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NATIONAL BIOETHICS ADVISORY COMMISSION

October 11, 2000

Dear Colleague:

Enclosed is a copy of the draft of NBAC's report on *"Ethical and Policy Issues in International Research"*. As in previous reports, we are interested in learning the views of many individuals and groups on this important subject. Therefore, I am inviting you to provide comments on this draft report, and would appreciate receiving them before November 13, 2000.

NBAC was established by President Clinton in October 1995 to advise him and other departments and agencies in the government on bioethics issues. In particular, NBAC makes recommendations for improving the protection of human subjects in research. This report, therefore, falls within NBAC's mandate.

The purpose of this report is to consider the ethical, legal, and policy issues that arise when research that is subject to U.S. regulations, is sponsored or conducted in other countries. NBAC's goal is to identify these issues and determine whether they are unique to international settings and deserve particular attention from policymakers. In this report NBAC is discussing issues such as: recruitment of subjects, informed consent, and the risks and potential benefits of conducting research. In addition, the Commission comments on the obligations of research sponsors to research participants, communities, and countries before, during, and after a trial. The draft report considers how and to what extent cultural and other factors influence these issues. Finally, NBAC analyzes many national and international guidelines and statements to make recommendations about possible ways to enhance international collaborative research.

You may provide written comments electronically or through mail or fax. Electronic submissions (by email or by website) are preferred as they will be processed more efficiently. The following are addresses for submitting comments:

6705 Rockledge Dr ♦ Suite 700 ♦ MSC 7979 ♦ Bethesda, MD ♦ 20892-7979
Telephone ♦ 301-402-4242 ♦ *Facsimile* ♦ 301-480-6900
Website ♦ www.bioethics.gov

- By Email: nbac@od.nih.gov
- NBAC Website: www.bioethics.gov
- By Mail: 6705 Rockledge Drive, Suite 700, Bethesda, MD 20892-7979
- By Fax: (301) 480-6900

If your comments are not postmarked by November 13, 2000, we can not guarantee your comments will be given full consideration.

We look forward to receiving your comments. Your views will help the Commission's deliberation on this important subject.

Sincerely,

Eric M. Meslin, Ph.D.
Executive Director

Enclosure

September 29, 2000: This is a summary of the recommendations found in NBAC's draft report, "Ethical and Policy Issues in International Research." Page numbers following each recommendation refer to the page in the chapter in which it is found. The full text of the report may be obtained from www.bioethics.gov. The recommendations are not final and should not be cited as such.

Ethical and Policy Issues in International Research
Summary of Recommendations

Chapter 1:
Ethical Issues in International Research: Setting the Stage

***Recommendation 1.1*: The federal government should encourage and facilitate ethically sound international collaborative research. To that end, it should help U.S. researchers identify sites and collaborators where research can be conducted in a manner that satisfies appropriate ethical and procedural requirements, including: [pg. 4]**

a) **independent prior review of research by a competent ethics review body**
b) **minimization of risk to research participants**
c) **favorable balance of the risks of harm and potential benefits**
d) **adequate care and compensation to participants for injuries sustained during research**
e) **individual informed consent from all competent adult participants of research that poses more than minimal risk**
f) **equal treatment of all participants, regardless of race, religion, gender or ethnic orientation, and** → sexual orientation
g) **equitable distribution of the burdens and benefits of research.**

***Recommendation 1.2*: Clinical trials conducted in developing countries by organizations or others from developed countries should be limited to those studies that are responsive to the health needs of the host country. [pg. 10]**

as defined by the host country

Chapter 2:
Ethical Considerations in the Design and Conduct of International Clinical Trials

***Recommendation 2.1*: Researchers should provide IRBs with a thorough justification of the research design they will use, including the procedures they will use to minimize risks to research participants. [pg. 3]**

***Recommendation 2.2*: Researchers and sponsors should design clinical trials that provide members of a control group with an established, effective treatment. This should be done whether or not that treatment is available in the country where the research is conducted. In cases in which the only relevant and effective study design would not provide the control group with an established, effective treatment, the proposed research protocol should include a justification for using this alternative design. The IRB must assess the justification provided, as well as the ethical appropriateness of the research design. [pg. 13]**

***Recommendation 2.3*: Researchers and sponsors should strive to involve representatives of the affected community from the earliest stages of design and implementation of research projects and should promote their sustained involvement throughout the duration of research activities. [pg. 16]**

possible or appropriate

Chapter 3: Voluntary, Informed Consent

***Recommendation 3.1*: Researchers must not deviate from the substantive ethical standard of informed consent in the consent process. Moreover, the consent process always should include all the basic elements of disclosure found at U.S. 45 CFR 46.116. IRBs may not, therefore, approve research proposals that deviate from the substantive ethical standard of informed consent. [pg. 6]**

***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, placebos and randomization, alternative therapies, and post-trial benefits. Researchers should describe in the protocol and justify to the IRB the procedures they plan to use for disclosing such information to participants. [pg. 10]**

***Recommendation 3.3*: IRBs should require that researchers include in the informed consent process and consent documents information about what benefits will be available to participants when their research participation has ended (see also Recommendation 3.12). [pg. 10]**

***Recommendation 3.4*: NIH, CDC, and other U.S. departments and agencies should support research that specifically addresses 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 where international researchers can share their knowledge of the informed consent process in these settings. [pg. 10]**

***Recommendation 3.5*: Researchers should develop and implement an appropriate process of community education and consultation before the research begins. Researchers should describe the steps to implement that process in the protocol and IRBs should review the appropriateness of this process. [pg. 14]**

***Recommendation 3.6*: Researchers should devise appropriate means to ensure that potential participants do, in fact, understand the information provided in the consent process, and should describe those means in the research protocol. [pg. 14]**

***Recommendation 3.7*: Researchers should consult with community representatives in a search for creative and innovative means to communicate all necessary information in a manner that is understandable to potential participants. [pg. 14]**

***Recommendation 3.8*: When culture or custom requires permission of a community leader before researchers may approach individual subjects, researchers should be sensitive to such local requirements. However, in no case may permission from a community leader or council replace the requirement of individual voluntary informed consent. [pg. 16-17]**

***Recommendation 3.9*: Researchers should strive to ensure that individuals agree to participate in research without coercion or undue inducements from community leaders. [pg. 17]**

***Recommendation 3.10*: 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 individual informed consent. [pg. 19]**

***Recommendation 3.11*: Researchers should use the same procedures in the informed consent process for both women and men. [pg. 21]**

***Recommendation 3.12*: Researchers working abroad who are subject to U.S. regulations should indicate in their research protocol how they will minimize the likelihood that potential participants will mistakenly believe that the purpose of the research is solely to administer treatment rather than to contribute to scientific knowledge. (See also Recommendation 3.2). [pg. 26]**

***Recommendation 3.13*: The provisions of U.S. 45 CFR 46.117 requiring written and signed consent documents for all research involving more than minimal risk (with the exceptions already noted in the regulations) should be modified to allow researchers working abroad, but subject to U.S. regulations, to obtain waivers of one or both of these requirements. [pg. 29]**

***Recommendation 3.14*: Researchers may vary the procedures by which they obtain informed consent as stipulated in U.S. regulations at 45 CFR 46.116(c) only with the prior approval of an IRB. Researchers must provide adequate justification for requests for such waivers. [pg. 29]**

***Recommendation 3.15*: Any waivers granted according to recommendations 3.13 and 3.14 should be audited by a competent body, and the results made available to the public. [pg. 29]**

Chapter 4:
When Research Is Concluded: Access to Benefits of Research by Participants, Communities, and Countries

do not have to be provided by the researchers

Recommendation 4.1: **After a clinical trial is concluded, arrangements should be in place to continue to provide to all participants (including members of a control group) any research intervention that was proven successful along with other interventions that were provided to participants during the research, if these participants would not otherwise have access to an established, effective treatment. The research protocol should specify how the duration, extent, and financing of this obligation will be explicitly negotiated among the relevant parties in advance. The agreed upon details regarding post-trial treatment must be included in the informed consent process (see also Recommendations 3.1 and 4.2). [pg. 13]**

Recommendation 4.2: **Research proposals submitted for IRB approval should include an explanation of how successful interventions will become available to some or all of the host country population. Where applicable, the investigator should describe any pre-research negotiations among sponsors, host country officials, and other appropriate parties aimed at making successful interventions available. Where investigators do not believe that successful interventions will become available to the host country population, they should explain to the relevant IRB(s) why the research is nonetheless responsive to the health needs of the country and presents a reasonable risk/benefit ratio. [pg. 21]**

Chapter 5:
Enhancing International Collaborative Research

***Recommendation 5.1*: U.S. sponsors and researchers should develop and implement strategies that assist in building local capacity for designing and conducting clinical trials in developing countries. Identifiable initiatives that assist capacity building should accompany each research project with the ultimate aim of playing a direct role in making host country researchers fuller and more equal partners with industrialized country researchers or sponsors. [pg. 9]**

***Recommendation 5.2*: 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. [pg. 9]**

***Recommendation 5.3*: In collaboration with other agencies that sponsor international research, the Office for Human Research Protections should develop policy guidance setting forth the criteria and process for determining whether other nations' guidelines and procedures provide "equivalent protection" of research participants, as specified at 45 CFR 46.101(h) and 21 CFR 312.120. Once it has been determined, pursuant to this policy guidance, that a nations' human research guidelines and procedures provide "equivalent protection," the sponsoring agency must treat review bodies established or accepted by the appropriate authorities in that nation as equivalent in stature to an IRB at a research institution possessing a valid federal Multiple Project Assurance. [pg. 18]**

***Recommendation 5.4*: Federal agencies that sponsor or regulate international research should endeavor to apply the policy guidance on "equivalent protection" in a uniform manner. Any differences that arise in the interpretation or application of the policy guidance should be resolved by the Office for Human Research Protections. [pg. 18]**

***Recommendation 5.5*: The Office for Human Research Protections (OHRP) should implement its revised assurance process. Once this revised process is implemented, it should be comprehensively evaluated by an independent body. This evaluation should be completed no later than three years after implementation of the new OHRP process. [pg. 24]**

***Recommendation 5.6*: Clinical trials conducted in developing countries and subject to U.S research regulations must meet prior approval by an independent ethics review committee in the country where the research will take place, as well as by a U.S. IRB. Researchers should include in the research protocol plans**

for facilitating communication between or among IRBs in the United States and with review bodies in the collaborating countries. [pg. 29]

***Recommendation 5.7*: When research is supported by a U.S. organization or entity that is not subject to U.S. research regulations, researchers are encouraged to comply with Recommendation 5.6 above. Researchers should include in the research protocol plans for facilitating communication between or among IRBs in the United States and with review bodies in the collaborating countries. [pg. 29-30]**

***Recommendation 5.8*: Federal agencies and others that sponsor international research in developing countries should provide financial support for the costs (administrative and operational) of compliance with requirements for oversight of research involving human participants. [pg. 31]**

Ethical and Policy Issues in International Research

National Bioethics Advisory Commission

Bethesda, Maryland, USA

September 29, 2000

This is a draft report prepared by the National Bioethics Advisory Commission and circulated for public comment. It does not represent final conclusions.

TABLE OF CONTENTS

CHAPTER 1
ETHICAL ISSUES IN INTERNATIONAL RESEARCH: SETTING THE STAGE

INTRODUCTION [1]

It has long been recognized that collaboration between peoples from different nations, whether in the form of trade, material assistance, cultural interchange of one type or another, or in other spheres of mutual interest, has great potential to generate substantial benefits for both parties. At the same time, such collaborations do not always proceed smoothly, as when controversy emerges about the nature of the collaboration or about the distribution of benefits. Such controversies are perhaps more likely when the nations involved do not share the same cultural, economic, political, and ethical perspectives, or when they are at different stages of development.

The increasingly global nature of health research, and in particular biomedical research involving human participants, in recent years has generated new ethical and logistical issues, especially when researchers and/or research sponsors from one country wish to conduct research in another country.[1] The research in question might simply be one way of assisting the host country in meeting a public health problem, or it might reflect a sponsor's assessment that the foreign location is a more convenient or efficient—or less troublesome—site for a particular clinical trial, or it might represent a joint effort to address an important medical problem faced by both parties. In any case, over the past several years as the pace and scope of international collaborative biomedical research have increased, attention has focused, once again, on the ethical issues that arise in the design, conduct, and follow-up of such research.

Some of these issues have begun to take center stage because of concern that research conducted by scientists from economically more prosperous countries in nations that are both poor and heavily burdened by disease may be seen as imposing burdens that are ethically inappropriate on the host country and those who participate in the research trial. For example, in a widely publicized case, some commentators denounced as unethical clinical trials in Africa sponsored and/or conducted by parties from resource-rich countries to test drugs that might reduce perinatal transmission of human immunodeficiency virus (HIV)(Angell 1997; Lurie and

Wolfe 1997)(See Exhibit 1.1.) Two kinds of concerns were expressed. First, involving research participants in placebo-controlled trials when an effective therapy exists treats these individuals differently than similar research participants would be treated in the developed nations, implying perhaps that they are not of equivalent worth or do not deserve equal concern. Second, some made the claim that an alternative research design could have addressed the health needs of the host country without using a placebo control.

Efforts to test possible AIDS vaccines through clinical trials sponsored or carried out by developed continue to come under ethical scrutiny. As a recent *Science* editorial pointed out:

> Multicenter AIDS vaccine trials are most efficient where the rates of HIV infection are high; hence the importance of vaccine trial sites in less developed countries in Africa, Asia, and Latin America. Ethical concerns about exploitation arise because the conduct of such trials in less developed countries often depends on both funds and vaccines from developed countries (Karim 2000, 2129).

Once again, the issue here is whether institutions and researchers from resource-rich nations that have the necessary materials and expertise to conduct such research are placing ethically unjustified burdens on the populations of the host countries, thereby exploiting them.

Another dimension to such collaborations also deserves attention, namely, whether 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 collaboration, or whether they in fact unnecessarily complicate or frustrate otherwise worthy and ethically sound research projects. This is an important issue, because beyond the provision of funds and experimental drugs and vaccines, such clinical trials and other forms of research with human beings carried out abroad often directly involve scientists from U.S. universities and other research institutes, as well as governmental agencies and U.S.-based companies that remain subject to U.S. regulations. To put the matter another way, the United States bundles its research regulations (and the ethical principles and commitments that underlie them) as part of the research projects it exports. Indeed, U.S. support of research involving human participants, whether carried out in the United States or abroad, is conditioned on meeting these ethical requirements. Consequently, collaborative research protocols conducted abroad often need approval not only by officials of the host country and local research institution, but also by the institutional review board (IRB) at the investigators' or sponsors' home institutions. Since U.S. IRBs must be satisfied that all U.S.

regulatory requirements are met in order to approve a study, it is appropriate to consider how these requirements are understood and applied in the context of research carried out abroad.

In broad scope, many of the ethical concerns regarding the treatment of human participants in the context of international collaborative research are similar to those found when examining research conducted in the United States, namely: choosing the appropriate research question and design; equitably selecting participants; obtaining voluntary informed consent; protecting privacy and confidentiality; and conducting independent ethical review of the proposed protocol.

In our view, two types of ethical requirements—substantive and procedural—must be carefully considered before research proceeds with human participants, irrespective of the location of the research. The three *substantive requirements* for ethically sound research with human beings that are widely accepted are:

1) adequate disclosure of information prior to voluntary consent
2) a favorable risk- benefit ratio, and
3) a fair distribution of the benefits and the burdens of the research.

In addition, ethically sound research must comply with an important *procedural requirement*, namely independent ethical review by a body competent to assess compliance with these substantive ethical standards.

However, the nature and understanding of these broad requirements are not identical everywhere. For example, while there is increasing recognition of the importance of obtaining informed consent (Ijsselmuiden and Faden 1992), questions have been raised about whether voluntary, informed consent as understood *and* procedurally implemented in the United States is either advisable or possible in some countries (Karim et al. 1998; Bankowski 1992). Moreover, some issues that have received little attention in U.S.-based research may have special meaning in the context of resource-poor countries, such as the potential obligations of sponsors and/or researchers to participants after the completion of a study.

This report highlights some of these and related issues, and in so doing also focuses on whether existing U.S. regulations and IRB practices unduly complicate international collaborative research, inadequately protect human participants, or impose inappropriate requirements on foreign research participants or on U.S.-sponsored researchers working abroad. This report focuses specifically on researchers and/or sponsors who are conducting

investigations abroad and are subject to U.S. research regulations. As part of a subsequent report on issues arising from the oversight of human subjects research in the United States, the Commission will address the implications of its conclusions about studies in developing countries for the regulation of domestic research.

Recommendation 1.1: The federal government should encourage and facilitate ethically sound international collaborative research. To that end, it should help U.S. researchers identify sites and collaborators where research can be conducted in a manner that satisfies appropriate ethical and procedural requirements, including:

a) independent prior review of research by a competent ethics review body
b) minimization of risk to research participants
c) favorable balance of the risks of harm and potential benefits
d) adequate care and compensation to participants for injuries sustained during research
e) individual informed consent from all competent adult participants of research that poses more than minimal risk
f) equal treatment of all participants, regardless of race, religion, gender or ethnic orientation, and
g) equitable distribution of the burdens and benefits of research.

ISSUES PROMPTING THIS REPORT [1]

Our attention was first drawn to the issues addressed in this report by suggestions from the public at our earliest meetings that our responsibility to examine the protection of the rights and welfare of human participants in research encompasses the issues that arise when research that is subject to U.S. human subject regulations is conducted and/or sponsored in other countries.

Second, since considerable controversy remains regarding the ethical issues in international collaborative research (Varmus and Satcher 1997; Nuffield Council 1999; Levine 1999; Dickens, Gostin, and Levine 1991; Clarke, et al. 1998), additional attention to these issues

provides an opportunity for ongoing public dialogue on how to provide appropriate protection to all research participants.

Moreover, we also heard—both from researchers and from Institutional Review Boards (IRBs) and federal regulators—concerns about how U.S. regulations are "exported" to other countries and interpreted by researchers and institutions there. These concerns arise particularly in research sponsored by the U.S. government or otherwise subject to U.S. regulation, most specifically, the Federal Policy for the Protection of Human Subjects (45 CFR.46, Subpart A, also known as the "Common Rule"), and parallel U.S. Food and Drug Administration (FDA) regulations for the protection of human research participants (21 CFR, Parts 50 and 56). In previous reports the Commission has noted that even for domestic researchers the U.S. regulations are at times difficult to interpret and require clarification (NBAC 1998; NBAC 1999). It should not be surprising therefore that understanding and interpreting U.S. research regulations in foreign settings could pose even more profound difficulties.

Third, international discussion has already identified the development of an ethically appropriate mechanism that will allow more effective research collaboration by investigators from different nations, each with a somewhat different set of ethical requirements as an important objective. In this regard, discussions are already taking place within the context of an emerging international effort to harmonize regulations governing clinical trials under the auspices of the International Conference on Harmonization (ICH 1996).

A fourth circumstance—the changing landscape of international research—prompted the decision to prepare this report at this time. Increasingly, scientists from developing countries are becoming fuller collaborators in research, as many of these countries have built their capacity both for technical contributions to research projects and for appropriate ethical review of proposed research protocols. Although funding for such collaborative research is likely to continue coming predominately from wealthier, industrialized countries with long experience in conducting research outside their own border—such as Canada, France, Germany, Japan, the Netherlands, Scandinavia, the United Kingdom, and the United States—collaborators from developing countries are seeking, quite appropriately, to become more equal partners in the research enterprise. If this trend continues, the role of U.S. regulations may change somewhat.

Finally, the current landscape of international biomedical research reflects the growing importance of clinical trials conducted by for-profit organizations. Some observers believe that

market forces have pressured these organizations to seek means for greater efficiency in the conduct of research, which may—absent vigilance—compromise protection of human participants in research. While the extent, relevance, and force of these pressures are still widely debated, it is clear that such pressures can exist regardless of the funding source.

SCOPE AND LIMITS OF THIS REPORT [1]

This report discusses the ethical issues that arise principally when research subject to U.S. regulations is sponsored or conducted in *developing* countries, where local technical skills and other key assets are in relatively scarce supply. Within this context, our attention primarily is focused on the *conduct of clinical trials*; in particular those trials—such as Phase III drug studies—that can lead to a successful product. 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. Clinical trials that are appropriately designed and conducted provide the most definitive and powerful technique for evaluating existing clinical practices and innovative methods of diagnosis, treatment, and prevention. In addition, since complex and important ethical concerns and dilemmas are likely to be more pressing in clinical trials than in many other types of research investigations, the Commission decided to limit the focus of this report accordingly.

Limiting the scope of the report in this way precludes a wide-range of analyses of other types of important international collaborative research—notably, health services research, educational research, and various demonstration projects—that are subject to U.S. regulation. The U.S. government sponsors and conducts a wide variety of applied research in the development of such interventions for possible implementation in public health programs in several developing countries. Among other activities, the Centers for Disease Control and Prevention (CDC) engage in public health research and medical care interventions aimed at improving access to health care; research employing study designs other than clinical trials to study and establish the effectiveness and feasibility of interventions intended to change behaviors to improve health, prevent acquisition of disease, or alter disease risk factors as well as environmental interventions with health-related goals. Examples include the prevention of diarrhea through point-of-use disinfection and safe storage of drinking water in Bolivia and

Zambia; training community healthcare workers in case management of childhood illnesses in Kenya; and behavioral interventions using entertainment-education strategies to promote reproductive health and STD (sexually transmitted disease)/HIV prevention in Africa and China.

By focusing this report on clinical trials subject to U.S. regulations but conducted in developing countries, the Commission aims to contribute to the evolving international discussion about the ethics of international research, a discussion that is now occurring in other arenas (Nuffield Council 1999). Although much of the discussion in this report can be applied to other areas and kinds of research, such activities merit their own distinctive ethical assessment.

ORGANIZATION OF THE REPORT [1]

The chapters in this report are organized to illustrate issues that occur in the design, review, and follow-up of clinical trials, since each of these steps in the process requires some form of ethics review. Chapter 2 focuses on ethical issues that arise in choosing a research question and appropriate study design. Chapter 3 addresses the ethical issues pertinent to the recruitment of participants and informed consent. Chapter 4 examines the difficult issue of what obligations, if any, sponsors or others have to provide post-study benefits to participants and others. In our view, this latter issue is important enough to be considered a part of the ethics review process. Chapter 5 focuses on ways to enhance research collaboration between developing and developed countries, including the relevant aspects of ethics review. What follows here is a brief overview highlighting the issues addressed in each of these chapters.

THE RESEARCH QUESTION AND CHOOSING A STUDY DESIGN [1]

Identifying the "research question" and the methodology necessary to answer that question is centrally important in research design (Sackett 1983; Meinert and Tonascia 1986; Spilker 1991). In addition, when clinical trials are conducted abroad, it is both ethically and scientifically important to understand why such a location—particularly a developing nation—has been chosen.

Choosing a Foreign Setting in which to Answer a Research Question [2]

Sponsoring and/or conducting research in developing countries often poses special challenges due to the combined effects of a distinctive history, culture, politics, legal system, and particular economic situations (London et al. 1997). For example, in the poorest countries, primary health care services are inadequate due to the collective effects of insufficient personnel (ranging from physicians to pharmacists), transportation and communication problems, and various logistical challenges, such as the unreliable availability of basic medical supplies, the dearth of health facilities, and inability of the population to pay. In addition, unsanitary living conditions and water supplies can make some medical therapies inappropriate or unproductive. Further, the price of modern pharmaceuticals often places them out of reach for both individuals and governmental purchasers.

Whether the sponsor is the U.S. government—through such agencies as the National Institutes of Health (NIH), CDC, or the U.S. Agency for International Development (USAID)—or a private-sector organization, some justification is needed for conducting research abroad other than the greater ease of a location in which less demanding requirements make research less complex. These perceived lower barriers may simply be procedural in nature—such as the speed with which ethics review occurs prior to initiating a study. However, when the United States (or any industrialized 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 resource-poor countries for some combination of the following four reasons.

First, the host country might have a desire for information about effective and affordable interventions for an indigenous health problem. Researchers from other countries around the globe have collaborated with U.S. researchers and received NIH support for investigations of malaria or dengue, which rarely occur in the United States, as well as infectious diseases, (e.g., tuberculosis, HIV/AIDS) or cancer, which do occur in the United States. In addition to the probable direct benefit to the population from such research, an indirect benefit is provided via assistance in building research capacity in these countries, including the development of an independent capability to conduct scientific and ethical review of protocols. One unit of NIH in

particular, the Fogarty International Center (FIC), has as its mission to make the results of scientific discovery available to all peoples in all parts of the world, especially by developing human capital and building research capacity in the poorest nations of the world through the training of scientists and technical staff, and the provision of facilities, equipment and other improvements in the medical and logistical infrastructure.[2]

Second, in order to be marketed, drugs and biologicals—even if already tested and approved in other countries—must be approved by national regulatory authorities, which in some countries may require domestic testing.

Third, it is more efficient to conduct research in a country where the condition being studied is more prevalent. Moreover, certain diseases associated with particular conditions—such as a tropical climate—can only be studied where those conditions exist.

Fourth, it might be less expensive and more efficient to conduct research in developing countries, because, for example, enrollment of participants can occur more quickly, or procedural requirements are less burdensome.

Whatever the reasons or combination of reasons for performing research abroad, it is ethically incumbent on both sponsors and researchers to ensure that these activities do not exploit the population of the host country.

Responsiveness of the Chosen Research to the Health Needs of the Population [2]

For any research with human beings to meet the basic ethical principle of beneficence, it must offer a favorable ratio of prospective benefits to risks. Plainly, the central focus of any inquiry into risks is the potential harm to research participants themselves, though risks to others are also relevant. The benefits that are weighed against such risks may include those that will flow to the fund of human knowledge as well as to present and future human beings whose lives may be made better because of the findings of the research in question. Yet, for clinical research to meet ethical expectations, as spelled out in basic documents such as the National Commission's *Belmont Report*, some of the benefits must also accrue to the group from whom the participants are selected. Failing to offer some prospect of benefit undermines the rule that persons ought never be used merely as means but always treated as ends in themselves, which is one manifestation of what *Belmont* terms the principle of respect for persons. Thus, in the context of

international research–particularly when the population of a resource-poor nation has been sought out as research subjects–U.S. research ethics demand not merely that research projects offer a favorable ratio of benefits to risks but that they respond to the health needs of the population being studied, since only research that is responsive to these needs can offer relevant benefits to the population, as the principles of beneficence and respect for persons demand.

Recommendation 1.2: Clinical trials conducted in developing countries by organizations or others from developed countries should be limited to those studies that are responsive to the health needs of the host country.

Versions of this "responsive-to-needs" requirement appear in numerous international guidelines. For example, the influential *International Guidelines for Biomedical Research Involving Human Subjects* issued in 1993 by CIOMS (the Council for International Organizations of Medical Sciences) state that: "Before 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" (Guideline 8). This requirement is echoed in the Guidance Document for HIV vaccine research recently issued by 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, 6). The UNAIDS document carries the basic premise of "responsive-to-needs" to the next level by insisting that when HIV vaccines are developed, "they should be made available and affordable to such populations" (UNAIDS 2000, 6).

Likewise, the World Medical Association's *Declaration of Helsinki*–which for more than 30 years has provided a leading reference point for the international research community in determining ethical behavior in research and is now being revised–includes in its current proposed revision a provision that "Medical research is only appropriate 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" (World Medical Association 2000).

Many researchers also concur with this ethical premise. For example, one researcher told the Commission 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." Even more strongly, the dean of a leading school of public health put 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."

Choosing a Research Design [2]

It is generally accepted that it is critical to select an ethically appropriate research design when using clinical trials as a vehicle to evaluate a particular perspective. In this report, we are especially interested in discussing the following question: *Can a research design that could not be ethically implemented in the sponsoring, developing country be ethically justified in the host country where the research is conducted*? In addition, we are interested in whether it would be an undue inducement to potential participants to enroll in a clinical trial to offer them better care or treatment than they could obtain outside the study. *Prima facie*, we do not believe this to be the case, but we recognize that determining what level of treatment should be provided to participants (including those in a control group not receiving the experimental drug) is a research design issue with ethical implications that must be addressed.

The Relevance of Routine Care to Ethical Research Design [3]

In 1997, an ethical controversy emerged over a series of placebo-controlled trials aimed at finding an affordable and feasible treatment to lower the rate of maternal-to-infant transmission of HIV in developing countries. The debate has had repercussions well beyond disagreement over the ethics of a particular study design (see Exhibit 1.1).

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 contentious studies followed an earlier 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 a high dose of AZT is administered to women midway through their pregnancy, again intravenously while in labor, and when special AZT treatment is provided to the newborn after birth.

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. 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 "076" regimen aimed to establish an AZT regimen that could reasonably be implemented for HIV-positive pregnant women in the 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. That is, 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 it is wrong for researchers coming from a country where an effective treatment is used to withhold that treatment from any study participants 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 comparing the experimental treatment with the standard treatment rather than with 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.[3]

Defenders of the placebo-controlled studies replied with four different 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 by participating in the study;
2) a placebo-controlled trial can be carried out with many fewer subjects and completed in a much shorter time than could an AZT-controlled study, so useful information and effective interventions pertinent to this population will be available much sooner;

3) the "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, so use of this active control would render the results of very little relevance to the health needs of the developing country (Levine 1999; Wilfertet 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 are long since 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.

The ensuing debate set in motion efforts to revise the *Declaration of Helsinki*, which was first issued by the World Medical Association in 1964 and amended several times in minor ways, most recently in 1996, and to revise the 1993 CIOMS *Guidelines*, which adopt much of the language in the *Declaration of Helsinki*. Guideline 15 in the CIOMS 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 result that a country whose rules for prior, independent review of research stipulate, for example, a different composition of research ethics committees than that stated in the U.S. research regulations would somehow be applying a different "ethical standard." As noted below, Chapter 3 seeks to distinguish between fundamental principles, the ethical standards such principles define, and procedural requirements for informed consent, for example that, while important, are simply methodologies for implementing the ethical standards and do not rest on fundamental ethical principles.

Standard of Care [4]

In many clinical trials, the standard of care for a given intervention often constitutes the control arm of the study. In this report we have chosen, for the most part, to avoid the phrase "standard of care" in describing the interventions that people in a community or country

normally obtain in the clinical setting. Instead, we refer 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, denoting the level of conduct against which a physician's or health provider's treatment of a patient will be judged in determining whether such 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 *ought* to be provided to participants in research. Moreover, when most people in a country or a region routinely receive no care, that amounts to an absence of care rather than a "standard" of care.

Further, an ambiguity lurks in the term "standard," which sometimes means "what is normally done," as in "standard practice." In this meaning, "standard practice" in some countries—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 "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 latter 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. To avoid such ambiguities, we have chosen to use the somewhat more cumbersome phrase "treatment that is routinely available."

Established, Effective Treatment [4]

The use of placebos as the "control" in Phase III clinical trials, while still the norm, has become more controversial in recent years. On its face, the use of a placebo cannot be squared with the requirements of the *Declaration of Helsinki* that all participants receive: "the best proven...therapeutic method" (World Medical Association 1964, as amended in 1996). Yet this provision has in turn been criticized as incoherent since the whole objective of a clinical trial is to test an intervention that differs from "the best proven method" currently in use.

A further objection to the Declaration is that it makes no sense to limit either the intervention being studied or the control to the "bet proven method" in situations where such a

high standard would never be feasible for the population in question because of resource constraints. To remedy this problem—of an ethical standard that would seem to render research either infeasible or irrelevant—the phrase "the highest attainable and sustainable therapy" has been suggested to replace "best proven method" (Levine 1999). "Highest attainable" is the best that one could reasonably provide under the conditions of the trial. "Highest sustainable" refers to the level of therapy that one could reasonably expect to be continued in the host country after the trial has been completed. A committee of the World Medical Association responsible for revising the *Declaration of Helsinki* did not adopt this replacement for the term "best proven method." Instead, a draft revision of the *Declaration* circulated by the World Medical Association in May 2000 uses the following phrase: "In any medical study, every patient—including those of a control group, if any—should be assured of proven effective prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of an inert placebo (an inactive intervention that resembles the experimental intervention as much as possible) in studies where no proven diagnostic or therapeutic method exists" (World Medical Association 2000, 5).

The Commission has concluded that the standard of "established, effective treatment" best conveys what is owed to research participants. We intend the phrase "established, effective treatment"—which was used in scientists' testimony before the Commission[4] —to refer to a treatment that is *established* (that is, has achieved widespread acceptance at the present time by the medical profession) and *effective* (that is, it is successful in treating the disease or condition) anywhere in the world. It is not limited to what is routinely available in the country where the research is being conducted. The phrase we propose, "established, effective treatment," is close to that found in the 2000 draft revision of the *Declaration of Helsinki*. Although any phrase requires some interpretation, we believe the proposed phrase is reasonably clear and defines a concept that is useful in developing recommendations in this area.

Without question it can be difficult to determine whether an intervention constitutes an established, effective treatment. Scientists may disagree as to whether an intervention shown to be effective in one population is likely to be as effective in another population that differs in significant ways (for example, patient's 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 include differences between Haiti and East Africa in population susceptibility to drugs to treat falciparum malaria, and the difference

between the United States, Canada, and Europe, in guidelines for coronary artery bypass surgery and for chemotherapy in the treatment of solid tumors. When the standard of care differs among nations, it may be ethical to withhold interventions in one population that are considered established, effective treatments in some countries, but not in others.

FAIR AND RESPECTFUL TREATMENT OF PARTICIPANTS [1]

Although many of the ethical issues that arise in international research also pose problems for research conducted in the United States, some issues are particularly notable in the international setting. Two such issues are the selection of participants for research and the duty to obtain their voluntary, informed consent to participate.

Selection of Participants [2]

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 selection of research participants. This is necessary in order to ensure justice in the conduct of research and to avoid the risk of exploitation. These ethical concerns echo an observation made by the National Commission in the *Belmont Report* more than 20 years ago that

> the 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, 5).

As noted above, broad agreement exists among researchers, ethics review committees, and in relevant national and international guidelines about the importance of satisfying certain substantive and procedural requirements for enrolling human participants in research. While it is true that much international research sponsored by both the U.S. government and private industry has conformed to these requirements, the concern is ever present both here 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 by using the latter to serve their own ends (those of the wealthy or powerful), without any compensating benefit for the less advantaged individuals or group. In any case, exploitation is a serious moral wrong, and a fundamental obligation exists to refrain from behavior that constitutes or promotes it. 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*.[5] It follows that we all have a fundamental obligation to avoid exploitation when we conduct research, especially in poorer, less advantaged countries.

It is not always apparent, however, as to the circumstances in which exploitation does or might occur within the context of international research. One document that addresses international research in the context of HIV/AIDS identifies several factors that make 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 instance, as a result of class, gender, and 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 carried out in resource-rich nations.

Voluntary, Informed Consent [2]

The requirement to obtain voluntary, informed consent from human participants before they are enrolled in research is a fundamental tenet of research ethics. This was the first requirement proclaimed in the Nuremberg Code in 1947 and it has appeared in all subsequent

published national and international codes, regulations, or guidelines pertaining to research ethics, including those in such developing countries as Uganda, India, and Thailand. Nevertheless, there is an ongoing discussion about the value and importance of particular approaches to informed consent in other countries (Preziosiet al. 1997; Benatar and Benatar 1998; Edi-Osagieet al. 1998). Problems of interpretation and application of the requirement to obtain voluntary, informed consent—and its underlying ethical principle(s)—arise for researchers, ethics review committees, and others. For example, the CIOMS *Guidelines,* a widely acknowledged source on the ethics of international research, specifically addresses 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 where men are expected to speak for their unmarried adult daughters and husbands are expected to speak for their wives, a woman may not be free to consent on her own behalf to participate in research. Finally, in many rural settings in developing countries, permission from a village leader is required before researchers may approach individuals to recruit them as volunteers.

As a result of such issues, the Commission was especially interested in problems that may arise from expecting developing country researchers to adhere strictly to both the substantive *and* the procedural imperatives of the U.S. requirements for informed consent. In particular, if cultural differences between the United States and other countries make it difficult or impossible to adhere strictly to U.S. regulations stipulating procedures for obtaining informed consent from individual participants, how should this problem be handled? Some difficulties are procedural in nature, whereas others reflect substantive differences in ethical standards. A number of issues arise including: procedural variations, such as requiring written consent and permitting oral consent; substantive ethical considerations, such as withholding crucial information from potential participants; the need in some cultures to obtain a community leader's or a family member's permission prior to seeking an individual's consent; and standards of disclosure to research participant in cultures where people lack basic information about modern

science or reject scientific explanations of disease causation in favor of traditional, nonscientific beliefs. Chapter 3 contains a series of recommendations that deal with these issues.

POST-STUDY OBLIGATIONS [1]

As noted above, one of the results of the publicity and controversy that surrounded the series of studies related to preventing perinatal transmission of HIV from mother to infant (see Exhibit 1.1) was a renewed concern about what is owed to research participants *during* a clinical trial. However, the controversy also highlighted a second question, namely: *What products or services should be made available, and on what terms, to research participants and to others in the country after completion of the research*? The latter question has not typically been considered in ethical assessments of research, whether research is conducted in developed or developing countries. But both of these questions are now being posed with special force, especially with regard to serious diseases that affect large numbers of people in developing countries.

In these respects, a feature of some ethical relevance that distinguishes most developing countries from those in the industrialized world is the lack of access by a large majority of the population to an adequate level of health care. The vast majority of resource-rich countries have long provided universal access to primary health care through a national health service or government-based insurance. Although the United States is among a small number of developed countries that do not provide universal access to health care, most of the U.S. population has 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 people have nearly no access at all, due to the complexities of U.S. health insurance coverage, geographical distribution of health care resources, and the persistence of poverty and near-poverty in some parts of the country. In the developing world, especially the poorest countries in Africa and Asia, substantially less health care is available (if at all), and where it is available access is severely limited. Despite some similarities, the conditions that limit access to health care in the United States and those that limit access in developing countries are not comparable. In the United States, lack of access to adequate health care results from policymakers having not chosen to allocate resources to provide universal health coverage to all, whereas in poor

countries most citizens lack access to health care because the resources are simply not available at all.

Access to health care is an important issue since an ethically appropriate clinical trial design will require an assessment of the level and nature of care or treatment available outside the research context, as well as any possible future health benefits 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 since this would leave the research participants worse off than they would otherwise have been. In contrast, a research design that tests an experimental treatment against a placebo can perhaps be implemented in a developing country without making the participants 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, not to make participants worse off than they would otherwise be remains a matter of debate.

These issues also prompt the question of whether sponsors of research should consider arrangements whereby some of the fruits of research would be available in the host country when the research is concluded. Making such arrangements would be one strategy in being responsive to the health needs of the population where the research is carried out. The question of what sponsors of research should make available at the conclusion of a successful clinical trial to participants and/or others in the host country is particularly significant for those developing countries in which neither the government nor the vast majority of inhabitants can afford the successful products of research conducted there.

The discussion in Chapter 4 is intended to provide an answer to the question: if sponsors of research conducted in the United States do not routinely make successful products or services available to research participants or to others following a trial, why should they strive to do so when they conduct research in developing countries? In addition, we discuss various arrangements, including "prior agreements"—documents that refer generally to arrangements made before a clinical trial begins—that address post-trial availability of successful products to participants and/or others in the host country after the study is completed. The parties to these agreements usually include some combination of producers, sponsors, and potential users of research products. Industry, academia, and organizations of various kinds are frequently producers and sponsors of such arrangements, while developing country governments and not-

for-profit health organizations are most likely to be users. While only a limited number of prior agreements, either formal (i.e., legally binding) or informal, are in place in international collaborative research today, it is useful to consider what role such agreements should have in the future.

ENHANCING INTERNATIONAL RESEARCH: BUILDING CAPACITY [1]

International ethical guidelines, such as the 1993 CIOMS *International Ethical Guidelines* (CIOMS 1993) and the UNAIDS Guidance Document for Preventive HIV/AIDS Vaccine Trials (UNAIDS 2000) also state that when industrialized countries sponsor research in developing countries, the sponsors have a responsibility to assist in building local and national capacity for designing and conducting trials, and for scientific and ethical review of proposed research projects. Enhancing research collaborations between developing and developed nations requires paying more attention to enhancing the capacity of resource poor countries to become even more meaningful partners in international collaborative research. Scientific and ethical review is by now well established in the countries and agencies that sponsor international collaborative research, but the procedures for such review are at different stages of development in some countries where clinical trials are carried out. Among the most helpful ways of enhancing international collaborative research is to make available the resources necessary to build both the technical capacity to conduct and sponsor research, and the ability to carry out prior ethical review of these studies. Chapter 5 addresses both of these issues.

ENHANCING RESEARCH COLLABORATION AND ACCOMMODATING DIFFERENT SYSTEMS FOR THE PROTECTION OF HUMAN PARTICIPANTS [1]

It is now widely accepted that research involving human participants should be conducted only after prior approval by an appropriate ethical review body that has assessed the research according to the established criteria of voluntary informed consent, risk-benefit ratios, and a fair distribution of the benefits and the burdens of the research. When research is sponsored or conducted in accordance with U.S. research regulations, an appropriately constituted and

designated IRB is empowered to make these assessments. Other countries have committees that function in largely similar ways.

With the increasing amount of U.S.-sponsored research undertaken in collaboration with other countries—many with quite different procedural requirements—a need exists to enhance the efficiency of those efforts through increased harmonization and understanding without compromising the protection of research participants. The challenge is to find a way to adhere to widely accepted substantive ethical principles while avoiding the undue imposition of other regulatory procedures that are peculiar to the United States.

For U.S. researchers and/or sponsors and their collaborators, some difficulties stem from procedural and administrative aspects of the U.S. research regulations or their implementation by the Office for Human Research Protections (OHRP)(formerly the Office for Protection from Research Risks, or OPRR)[6] which are, at times, experienced as unnecessarily rigid by both U.S. and host-country researchers. For example, one operational difficulty is the question of interpreting the U.S. requirement that another country's guidelines/rules for research provide "equivalent protection" of research participants (45 CFR 46.101(h)), in which case, clinical trials operating under such rules would be eligible for U.S. grant support, as well as meeting FDA requirements.

Although many countries have promulgated extensive regulations or have officially adopted international ethical guidelines invoking high standards for research, OPRR never formally determined that guidelines or rules from any other countries afford protections equivalent to those in U.S. regulations—even such countries as Canada and Australia, where research ethics requirements closely parallel (and to some extent exceed) those of the United States.[7] The result is that researchers from the rest of the world collaborating with U.S.-sponsored researchers must adhere to U.S. research regulations, obtain a special single "project assurance" from the Office for Human Research Protections (OHRP) or forgo collaboration in this type of biomedical research.

Some people, both within the United States and abroad, see this as being excessively and unnecessarily chauvinistic, especially if the main reasons for requiring compliance with U.S. regulations is to provide the legal basis for U.S. control over research and legal capacity to ensure that research participants are protected from harm from a U.S. perspective. One prominent legal authority has suggested that "foreign populations may find that pursuit of their

interests under their local laws and regulations is compromised by provisions that originate in the U.S."[8] A second important question concerns the actual nature of the variation in national and international ethical guidelines. The Commission reviewed the guidelines, codes, and regulations from 17 countries and 7 organizations to more fully understand existing provisions for international collaborative research. The analysis identified substantive ethical requirements in the guidelines of other countries that are absent from the U.S. regulations governing research. In contrast, we found no substantive ethical provisions in the U.S. regulations that do not appear in other national or international rules. More importantly, if these variations cannot be mediated by joint efforts, unproductive difficulties may arise in international research, preventing important and ethically sound research from going forward.

Spokespersons from developing countries have maintained that people from the country in which the research is to be conducted are in the best position to decide what is appropriate, not those who are unfamiliar with local health needs and cultural attitudes. That is, no doubt, the case most of the time, but both researchers and sponsors always have an obligation to ensure that the research project at very least meets their understanding of the ethical treatment of research participants.

CONCLUSIONS [1]

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

Ethics is not, and should not be, a barrier to the research enterprise. Indeed, ethics 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 with 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 also embodying appropriate protections for the rights and welfare of human participants.

Most people hold that a world in which all have access to good medical care would be preferable to one in which many lack such access. Further, most would agree that volunteering to participate in clinical research should be done primarily for altruistic reasons and only secondarily for personal gain, whether financial or medical. In addition, it is widely felt that those who volunteer to be research participants should receive society's respect and gratitude, as manifested (in part) by ensuring they are treated fairly and respectfully and can enjoy the benefits of the research in which they participated. Thus, researchers and sponsors should strive to conduct research both here and abroad in a way that furthers these aspirations. Regrettably, financial, logistical, and public policy obstacles often stand in the way of immediately achieving these goals.

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

Moreover, while the recommendations in this report focus principally on clinical trials conducted in developing countries, consideration should also be given to applying them to other areas of research. However, although many ethical issues that arise in clinical trials aimed at assessing therapeutic efficacy for individuals also arise for other types of research, the relevance, scope, and implications of our recommendations may be quite different. Similarly, many of the issues and recommendations discussed in this report may equally apply to research conducted in the United States, but are principally focused on research conducted abroad and subject to U.S. research regulations.

Some of the recommendations made in this report will evoke disagreement. We seek to justify our recommendations with evidence, reasoned arguments, and principles articulated in guidelines and declarations pertaining to research involving human beings. Although we have tried to avoid making recommendations that are hopelessly aspirational, we believe that adherence to the highest ethical standards calls for a reexamination of past and current practices with an eye toward continuing improvement.

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[1] Traditionally, and in current regulations, those studied in experimental research are referred to as "research subjects." For many, however, the term "subject" also suggests negative connotations about research participation. Although in past reports the Commission used the commonly accepted term, "subject," more recent deliberations and considerations have led to the Commission's adoption of the more appropriate term, "participant."

[2] http://www.nih.gov/fic/about/welcome.html (last accessed August 2, 2000)

[3] 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.

[4] Lagakos, S.W., and K. Dickersin. Testimony before NBAC. December 2, 1999. Baltimore, MD. Meeting transcript, p. 103, 135, 158-161.

[5] Andreopolis, G.J. Testimony before NBAC. May 4, 2000. Madison, WI. Meeting transcript.

[6] Until June 2000,OPRR was the federal agency responsible for implementing U.S. regulations pertaining to protection of human research participants in other countries.

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

[8] See Dickens, B. 2000. "The Challenge of Equivalent Protections." This background paper was prepared for NBAC and is available in Volume II of this report.

CHAPTER 2

ETHICAL CONSIDERATIONS IN THE DESIGN AND CONDUCT OF INTERNATIONAL CLINICAL TRIALS

INTRODUCTION [1]

The wide range of health concerns facing the world raises many different kinds of questions on the frontiers of biomedical science. Moreover, the multiple contexts within which biomedical research investigations proceed also call for a wide array of research designs to forge scientific developments and advance clinical knowledge and treatment approaches. Research designs, therefore, necessarily take many forms. It is essential, however, that the design of every research project involving human participants is adequately evaluated to ensure both scientific merit and sound ethics.

Current federal regulations in the United States require Institutional Review Boards (IRBs) to determine that "[r]isks to subjects are minimized by using procedures which are consistent with sound research design..." (45 CFR 46.111(a)(1)). The regulations further require 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)). While the federal regulations do not tell IRBs to review the scientific merit of a research design, research with flawed methodology will not generate valid or reliable data about the efficacy of the experimental intervention. In such cases, participants will incur the risks, inconveniences or discomforts of being involved in research that lacks the potential to produce generalizable and beneficial knowledge. Thus, the scientific merit of research is an ethical issue because it would be unethical to put people at risk or even to inconvenience or discomfort them through participation in a poorly designed study (OPRR 1993). IRBs ought, therefore, assess both the scientific and the ethical aspects of the protocols they review.[1]

Even when a clinical trial uses a scientifically sound research design and addresses important questions, conducting the research might be unethical if doing so would violate certain ethical principles that are more important than a particular advance in biomedical science. Making a determination about the appropriate design for a clinical trial also 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.

For some purposes it may be useful to classify international collaborative research projects between developed and developing countries as lying along a particular continuum. At one end of the continuum is research that has no practical relevance to the health needs of the host country. At the other end of the spectrum is research that is directly relevant to the host country but not to the sponsors or the researchers. These two extremes frame a spectrum of situations that clearly differ from one another, 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 particular continuum.

The particular focus of this chapter is on the ethical requirement to choose a design that minimizes the risk of harm to human participants in clinical trials and that does not exploit them. This focus brings to the forefront the question of the obligation of sponsors and researchers to the research participants *during* the trial. Some of the chief considerations with respect to both research design and obligations owed to research participants are:

- whether the research is responsive to the health needs of the host country;
- the ability of the study design to answer the primary research question;
- whether effective treatment already exists for the condition being treated by the intervention being studied;
- whether the condition for which a new treatment 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;
- the probability and magnitude of benefit to the study participants;
- the balance of the risks to subjects and the probable benefits to subjects and to others; and
- the future availability of the experimental intervention, if successful, to participants and/or others in the host country after the trial.

Because the choice of a study design for any particular trial will depend on these and other factors, it would be foolish—indeed wrong—to prescribe any particular study designs as ethically appropriate 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 IRBs with a thorough justification of the research design they will use, including the procedures they will use to minimize risks to research participants.

ETHICAL ISSUES IN CLINICAL TRIAL DESIGN [1]

A primary goal in assessing the scientific quality of a particular research design is to insure that the information generated by the clinical trial can be usefully interpreted and does not, therefore, suffer from any type of bias inherent in the design itself. In this context, bias in clinical trials refers to the tendency of any aspect of the methodology or the interpretation of data from a trial to lead to inappropriate conclusions about the effects of an intervention that are systematically different from the truth (FDA 1999). Ensuring trial designs that both avoid various forms of bias and generate data that can answer the scientific questions being addressed cane be difficult. Fortunately, a significant literature has been developed that addresses this challenge (Sackett 1983; Meinert 1986; Spilker 1991). Exhibits 2.1 and Exhibit 2.2 summarize the phases of investigating a new clinical intervention, and the principal types of clinical trial designs commonly used.

Exhibit 2.1: Phases of Drug Development

The development of a new drug is a long and complex process involving multiple steps, including drug discovery, preclinical testing, and finally an ordered program of clinical tria The development of other medical interventions, such as new vaccines, gene therapy and medical devices, also follows a similar process.

The first step in the development process is *discovery*. During the drug discovery process, chemical compounds are identified and/or synthesized, and tested for biological activity. Out 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 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 two percent of compounds evaluated in preclinical testing end up being tested in humans (Mann 1999; PhRMA, 1999).

An investigational new drug application (IND) or an investigational device exemption (IDE) must be submitted to FDA before a drug, biologic, or device can be studied in humans. Once FDA issues an IND or IDE, testing of an experimental intervention in a clinical trial can begin. Clinical trials are usually classified into 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 are commonly conducted in normal volunteers (rather than patients with the condition in question). However, Phase I trials that involve potent and potentially toxic chemicals, for example (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 may clinically significant effects in participants with the disease for which the new intervention is being developed. If the results of these trials are promising, then a larger *Phase III* trial aimed at establishing whether or not there is efficacy may be conducted. Phase III trials are large, frequently multi-institution studies, and typically involve from 100 to 1000s 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). A pivotal trial is an adequate and well-controlled trial in which the hypotheses about the intervention's safety and efficacy are stated in advance and evaluated. The goal of such a trial is to eliminate systematic biases and increase statistical power. By providing firm evidence of safety and efficacy, pivotal trials are designed to produce data that will be accepted by FDA as adequate to support a New Drug Application. On average, it takes almost seven years to complete the required clinical trials (Phase 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 of the safety and efficacy of an experimental intervention, a New Drug Application (NDA) is submitted to FDA for approval of a new drug, a Biologic License Application (BLA) is submitted for approval of a new vaccine or other biologic, or a Product License Application (PLA) is submitted for approval of a new device. Occasionally, FDA requires *Phase IV trials*, which are usually performed after the drug 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 reveal rare but serious side effects.

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 to choose an approach that addresses the scientific question being asked, the intervention being tested, and the group of participants involved, while simultaneously considering the risks and benefits to the participants.

add-on design: a placebo-controlled trial of an experimental intervention is tested in people already receiving an established, effective treatment.

cross-over 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 a standard therapy (also called noninferiority trials); 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 2x2 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 arms, each arm being allocated a different treatment.

randomized withdrawal design: participants who respond positively to an experimental intervention are randomized to either continue receiving that intervention or to receive placebo.

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

From the perspective of the protection of human participants in research, one of the most critical issues concerns the use and treatment of control groups, which often are 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 is truly caused by the experimental intervention being tested, or by other factors, such as the natural progression of the disease, observer or participant expectations, or other treatment (FDA 1999). The experience of an appropriately selected control group lets the investigator know what would have happened to

study participants if they had not received the test intervention, or what would have happened with a different treatment known to be effective (FDA 1999). (See below for a description of control groups.)

Carefully designed clinical trials have been 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 growing steadily. Among the many ethical considerations in evaluating any proposed clinical trial, three in particular provide the focus for this chapter: equipoise, randomization, and the nature and treatment of control groups. Other factors include whether an established, effective treatment exists for the disease being studied, the severity of the disease, the population under study, and the relative risks and benefits to the participants.

Equipoise [2]

Among the most important ethical and scientific justifications for beginning a clinical trial is that there is uncertainty about whether the experimental intervention is better than the status quo (which may be an existing treatment or no treatment). This state of uncertainty is known as "equipoise," and the ethical conduct of a clinical trial requires that it begin in a state of equipoise. Equipoise has been defined as the point where a rational, informed person would have no preference between two (or more) available treatments (Lilford and Jackson 1995). When used in the context of research, equipoise describes a state of genuine uncertainty about whether the experimental intervention or the control arm offers greater benefit or harm than does the control arm. In the *clinical context*, having reasons to believe that one intervention is superior to others ethically compels the clinician to recommend the intervention. 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—not necessarily on the part of the individual investigator—about the preferred treatment" (Freedman 1987).

At the end of a clinical trial, when it is determined whether or not an experimental intervention has efficacy, the state of clinical equipoise has been eliminated. Therefore, although a clinical trial starts in a state of equipoise, investigators hope that analysis of the data collected during the trial will remove the uncertainty.

Randomization [2]

Randomization is the process by which participants in a clinical trial are randomly assigned to different interventions that gives each patient an equal chance of falling into one or another group. It 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). Randomization is the only way to equalize all factors, known and unknown, between study groups (Fletcher, Fletcher and Wagner 1982). The rationale is to minimize any inherent differences among participants in the various arms of the trial by equally distributing people with particular characteristics to the intervention and control arms. The consensus view among clinical investigators is that nonrandomized controls can create severe bias, thus, the results of the trials such controls are often unreliable. Along with the use of placebos and double-blinding (where neither investigator nor participant know which intervention, if any, the participant is receiving) randomization is an essential component of the gold standard for the evaluation of therapeutic interventions. At times, however, such trials are not practical to conduct.[2]

Control Groups [2]

The first documented example of a controlled clinical trial was James Lind's experiment in 1747 with 12 sailors aboard the *H.M.S. Salisbury* who had scurvy (Lind 1753). Lind divided the sailors into six groups of two each and compared the effects of giving 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 to determine the effects of new therapies.

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; see also Exhibit 2.1). The use of each type of control group has its strengths and weaknesses, depending on the scientific question being

asked, the intervention being tested, and the group of participants involved. Therefore, since 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. Placebo concurrent control and active treatment concurrent control trials are described below;, the former because they are considered the gold standard, and the latter because they have been proposed as a more ethical alternative to the placebo control.

Placebo Concurrent Control [3]

A placebo is an intervention that resembles the intervention being tested but that is inert and not expected to have any effect on the condition being treated. Placebo-controlled trials not only control for the "placebo effect" (changes in a person's physical or mental condition resulting from believing that he or she is receiving an active treatment), but also for changes due to the natural course of the disease, participant or investigator expectations, use of other therapy, and subjective elements of diagnosis or assessment (FDA 1999). By including a group that receives a placebo, the action of the experimental intervention can be distinguished from these other potential factors.

For some clinical trials, the decision about the appropriateness of using a placebo is not problematic. It is generally accepted that when no established intervention exists to treat or prevent, it is ethically acceptable to give the control group a placebo because in such trials there is nothing with which to compare the experimental intervention. On the other hand, many 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 for the condition being studied. For example, many experts believe it is not ethically acceptable to perform placebo-controlled trials for clinical trials of new thrombolytics (blood clot dissolving agents), beta blockers, aspirin or Angiotensin-Converting Enzyme (ACE) inhibitors to improve survival after heart attacks, or for new chemotherapeutics for leukemia or testicular cancer, when established effective treatments exist.[3] (Even here, exceptions might exist if the established, effective treatment does not work in certain populations or has such serious side effects that some patients refuse therapy.)

The use of placebos in clinical trials is an ethical issue on which thoughtful and reasonable people disagree. The argument against the use of placebos is often grounded in the *Declaration of Helsinki*, which states "In any medical study every patient – including those of a control group, if any–should be assured of the best proven diagnostic and therapeutic method" (World Medical Association 1964 as amended in 1989). Giving research participants placebo in place of an established, effective treatment deprives them of the "best proven diagnostic and therapeutic method." Critics argue that: 1) research participants should not face unnecessary pain or disease on account of 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 to enroll patients in a study in which some participants are expected to do worse than others (Barinaga 1988).

Others argue that the use of a placebo is acceptable if it does not harm the participants and only results in discomfort (Temple 1996). The E-10 guidance from the International Conference on Harmonization (ICH) concludes that with informed consent and appropriate review by an IRB, research participants can be asked to participate in placebo-controlled trials, even if there is existing therapy, when the only risk from lack of treatment is discomfort. [4] In such cases, it is necessary to ensure that the setting is not coercive and the participants are fully informed about other available therapies and the consequences of delaying treatment (FDA 1999).

Considerable controversy also arises regarding the ethics of using a placebo when an established, effective treatment exists for the disease in question may exist but this intervention *is not and will not be* routinely available to the study population from which research subjects will be recruited. Some contend that there is an obligation to make the established, effective treatment available to the study subjects, at least during the trial, and perhaps even after its completion if the participants' condition warrants continued use of the treatment (see Chapter 4 for further discussion). Others argue that there is no obligation on the part of researchers or sponsors to provide treatments to participants in research if those treatments are otherwise unavailable in the country or community where the research is conducted (Halsey et al. 1997).

While the placebo-controlled, randomized, double-blind clinical trial is the gold standard for new drug evaluation, it is not always ethical to use this trial design (Freedman, Wiejer, and Glass 1996). In situations where the best scientific design is not ethically acceptable, it may be

necessary to reconsider the primary research question, choosing one for which an ethically acceptable design can be proposed (Levine 1998).

Active Treatment Concurrent Control [3]

While placebos are a frequently used control for clinical trials, increasingly it is commonplace to compare an experimental intervention to an existing established, effective treatment. These types of studies are called active-control (or positive control) studies, and can take two forms, a *superiority trial* where the question is whether the new drug will be superior to the active control, and an *equivalence* (noninferiority) *trial* where 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 where it would not be ethical to give participants a placebo because doing so would pose undue risk to the health and/or well-being of the participants.

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 (where neither the investigator nor the participant are aware of the intervention being administered), but this is not always possible. For example, many oncology studies are considered impossible to blind because of different regimens, different routes of administration, and different toxicities. In a study where 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 is so variable from patient to patient and it is often difficult to prove that a standard therapy has had an effect, studies of anti-depressants usually include both an active control and a placebo control.[5]

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 the established, effective treatment to the control group whether or not it is available in the host country. One prominent view appears in the following proposition:

A) 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

because the opportunity to obtain this treatment would render the choice to enroll in the study irresistible and/or because persons receiving this treatment would have little likelihood of being able to get it once the trial was completed.[6]

The Commission does not agree that it is always unethical to provide members of a control group with an established, effective treatment that is unavailable in the country where the research is conducted. There are cases where trials using the established, effective treatment as a control would benefit participants and generate valuable information that is responsive to the health needs of the host country. We need, then, to consider a different formulation that expresses a less absolutist proposition:

B) Researchers and sponsors are under no obligation 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.

Proposition B is "weaker" than A since the latter contends that providing an established, effective treatment would be *unethical*, whereas B maintains that provision of the established, effective treatment, while possibly desirable, is not ethically obligatory. To examine the various alternatives, we need to contrast proposition B with another candidate:

C) 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 country where the research is conducted.

Choosing between propositions A, B, and C rests on a determination of what is owed to research subjects in a randomized, controlled trial. Supporters of proposition B maintain that the obligation of researchers and sponsors to research participants does not go beyond what is routinely available to the majority of people in the country where the research is conducted. A defense of proposition C derives from the circumstance that a special relationship is created when sponsors and investigators from a developed country enter a developing country to conduct research. In the context of U.S. research ethics, the obligations that arise from these situations

also can be seen to flow from the basic principles of research ethics described in the *Belmont Report* (National Commission 1979). For many, these obligations arise regardless of the prevailing economic situation.

The relevant principles of ethics for addressing these propositions are familiar ones, and are found in many national and international guidelines. As applied to this research context, the most straightforward interpretation, for example, of the principle of beneficence, "maximize possible benefits and minimize possible harms," is for sponsors and investigators to make available an established, effective treatment (Proposition C), whether or not it is routinely available, since providing the treatment to the control group would maximize possible benefits and minimize possible harms. Therefore, assuming that the sponsoring agency or organization is able to provide an established effective treatment, and that the host country collaborators 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 country where the research is conducted.

A tension exists, however, between this version of the principle of beneficence and the need for a control group that is relevant to the question facing the host country, which may not be the relative efficacy of the new intervention (compared to the established therapy available in the developed countries) but the absolute efficacy of the intervention compared with the absence of any treatment. The resolution of this tension is central to the assessment carried out by ethics review committees, whose responsibility includes an evaluation of the ethical appropriateness of the study design. Two criteria can be used in making this assessment:

- That participants should receive an established, effective treatment unless a strong case can be made that the only viable alternatives to a "lesser" level of care are (a) not being able to conduct the study at all, or (b) generating data that will not be useful in advancing the care of people in the host country; and
- That individuals serving as controls will receive care at least as effective as the current state of care in the host locale and thereby serve as a legitimate standard against which to measure the new intervention.

Recommendation 2.2: Researchers and sponsors should design clinical trials that provide members of a control group with an established, effective treatment. This should be done whether or not that treatment is available in the country where the research is conducted. In cases in which the only relevant and effective study design would not provide the control group with an established, effective treatment, the proposed research protocol should include a justification for using this alternative design. The IRB must assess the justification provided, as well as the ethical appropriateness of the research design.

Selection of the Participant Population and Sample Size [2]

Another important issue in study design 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 sub-group of the patient population in which the drug may eventually be used (CPMP 1995). This is done mainly to maximize the chance of observing specific clinical effects of interest. By the time the experimental intervention enters the pivotal Phase III trials, the participants should more closely mirror the intended users (CPMP 1995). Therefore, in these trials, the criteria for selection of participants usually are relaxed as much as possible, without jeopardizing the possibility of conducting a successful trial (CPMP 1995). However, even a Phase III clinical trial is usually not totally representative of future users due to several factors, including the geographical location of the trial, the time when it is conducted, and the medical practices of the particular investigators and clinics (CPMP 1995). Multicenter trials help to reduce the influence of such factors. If a multicenter trial is not feasible, every effort should be taken to reduce the variations reflected in these factors as much as possible.

Sample size determination is another important component of clinical trial planning. The determination of sample size depends on the design of the trial and the primary objective of the trial. The number of participants in a clinical trial should always be large enough to provide a reliable answer to the questions posed, but should also be the minimum necessary to achieve this aim (CPMP 1995). Numerous methods and statistical models have been developed to calculate the size of the participant sample needed.

The issue of sample size has been raised in the debate about placebo-controlled trials and equivalence trials. Most equivalence trials require a larger number of participants than placebo-controlled trials, and this argument has been used against the former type of trial. Since placebo-controlled trials involve fewer subjects, the trial will be completed more quickly and any resulting treatment will be made available sooner (Levine 1998). The sooner a new treatment is introduced, the more people stand to benefit from the use of that treatment. 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 quite similar to those needed for placebo-controlled trials.[7]

Each of these issues in the choice of research design—equipoise, randomization, types of controls, participant population, and sample size—involves scientific questions that have ethical relevance (Levine 1986; Freedman 1987; Sutherland, Meslin, and Till 1994) and are therefore properly the concern of IRBs in their assessment of research. One additional issue, which recently has been identified as important in the design of clinical trials and has particular relevance to international collaborative research, is the involvement of community and study participants in the design of studies.

INVOLVEMENT OF COMMUNITY AND STUDY PARTICIPANTS IN THE DESIGN OF RESEARCH [1]

Over the past three decades, researchers have increasingly involved communities in the design of research that affects their members (Arole and Arole, 1994; Taylor 1984; Taylor 1983; Taylor 1970; CDC 1997). This development deserves the attention of researchers and sponsors (NBAC 1999, 72).

Increasingly, research participants, health advocates, and other members of the communities from which participants are recruited are becoming involved in the design of clinical trials. There are a number of reasons for such involvement. For example, by consulting with the community insight can be gained as to whether the research question is really relevant and responsive to health needs of the country. Community consultation can improve the informed consent process and resolve problems that arise because of difficult or unfamiliar concepts. Such discussions can provide insight into whether the balance of benefits and harms in the study are considered acceptable and whether the interventions and follow-up procedures are satisfactory. Community consultation can also reveal the best methods for recruiting participants.

One instance of community consultation involved study participants and health advocates in early stages of breast cancer research, in which laypersons received training in science and epidemiology that enabled them to serve on the committees that review proposed research.[8] Sessions lasting four days have been offered four times a year in the United States, and the project has expanded to other countries as well. In another example, the Joint United Nations Programme on HIV/AIDS (UNAIDS) has, from 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 whose duties include the basic IRB function of ethical review of research protocols. This committee uses an assessment form in its review of proposed research, and included on the form is a section entitled "Community Involvement and Impact." Questions in this section are as follows:

- 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?
  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?

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

In anticipation of an increasing number of HIV/AIDS preventive vaccine trials being initiated, UNAIDS issued a Guidance Document in February 2000, entitled "Ethical Considerations in HIV Preventive Vaccine Research." Guidance Point 5 in this document states: "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).

Recommendation 2.3: Researchers and sponsors should strive to involve representatives of the affected community from the earliest stages of design and implementation of research projects and should promote their sustained involvement throughout the duration of research activities.

OTHER ISSUES IN RESEARCH DESIGN [1]

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

Monitoring the Interim Results of a Study [2]

Randomized 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 be stopped. Responsibility for the review of interim data is often given to an independent group with expertise in the clinical problem, biostatistics, and bioethics, for example a Data and Safety Monitoring Board (DSMB) or a Data Monitoring Board. Such boards make judgments, based on interim data, about whether a study should continue as planned or be changed in some way (DeMets 1999). 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 occur (CPMP 1995). In addition to examining the evolving results of the trial, such boards should be aware of advances in the field and assess whether the study design remains ethically and scientifically valid. This is especially important for diseases for which progress in the development of effective therapies has been rapid. For example, trials in which the control group receives an established effective treatment may be deemed no longer ethical because a new treatment has been found that is clearly more effective. In addition, trials may no longer be ethical because they have no reasonable hope of leading to an unequivocal result, or they have

already demonstrated a definitive difference between the control group and the experimental arm. Trials that are deemed to be no longer ethical 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 in order to safeguard the best interests of the participants.

Repeating a Study [2]

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?

First, when there is scientific evidence that differences in biological factors exist between two populations that could potentially yield different outcomes, repeating the study can be justified.

If there is no scientific reason to question the effectiveness of the new treatment in the population of the developing country, then it would be ethically problematic to repeat the study. This conclusion turns on the answer to a burden-of-proof question: must there be evidence that the two populations have sufficient biological differences? Or does a lack of evidence that the populations are sufficiently similar justify repeating the trial? If there is genuine disagreement or uncertainty within the scientific community about whether biological differences are likely to yield disparate results in the second country, that can provide an ethical justification for repeating the trial.

Another possible reason to repeat a study is because of the potential for government policy in the developing country to change as a result of conducting the study. It is more difficult to derive an ethical conclusion from this reason. Policy makers in many countries will not accept the results of trials conducted elsewhere.[9] This reluctance can stem from legal or regulatory considerations, for example, a policy that requires a determination of the adequacy of other countries' scientific, technical, or ethical review procedures. But a reluctance to accept data from studies conducted in other countries may also represent a political stance on the part of a Ministry of Health or legislative body: a refusal to recognize the relevance of research results coming from other countries because of national pride or political rivalries. Although the latter

reasons cannot by themselves serve as an ethical justification for conducting a study that has proven results elsewhere, the extreme health needs of the 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 [1]

This chapter has focused on a specific set of ethical issues related to the choice of a research design for clinical trials. The discussion of some alternative designs is intended to demonstrate that no single design is appropriate for answering all research questions that might be posed. In addition, the very choice of a research question has ethical implications. We make no attempt to draw a conclusion about the precise circumstances in which, for example, the use of a placebo is acceptable in a particular clinical trial. Rather, we have identified a set of ethically and scientifically relevant considerations that must be taken into account from the earliest stages of research design about which potential participants, investigators, IRBs and sponsors must be cognizant.

We recognize that some people will disagree with our position that researchers and sponsors should, in general, make every effort to design clinical trials that provide members of a control group with an established, effective treatment whether that treatment is available in the country where the research is conducted. In taking this position, we seek to apply the same ethical standard to research conducted in developing countries as is applied in countries that have established, effective treatments available to the general population. To do otherwise would leave the door wide open to conducting the type of research in a developing country that could not be conducted in a wealthier country, while 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 country in which it is conducted—then it should be possible to choose an appropriate research design that both avoids exploitation of countries with few resources and also permits those countries to be the sites of research that can potentially benefit their populations.

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Endnotes

[1] In two previous reports the Commission made a recommendation in this regard (NBAC 1998; NBAC 1999), which is just as relevant to the current discussion.
[2] Lagakos, S. Testimony before NBAC. December 2, 1999. Baltimore, Maryland. Meeting transcript.
[3] Temple, R. Testimony before NBAC., September 18, 1997. Bethesda, Maryland. Meeting transcript.
[4] Temple, R. Testimony before NBAC., September 18, 1997. Bethesda, Maryland. Meeting transcript.
[5] Temple, R. Testimony before NBAC., September 18, 1997. Bethesda, Maryland. Meeting transcript.
[6] Sommer. Testimony before NBAC. September 16, 1999. Arlington, VA. Meeting transcript, 189.
[7] 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. Meeting testimony. http://www.house.gov/reform/hearings/healthcare/fda498/index.htm
[8] Dickersin, K. Testimony before NBAC. December 2, 1999. Baltimore, MD. Meeting transcript, 146.
[9] Sommer, A. Testimony before NBAC. September 16, 1999. Arlington, VA. Meeting transcript, p. 179–180; 188–189; 215–218.