

Researchers in the Kass/Hyder survey commented that host country ethics review committees were variable in their level of experience and expertise and noted that, in some cases, researchers felt that the host country committees should be given more authority. They also raised issues about local culture and the ability of U.S. IRBs to effectively recognize local concerns. Others pointed to deficiencies in local review committees and remarked that different countries and locales were at different stages of evolution in the development of ethics review processes. In fact, survey data indicate that lower levels of overall development in host countries are associated with difficulties in ethics review, including greater delays in obtaining ethics clearance and greater likelihood that researchers would abandon a research project because of a lack of host country ethics clearance.[43] Several individuals responding to NBAC's request for comments noted that collaborative ethics training projects are needed in their countries, and survey respondents made similar proposals.

Even where published guidelines or regulations exist, they cannot serve as adequate protection for research participants unless they are properly implemented and enforced. For example, researcher Sana Loue testified that there is no infrastructure in Uganda that has oversight and enforcement authority over the operation of research ethics committees at the institutional and

Exhibit 5.2: National and International Guidelines Reviewed by NBAC

- Australia – *National Statement on Ethical Conduct in Research Involving Humans* (NHMRC 1999)
- Brazil – *Resolutions No. 196/1996, 251/1997*, and *292/1999* (NHC 1996; NHC 1997; NHC 1999)
- Canada – *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (MRC-CA, NSERC, SSHRC 1998)
- China – *Guidelines on Ethical Review of Medical Research* (Committee on Research Involving Human Subjects 1998)
- Council for International Organizations of Medical Sciences – *International Guidelines for Ethical Review of Epidemiological Studies* (CIOMS 1991)
- Council for International Organizations of Medical Sciences – *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS 1993)
- Council of Europe – *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine* (Council of Europe 1997)
- *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects* (WMA 1964, as amended in 2000)
- Denmark – *Act on a Scientific Ethical Committee System and the Handling of Biomedical Research Subjects*[44]
- Finland – *Decrees 785/1992, 494/1998* and *986/1999*
- France – *Law 88-1138 Regarding the Protection of Persons Agreeing to Biomedical Research*[45]
- India – Indian Council of Medical Research. *Ethical Guidelines on Biomedical Research Involving Human Subjects* (ICMR 2000)
- International Conference on Harmonisation – *ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice* (ICH 1996)
- Joint United Nations Programme on HIV/AIDS – *Ethical Considerations in HIV Preventive Vaccine Research: UNAIDS Guidance Document* (UNAIDS 2000)
- Netherlands – *Law Regarding Medical-Scientific Research on Humans*[46]
- New Zealand – *HRC Guidelines on Ethics in Health Research* (HRC 1997)
- The Nuremberg Code (Nuremberg Code 1947)
- South Africa – *Guidelines on Ethics for Medical Research* (MRC-SA 1993)
- Thailand – *Rule of the Medical Council on the Observance of Medical Ethics* (MOPH 1995)
- Uganda – *Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda* (National Consensus Conference 1997)
- United Kingdom – *Guidelines for Good Clinical Practice in Clinical Trials* (MRC-UK 1998)
- United Kingdom – *Interim Guidelines for Research Involving Human Participants in Developing Societies: Ethical Guidelines for MRC-Sponsored Studies* (MRC-UK 1999)
- United States – Food and Drug Administration (21 CFR 50; 21 CFR 56; 21 CFR 312)
- United States – The Common Rule (45 CFR 46)
- United States – Agency for International Development (22 CFR 225)

national levels. In the Ugandan context, the situation is further complicated by a controversy between the National Drug Authority, the Uganda National Council of Science and Technology, and the Ministry of Justice regarding exactly who should assume responsibility for the oversight of ethics committees. Although the consequences of violating the Ugandan guidelines for the protection of research participants include a prohibition against ever again conducting research in Uganda, the termination of a specific research project, or the temporary suspension of a research project pending further investigation, mechanisms for monitoring and enforcing these guidelines have not yet been put into place.

Nonetheless, because some mechanism must be available to provide ethics review before research is conducted in another country, it is in the interests of all

parties to develop such a capacity in the host country. And because the number of U.S.-sponsored research studies conducted in collaboration with and situated within developing countries is increasing, self-interest dictates a need to have effective local review mechanisms in place so that the efficiency of these efforts may be enhanced without compromising the protection of research participants. Although, ideally, local ethics review will enhance the protection of human participants in clinical trials—regardless of the country in which the research occurs—NBAC recognizes that it will take time for all countries to develop the infrastructure needed to conduct such review.

> ***Recommendation 5.7:*** **Where applicable, U.S. sponsors and researchers should assist in building the capacity of ethics review committees in developing countries to conduct scientific and ethical review of international collaborative research.**

Conclusions

This chapter has identified ways in which U.S. regulations might be improved to accommodate some of the barriers to successful international research collaboration without lowering the substantive ethical standards embodied in the U.S. regulations. It has focused in particular on the assurance process and on the abilities of U.S. federal agencies to adopt a common set of criteria for making determinations of equivalent protection. In addition, this chapter has identified two ways that additional benefits can flow to the developing countries in which clinical trials have been conducted—through building capacity to conduct research and through building capacity to conduct scientific and ethics review. In addition, NBAC discussed some of the current challenges faced by ethics review committees and reiterated the need for ethics review in the host country as well as by a U.S. IRB.

NBAC recognizes, however, that establishing the means to enhance international collaborative research must go beyond regulations (King et al. 1999). Chapter 4 describes the relationship between researchers and participants as unique. Although it is necessary to ensure that research is conducted in an ethically defensible manner, this issue is infrequently discussed in the context of traditional research ethics or in relationship to the cross-cultural environment in which international collaborative research is conducted. Trust is not subject to laws or regulations. Rather, it is the foundation for the creation of relationships between individuals involved in research and for the connections and interactions that flow from them. An international collaboration may consist of researchers from many countries and sponsors from varying disciplines, institutions, communities, and countries, all of whom bring different viewpoints and perspectives to the table. The relationships and, ultimately, the level of trust established among individuals, institutions, communities, and countries are determined by complex and often contradictory social, cultural, political, economic, and historical factors. It is essential, therefore, for sponsors, the countries from which they come, and researchers to work together to enhance these collaborations by creating an atmosphere that is based on trust and respect.

Notes

1 Available at http://ohrp.osophs.dhhs.gov/humansubjects/assurance/assurancepurps.htm. Last accessed January 5, 2001.

2 USAID and other federal agencies that are signatories to the Common Rule also have the authority to negotiate assurances. When USAID provides support to a U.S.-based institution conducting research in another country, a DHHS-approved assurance may be applied to USAID-sponsored research. If not, the institution must obtain an assurance from USAID. In this type of situation, USAID trusts and relies heavily on the judgment of the U.S.-based IRB to protect human research participants. Although USAID may be familiar with the institution's assurance, it does not examine each new project or protocol. The foreign institution can then rely on review by the IRB of its U.S. partner holding the assurance. USAID encourages, but does not require, that a host country IRB also review the research. When USAID supports research in other countries, the recipient organization, institution, or country can agree to be bound by a USAID assurance. USAID, however, may ensure that requirements for protecting research participants are met through determinations of equivalent protections, discussed later in this chapter.

3 From data collected by Kass, N., and L. Dawson 1999, *Preliminary Focus Group Report*, 31. For Kass, N., and A. Hyder, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations." This background paper was prepared for NBAC and is available in Volume II of this report.

4 Plowe, C., Testimony before NBAC. February 29, 2000. Herndon, Virginia. Meeting transcript, 102.

5 From data collected by Kass, N., and L. Dawson, 1999, *Preliminary Focus Group Report*, 30. For Kass, N., and A. Hyder, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations."

6 Ibid., 115–117.

7 From data collected by Kass, N., and L. Dawson, 1999, *Preliminary Focus Group Report*, 31. For Kass, N., and A. Hyder, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations."

8 Public Law 717, 75th Congress.

9 Public Law 184, 78th Congress.

10 On January 24, 2001, OHRP announced the establishment of an Office of International Activities. The proposed office would provide an independent body to provide additional review and input for U.S.-sponsored research involving foreign populations.

11 See Kass and Hyder, 76.

12 Ibid., 77.

13 Ibid., 159.

14 Ibid., 209.

15 See Dickens, B.M., "The Challenge of Equivalent Protection," 26. This background paper was prepared for NBAC and is available in Volume II of this report.

16 From data collected by Kass, N., and L. Dawson, 1999, *Preliminary Focus Group Report*, 30. For Kass, N., and A. Hyder, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations."

17 Ibid., 159.

18 See Kass and Hyder, 51.

19 Ibid.

20 Ibid.

21 See Marshall, P., "The Relevance of Culture for Informed Consent in U.S.-Funded International Health Research," 31. This background paper was prepared for NBAC and is available in Volume II of this report.

22 Pape, J.P., Testimony before NBAC. February 29, 2000. Herndon, Virginia. Meeting transcript, 30.

23 Ibid.

24 See Kass and Hyder, 147–149.

25 See Marshall, 32.

26 Plowe, C., Testimony before NBAC. February 29, 2000. Herndon, Virginia. Meeting transcript, 103–104.

27 From data collected by Kass, N., and L. Dawson, 1999, *Preliminary Focus Group Report*, 30. For Kass, N., and A. Hyder, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations."

28 Ibid., 13, 210.

29 Garcia, H., Public comment submitted to NBAC. Received November 9, 2000; Wikler, D., Public comment submitted to NBAC. Received November 13, 2000.

30 From data collected by Kass, N., and L. Dawson, 1999, *Preliminary Focus Group Report*, 32. For Kass, N., and A. Hyder, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations."

31 Ibid., 30.

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

33 Puglisi, J.T., Testimony before NBAC. March 3, 1998. Tysons Corner, Virginia. Meeting transcript, 9.

34 See Dickens, 6.

35 Ibid., 3.

36 Plowe, C., Testimony before NBAC. February 29, 2000. Herndon, Virginia.

37 See Kass and Hyder, 222.

38 Ibid., 67.

39 Keusch, G.T., Letter of Welcome, Fogarty International Center. Available at www.nih.gov/fic/about/welcome.html. Last accessed January 4, 2001.

40 Fogarty International Center. International Research Ethics Initiatives. Available at www.nih.gov/fic/news/bioethics.html. Last accessed January 12, 2001.

41 Global Forum for Health Research website. Available at www.global forumhealth.org/default2.htm. Last accessed September 2, 2000.

42 From data collected by Kass, N., and L. Dawson, 1999, *Preliminary Focus Group Report*, 30. For Kass, N., and A. Hyder, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations."

43 See Kass and Hyder, 209–210.

44 Act No. 503 of 24 June 1993.

45 Law 88-1138 of December 20, 1988, regarding the protection of persons agreeing to biomedical research, J.O. December 22, 1988, at 16032.

46 Law of 26 February 1998, containing regulations with regard to medical-scientific research on humans, Staatblad (Official Law Gazette of the Netherlands), 161.

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Appendix A

Acknowledgments

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Appendix B

Comparative Analysis of International Documents Addressing the Protection of Research Participants

Comparative Analysis of International Documents Addressing the Protection of Research Participants[1]

Document/Country of Origin	Consent	Privacy and Confidentiality	Prior Review	Compensation for Injury	Obligations to Participants During/After the Trial[2]	Interventions Made Available to Countries	Harmonize Standards: Countries/ Documents	Force of Law	Covers Privately Funded Research
Nuremberg Code (1947)	●				●				●
Declaration of Helsinki (2000)	●	●	●		●	●	●		●
Council of Europe (1997)	●	●	●	●	●		●	[3]	●
Council for International Organizations of Medical Sciences (1993)	●	●	●	●	●	●	●	[4]	●
International Conference on Harmonisation (1996)	●	●	●	●	●		●	●	In some cases
UNAIDS (2000)	●		●	●	●	●			●
Australia (1999)	●	●	●	●	●		●	●	●
Brazil (1996–1999)	●	●	●	●	●	●	●	●	●
Canada (1998)	●	●	●			●[5]	●	●	●
China (1998)	●	●	●	●	●				
Denmark (1992)	●	[6]	●					●	●
Finland (1992–1999)	●	●	●		●		●	●	●
France (1988)	●		●	●				●	

1 ● indicates that the document or country makes mention of a topic. For a more complete presentation of the actual provisions contained in a particular document, see Volume II of this report.

2 This category includes many different obligations to research participants covering topics such as treatment, stopping trials, provision of post-trial interventions, etc. Note that some provisions focus only on obligations during a trial, while others focus on post-trial obligations.

3 Although this document does not have the force and effect of law, there are related provisions concerning judicial protections and sanctions.

4 Although this document does not have the force and effect of law, there are related provisions concerning sanctions and noncompliance.

5 The Canadian document mentions an obligation to engage in discussions about post-trial access, but it does not impose an affirmative obligation to make interventions available.

6 The Danish Council of Ethics has a separate report entitled *Protection of Personal Sensitive Information*.

Document/Country of Origin	Consent	Privacy and Confidentiality	Prior Review	Compensation for Injury	Obligations to Participants During/After the Trial	Interventions Made Available to Countries	Harmonize Standards: Countries/ Documents	Force of Law	Covers Privately Funded Research
India (2000)	●	●	●	●	●		●	●	
Netherlands (1998)	●	●	●	●	●			●	●
New Zealand (1997)	●	●	●	●				●	
South Africa (1993)	●	●	●	●	●				
Thailand (1995)	●		●		●			●	●
Uganda (1997)	●	●	●	●	●	●	●	●	●
United Kingdom (1999)	●	●	●	●	●	●[7]	●		
United States (FDA) (2000)	●	●	●	●	●	●	●	●	●
United States (Common Rule) (2000)	●	●	●	●	●		●	●	In some cases
United States (USAID) (2000)	●	●	●	●	●		●	●	In some cases

7 The *Interim Guidelines for Research Involving Human Participants in Developing Societies: Ethical Guidelines for MRC-Sponsored Studies* from the United Kingdom mentions an obligation to engage in discussions about post-trial access but does not impose an affirmative obligation to make interventions available.

Appendix C

Prior Agreements

The World Health Organization

The World Health Organization (WHO) is an intergovernmental, technical unit of the United Nations system consisting of 191 Member States. In conjunction with its role "of harnessing support from among a variety of players to meet its health development agenda" (WHO 1999b, 2), WHO collaborates with industry to promote the research and development of new health-related products and technologies for the prevention, diagnosis, control, and treatment of diseases that are of priority to WHO. It is also committed to improving access to products in its study populations. The types of products that are developed through social science research, biomedical research, operations/service research, and epidemiological research include information, drugs and devices, changed practices, and improved services.[1] An essential element of these collaborations is the negotiation of agreements prior to the commencement of work to ensure that final products will be made widely available to developing countries at low cost. WHO's collaborative partners include pharmaceutical and biotechnology companies as well as manufacturers of health-related instruments and equipment. It is estimated that WHO has employed well over a dozen such agreements.[2]

WHO requires that any commercial enterprise with which it collaborates "be a suitable partner" (WHO 1999b, 3). In determining the suitability of a potential collaborator, WHO considers three factors: first, whether the major products or services of the industry are beneficial to health; second, whether the industry engages on a large scale in practices that are negative to health; and third, whether the likely public health benefit will outweigh any possible harmful practices, products, or services (WHO 1999b).

Generally, WHO collaborates with industry in two ways. First, it may design, conduct, and fund studies, trials, and other development work on proprietary industry products in which WHO expresses an interest and/or is invited to collaborate. Second, it may license certain intellectual property that WHO owns to industry for further development into a final product. Industry also licenses and manufactures such products. Intellectual property is usually acquired by WHO through research performed by institutions that it funds. However, such property is of little direct benefit to the organization because it lacks the facilities, resources, and know-how to further utilize it. This type of effort may include the provision by WHO of technical and financial support.

Prior agreements between WHO and its industrial partners are mindful of the organization's interest in ensuring that successful products are made available to the public sector, and to developing countries in particular, on preferential terms and of industry's interest in obtaining a reasonable return on its investment (WHO 1985). The agreements follow standard principles set forth in WHO's *Policy on Patents: Information Paper on WHO Patents Policy* (1985) and its *Guidelines on Interaction with Commercial Enterprises* (1999b) and are negotiated on a case-by-case basis. As a result, their final terms and conditions may differ depending on a variety of factors, such as the ownership of the intellectual property rights in question, the stage of the product's development at the time of negotiations, and the past and expected future contributions to the collaboration by the parties. The negotiations are then memorialized in a document called a Memorandum of Understanding (MOU) (WHO 1999a).

In all of its collaborations, WHO seeks to ensure that its public sector objectives are achieved by requiring that prior agreements provide that products and technologies developed with WHO support will be made generally available to both the public and to public sector agencies. The MOU defines a public sector agency as "a government, or a department or agency thereof, or a recognized non-profit organization or entity, including WHO and any other organization within the United Nations system" (WHO 1999a, 6). Agreements usually provide that the product will be made available to the public either by the industry partner or through a license to WHO, if the industry partner decides to abandon the project. In addition, the industry partner must agree to make the product available to public sector agencies for use in the public sector of developing countries "in sufficient quantities to meet the needs of such agencies" for distribution in such countries (WHO 1999a, 3).

In addition to commitments relative to quantity, commitments are also sought relative to pricing. Pricing commitments obtained from industry partners by WHO on behalf of public sector agencies may differ depending on whether the product will be distributed through the private sector. If it is to be distributed through both the private and public sectors, the price at which the product is made available to public sector agencies "shall be (i) preferential compared to the Private Sector price, and (ii) set at the lowest possible level permitting a commercially reasonable return on combined worldwide sales of the Compound for Distribution in both Public and Private Sectors" (WHO 1999a, 3). The product can be sold in the private sector at whatever price the industry partner chooses. Pricing commitments from industry partners can also take the form of "cost, plus a modest mark-up" or of a maximum price, depending on the circumstances.[3] "Cost, plus a modest mark-up" can be used at any stage of the collaboration, provided the terms can be defined and agreed upon. In contrast, a maximum price commitment can only be used if the development work is at such a point that the parties are able to determine what it will "cost to make a product."[4] If the product will not be distributed through the private sector, availability to public sector agencies shall be "at the lowest possible, commercially reasonable price" (WHO 1999a, 3). Bulk purchase is another mechanism used to ensure availability of products at the lowest cost possible.[5] To a much lesser degree, WHO may receive royalties that are invested in the public interest either to offset the cost of products or to fund further research to meet the needs of developing countries.[6]

In addition to quantity and pricing commitments, a final item that is negotiated in each case is the period of years during which product availability is ensured. Although there is no fixed time, "at the end of the agreed period of time the company concerned must agree to provide technology transfer to enable the country or countries concerned to continue either to manufacture the product themselves or through a sublicensing agreement to have somebody else manufacture it for them."[7]

Over the years, WHO and the private sector have successfully collaborated on a variety of projects in many areas, of which tropical diseases and reproductive health are just two examples. Drugs to combat malaria, schistosomiasis, and onchocerciasis have been developed in this way. So have new and improved contraceptives, including emergency contraception, injectable hormonal preparations for men and women, vaginal rings, and immunocontraceptives.[8]

The International AIDS Vaccine Initiative

The International AIDS Vaccine Initiative (IAVI) is an international scientific nonprofit organization founded in 1996 with the single aim of accelerating the development of safe, effective, and accessible HIV vaccines for global use. IAVI's research focus is on vaccines for developing countries. Through the investment of what it calls "social venture capital," IAVI's goal is to develop vaccines that "would be inexpensive to manufacture, easy to transport and administer, stable under field conditions and require few inoculations" (Zonana 1999, 5). IAVI's work is driven by the belief that a vaccine represents the world's best hope to end the AIDS epidemic.

In June 1998, IAVI issued a *Scientific Blueprint for AIDS Vaccine Development* (IAVI 1998) that links promising vaccine approaches with countries in which to test them. It seeks to accelerate product development and clinical trials through public/private partnerships among

vaccine developers, manufacturers, and those who will test the vaccines. Because it is in developing countries where the epidemic is the most severe and the need for a vaccine is greatest, most of IAVI's efforts are focused there. These collaborations seek to ensure that people in developing countries for whom particular vaccines are designed benefit from those vaccines once they are developed.

To date, IAVI has invested about $15 million to create four North-South vaccine development partnerships. It also contributes expertise "as needed, in areas ranging from project management to regulatory affairs and infrastructure for clinical trials."[9] The first is an academic partnership with the University of Oxford and the University of Nairobi to develop for East Africa two separate vaccine constructs to be used in combination. Phase I clinical trials began in Oxford in August 2000, and the Kenyan government has approved Phase I clinical trials, which have begun in Nairobi.

The second is an industry/academic/developing country government collaboration, which involves Alphavax Human Vaccines, Inc., a small North Carolina biotechnology firm, and three institutions in South Africa: the University of Capetown, the National Institute of Virology, and the Medical Research Council. The goal of this collaboration is to develop a vaccine to be tested in South Africa (AVAC 1999).[10]

In February 2000, IAVI entered into a third partnership with Targeted Genetics Corporation (TGC), of Seattle, Washington, and the Children's Research Institute on the campus of Children's Hospital, in Columbus, Ohio, to develop a vaccine for Southern and Eastern Africa that will utilize a vector technology developed by TGC to deliver HIV genes as a form of genetic immunization. TGC's manufacturing process is based on a cell line originally developed by a researcher at the Children's Research Institute, which holds the patent to the technology. The vaccine being developed has the characteristic of giving long-standing protection from a single dose and, therefore, may be particularly appropriate for areas where vaccine delivery is difficult. Finally, in May 2000, IAVI entered into a fourth partnership with the Institute of Human Virology. The vaccine under development in partnership with Uganda will be designed to use genetically modified *Salmonella* bacteria as an oral delivery system for DNA. The ease of use and extremely low cost make this a very promising vaccine for large-scale field use. IAVI expects to launch more partnerships later this year.

IAVI's focus on encouraging industrial participation in AIDS vaccine development is based on the belief that private sector involvement and ingenuity in this process are crucial. A successful AIDS vaccine will necessarily rely on technologies covered by new and existing patents. Realistically, however, prospects for the development of an AIDS vaccine by the pharmaceutical and biotechnology industries alone are unlikely for four reasons. First, the development costs of a vaccine are high; second, a very large percentage of the potential vaccine market probably will be in developing countries without the resources to buy the vaccine; third, because there is a difference in the predominant viral strains in developed and developing countries, the vaccine that is developed may have to be region specific (Nchinda 1999); and fourth, the highly charged political environment for HIV/AIDS is becoming a disincentive for vaccine development.

IAVI has been instrumental in structuring prior agreements with industry partners to facilitate developing country access to vaccines developed with IAVI resources at reasonable prices. According to Seth Berkley, IAVI's president, "[d]ealing with the access issue at the start of the process represents a wholly new approach to vaccine development that will ultimately benefit both industrialized and developing countries" (Zonana 1999, 5).

IAVI's prior agreements with its industrial partners call for reasonable pricing policies for the public sector in developing countries. The public sector is considered the governments and not-for-profit organizations serving developing countries. In return for financing the early vaccine development, companies agree to make the vaccine available to the public sector in developing countries in quantities reasonable to demand and at a cost of manufacturing plus a reasonable profit, which is defined. If companies do not do so, IAVI has the right to transfer the intellectual property and background technology to another manufacturer. If the costs of manufacture seem unreasonable, IAVI is permitted under the terms of the agreement to obtain alternative bids for manufacture. If a

third party can produce the vaccine for less, the company must match that price or contract the manufacturing from the third party. The vaccine can be sold at the price the market will bear in the developed world and in private markets in the developing world. If its partner is unable to meet its overall obligations under the agreements, IAVI retains the right to choose from several options to ensure global accessibility.

Investment in industry is not the only component of IAVI's strategy for making vaccines available in developing countries. IAVI is also working on the creation of vaccine purchase funds along with the World Bank in an effort to provide additional financial incentives for industry to engage in vaccine development. Vaccine purchase funds are "mechanisms that can create a market in the developing world to purchase these vaccines and to distribute them. The idea would be that...before the vaccine is ever made [we] would have a mechanism in place to have the vaccines purchased."[11] The creation of these funds is based on the notion that although companies should not lose money on the vaccines they produce, the financial return that companies can expect to receive (and must be willing to accept) will differ according to the market in question. The profit margin in the developing world would be next to nothing; however, companies that are willing to deal in those markets receive other important benefits, such as economies of scale and entrée into those markets.[12]

To help ensure that sufficient quantities of successful vaccines are available to the developing world, IAVI is investigating other mechanisms for vaccine production. It is helping to launch national vaccine development programs in several developing countries with a significant AIDS problem. These countries, which include South Africa, India, and China, not only have large markets, but they also have large vaccine industries and therefore the potential capability to produce vaccines locally.

In addition to the involvement of industry, IAVI believes that international funding from governments is critical to creating the global consortium necessary to ensure that a safe and effective vaccine is developed that will be accessible to the developing country poor. Thus far, IAVI has received financial support from Canada, the United Kingdom, and the Netherlands. The United States is the fourth country to provide support for IAVI's work through the FY 2001 Foreign Operations Appropriations.[13] (See Exhibit 4.1.)

When asked if the types of agreements that IAVI has forged will work in other contexts for other diseases with different partners, Seth Berkley explained that he sees IAVI's quest for an AIDS vaccine "as a chance to begin to develop the mechanisms that make sense, that can be used across the whole range of different products. When we sit down and compare the issues on malaria to HIV, they are not that different."[14]

IAVI has updated its 1998 *Blueprint* in *Scientific Blueprint 2000: Accelerating Global Efforts in AIDS Vaccine Development* (IAVI 2000c), which is designed to continue to accelerate the development of AIDS vaccines for use throughout the world. The 2000 *Blueprint* calls for the establishment of four to eight new Vaccine Development Partnerships with the goal of initiating efficacy trials of three of the most promising AIDS vaccines within five to seven years. IAVI has created yet another blueprint, *AIDS Vaccines for the World: Preparing Now to Assure Access* (IAVI 2000a), which "presents a strategy for addressing the many economic, political, and logistical obstacles to immediate and widescale access in the developing world" and seeks to avoid "the typical ten to twenty year delay in introducing new vaccines to poor countries" (IAVI 2000b, 9).

VaxGen

VaxGen, a California-based biotechnology company, developed an AIDS vaccine known as "AIDSVAX." AIDSVAX is the first vaccine candidate in the world to enter Phase III efficacy studies. The company raised money to finance its own trials in an effort to get the vaccine tested as quickly as possible (AVAC 1999). Two trials are being conducted on two different vaccines. Each vaccine is designed to prevent a particular strain of the virus prevalent in the country in which it is being tested. The first trial is being conducted in the United States. Between June 1998 and October 1999, more than 5,400 participants were recruited, mostly men who have sex with men. Thailand is the site of the second trial, also currently ongoing. Recruitment of 2,500 participants, all

intravenous drug users at high risk of becoming HIV infected, began in March 1999 and concluded in August 2000.

The Thai government, the Bangkok municipal government, and Mahidol University have been proactive in working with VaxGen in testing the potential vaccine candidate on the Thai population. Despite the implementation of other interventions, Thailand has one of the fastest growing rates of HIV infection in the world, and the government has made the development of an AIDS vaccine a health priority. Thailand was chosen as a study site for several reasons. One reason is the strong professional relationship that has developed between key individuals at VaxGen and Thai researchers. Another reason is that the two predominant strains of the HIV virus present in Thailand are similar, making it easier to test the vaccine. Finally, WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) selected and supported the building of infrastructure to conduct vaccine trials, and UNAIDS and the Centers for Disease Control and Prevention (CDC) have supported cohort development over a number of years. The CDC has developed a cohort of injecting drug users from methadone clinics run by the Bangkok Metropolitan Association, which is now being recruited for the vaccine trial.[15]

As a condition of participating in this study, the Thai government required first that any vaccine tested in Thailand have a reasonable likelihood of preventing infection by the particular strains of the virus most prevalent in the country. AIDSVAX B/E was developed specifically to prevent further infections by the two subtypes, B and E, that are prominent in those infected through sexual exposure and in the injecting drug user population. The Thai government also required that the country receive research benefits in two forms—the product itself and capacity building.

In its discussions with the Thai Ministry of Public Health, VaxGen offered an informal agreement that should there be a licensed product, the country would receive special treatment from the company in making the product available in Thailand.[16] VaxGen has agreed to make a concerted effort to decrease the cost of the vaccine for the country. Or, if feasible, because Thailand has a strong local pharmaceutical industry, arrangements could be made for a bulk shipment of the product with filling and finishing in Thailand.[17] This arrangement was described by one Thai AIDS researcher as a "letter of intent" and the first of its kind in any vaccine trial in the world (IAVI 1999, 7). Discussions about ways of making the product available after completion of the study are ongoing between the parties. Although there is a formal agreement governing the conduct of the Phase III study in Thailand, nothing beyond the letter of intent has been requested by the Thai government.

Many of the benefits that will accrue to Thailand as a result of participating in the study take the form of capacity building. The Thais view the transfer of such knowledge and technology as extremely important. Capacity building is occurring in three ways. First, VaxGen is transferring its data management capabilities to Thailand. A complete data center has been established so that the Thais have state-of-the-art hardware and software. VaxGen is teaching the Thai data management unit how to collect, monitor, and validate data to comply with international clinical research guidelines. Second, the company has developed a repository of laboratory specimens. Technical know-how is being provided to the Thais about how to store, track, locate, and connect data to specimens. Third, VaxGen is training the Thais in clinical research and good clinical practices relative to conducting Phase III trials. The Thais' experience has been previously limited to Phase I and II trials. By having the Thais engage in these types of capacity-building activities, the goal is to provide them with the necessary skills and knowledge to enable them to function independently and conduct Phase III clinical trials on their own. Capacity building is occurring as the result of a verbal commitment between VaxGen and the Thais. It is not part of the letter of intent.[18]

The prior agreement negotiated between VaxGen and the Thai government was portrayed in a far less flattering light in the last of a six-part series, "The Body Hunters," that ran in the *Washington Post* in late December 2000 (Flaherty and Struck 2000). The article made several allegations concerning post-trial benefits sought by the Thais for either research participants or the country itself that VaxGen would not agree to provide. First, VaxGen refused to pledge care for research participants who

became HIV infected during the trial. Thai health authorities finally agreed to provide the best local treatment, described as "years behind what an American could expect." Second, VaxGen refused to guarantee that the vaccine, if proven effective, would be sold to the Thais at a reduced price. Flaherty and Struck noted that "[a] 'gentlemen's agreement' the company wrote in 1998 to Thai health officials suggested that if the Thais helped with packaging the vaccine, VaxGen might be able to reduce the country's costs for the vaccine." But, according to the company president, VaxGen "can't give vaccine away and bankrupt the company." Finally, VaxGen rejected the Thai requests for profit-sharing or a manufacturing plant to be located in the country. Said one Thai representative who reviewed the study and is now a member of the Thai Senate, "We were making test subjects available and we were agreeable to that. But on the other hand, we did not have that much bargaining power. Our situation was desperate." VaxGen has invested almost $600,000 in equipment and facilities that will remain in Bangkok when the study is over (Flaherty and Struck 2000).

UNAIDS

UNAIDS has employed prior agreements in two instances. One agreement was made with the manufacturers of the female condom before the research began. That agreement stipulates that the product should be made available to the public sector in developing countries at a preferential price. The price at which the product is sold in Brazil, Lesotho, South Africa, Thailand, Zambia, Zimbabwe, and other developing countries is U.S. $0.61. The manufacturers' price in industrialized countries is reported to be significantly higher. Thus far, the manufacturers of the female condom have complied with the agreement.

UNAIDS also entered into a preferential pricing agreement with Columbia Laboratories prior to the commencement of UNAIDS-funded microbicide trials in Côte d'Ivoire, South Africa, Benin, and Thailand. It is expected that the product, if proven successful, will be made available by Columbia Laboratories, its manufacturer, to all trial participants at no cost until it is registered in the markets in the countries where the research is conducted. After that time, it will be available at a reduced price in the private sector of all developing countries.[19]

Notes

1 Griffin, P.D., Testimony before the National Bioethics Advisory Commission (NBAC). January 13, 2000. Washington, D.C.

2 E-mail communication between P. David Griffin, WHO, and Alice Page, NBAC. July 18, 2000.

3 E-mail communication between P. David Griffin, WHO, and Alice Page, NBAC. February 11, 2000.

4 E-mail communication between P. David Griffin, WHO, and Alice Page, NBAC. July 18, 2000.

5 Griffin, P.D., Testimony before NBAC. January 13, 2000. Washington, D.C.

6 Ibid.

7 Ibid., Meeting transcript, 144.

8 Ibid.

9 Available at www.iavi.org/programs_z_science_4-1-7.html. Last accessed February 2, 2001.

10 Available at www.iavi.org. Last accessed January 9, 2001.

11 Berkley, S., Testimony before NBAC. January 13, 2000. Washington, D.C. Meeting transcript, 303.

12 Ibid.

13 Public Law 106-429.

14 Berkley, S., Testimony before NBAC. January 13, 2000. Washington, D.C. Meeting transcript, 308.

15 E-mail communication from Marlene Chernow, VaxGen, to Alice Page, NBAC. May 1, 2000.

16 E-mail communication from Donald Francis, VaxGen, to Alice Page, NBAC. November 17, 1999.

17 Ibid.

18 E-mail communication from Marlene Chernow, VaxGen, to Alice Page, NBAC. May 1, 2000.

19 E-mail communication from Julian Fleet, UNAIDS, to Alice Page, NBAC. May 17, 2000.

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Appendix D

Public Comments on NBAC's September 29, 2000, Draft

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Kate Phillips, Council on Governmental Relations (Washington, DC)

Christopher Plowe, American Society of Tropical Medicine and Hygiene (Northbrook, IL)

Peter N. Poon and John H. Mather, Department of Veterans Affairs, Office of Research Compliance and Assurance (Washington, DC)

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Norma Reyes, Ethical Committee of the National Institute of Health (Lima, Peru)

Udo Schuklenk, University of the Witwatersrand (Johannesburg, South Africa)

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Daniel Wikler, World Health Organization (Geneva, Switzerland)

Catherine Wilfert and Kate Carr, Elizabeth Glaser Pediatric AIDS Foundation (Washington, DC)

Erin D. Williams, Foundation for Genetic Medicine, Inc. (Manassas, VA)

Wayne L. Wilson (Apex, NC)

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Peter F. Wright, Vanderbilt University Medical Center (Nashville, TN)

Dezhong Xu, Fourth Military Medical School (Xi'n, China)

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Stanley Zinberg, American College of Obstetricians and Gynecologists (Washington, DC)

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Appendix E

Public and Expert Testimony

September 16–17, 1999 (Arlington, Virginia)

Public:
Peter Lurie, Public Citizen

Expert:
Donald Burke, Johns Hopkins School of Hygiene and Public Health
Jack Killen, National Institutes of Health
Alfred Sommer, Johns Hopkins School of Hygiene and Public Health
Jeremy Sugarman, Duke University School of Medicine
Patricia Marshall, Loyola University-Chicago
Liza Dawson, Johns Hopkins School of Hygiene and Public Health
Noreen Teoh, Johns Hopkins School of Hygiene and Public Health
Elisa Eiseman, RAND Corporation

October 21–22, 1999 (Washington, DC)

Public:
Adnan Hyder, Johns Hopkins University
Susan Poland, Kennedy Institute of Ethics, Georgetown University

Expert:
Sam Avrett, AIDS Vaccine Advocacy Coalition
Sana Loue, Case-Western Reserve University

December 2–3, 1999 (Baltimore, Maryland)

Public:
Kohar Jones
Peter Lurie, Public Citizen
Steven Goodman, Johns Hopkins University School of Medicine

Expert:
Christopher Whalen, Case-Western Reserve University
Sidney Wolfe, Public Citizen
Stephen Legakos, Harvard University School of Public Health
Dennis Dixon, National Institute of Allergy and Infectious Diseases
Kay Dickersin, Brown University
Gary Chase, Henry Ford Health Sciences Center
David Lepay, Food and Drug Administration

January 13–14, 2000 (Washington, DC)

Expert:
Robert Levine, Yale University School of Medicine
Ruth Faden, Johns Hopkins University
P. David Griffin, World Health Organization
Leonard Glantz, Boston University School of Public Health
Seth Berkley, International AIDS Vaccine Initiative

February 29–March 1, 2000 (Herndon, Virginia)

Expert:
Jean Pape, University of Haiti
Grace Malenga, University of Malawi College of Medicine
Christopher Plowe, American Society of Tropical Medicine and Hygiene

April 6–7, 2000 (Washington, DC)

Expert:
Bert Spilker, Pharmaceutical Research and Manufacturers of America
R. Sebastian Wanless, Bristol-Myers Squibb
Rose Snipes, Glaxo Wellcome
Bernice Welles, Genentech, Inc.

May 4–5, 2000 (Madison, Wisconsin)

Expert:
Norman Fost, University of Wisconsin-Madison
Susan Nayfield, National Cancer Institute
Sofia Gruskin, Harvard University School of Public Health
George Andreapoulos, University of New York
Bernard Dickens, University of Toronto

June 5–6, 2000 (San Francisco, California)

Public:
Jerome Weinberg, Glendale Adventist Medical Center

September 12–13, 2000 (Washington, DC)

Public:
Francis Crawley, European Forum for Good Clinical Practice
Steven Peckman, University of California at Los Angeles

December 7–8, 2000 (Washington, DC)

Public:
Peter Lurie, Public Citizen
Sidney Wolfe, Public Citizen
Oluwole O. Odujinrin, Cell Therapeutics, Inc.

January 18–19, 2001 (Vienna, Virginia)

Public:
Sidney Wolfe, Public Citizen

Appendix F

Commissioned Papers and Staff Analysis

The following papers, prepared for the National Bioethics Advisory Commission, are available in Volume II of this report:

The Challenge of Equivalent Protection
Bernard M. Dickens
University of Toronto

Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations
Nancy Kass and Adnan A. Hyder
Johns Hopkins University

The Relevance of Culture for Informed Consent in U.S.-Funded International Health Research
Patricia A. Marshall
Loyola University-Chicago

Comparative Analysis of International Documents Addressing the Protection of Research Participants
Staff Analysis
National Bioethics Advisory Commission

International Perspectives on Protecting Human Research Subjects
Jeremy Sugarman, Benjamin Popkin, Judith Fortney, and Roberto Rivera
Duke University

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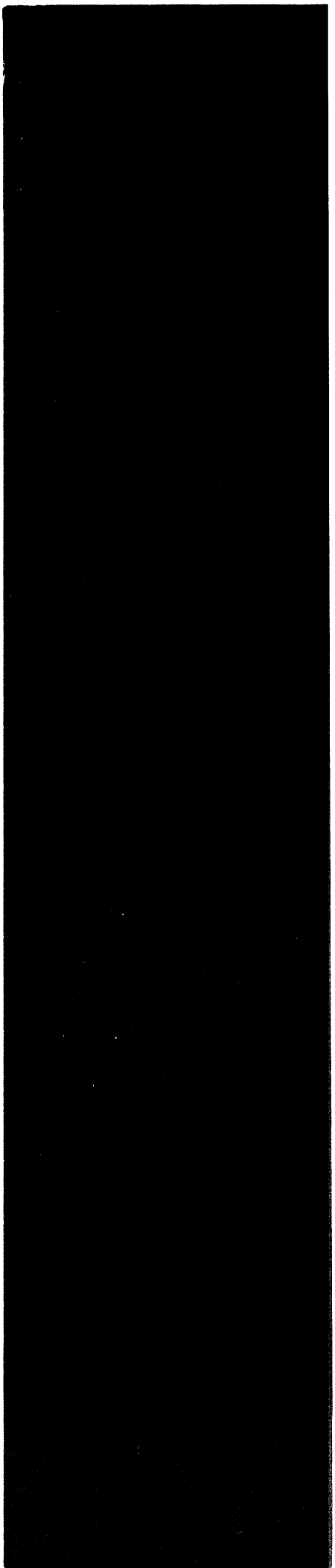
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