Chapter Five

Ensuring the Protection of Research Participants in International Clinical Trials

Introduction

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

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

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

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

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

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

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

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

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

Assurances

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

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

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

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

Criticisms of the SPA Process

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

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

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

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

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

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

OHRP's Proposed Revisions to the Assurance System

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

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

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

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

Ethics Review

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

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

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

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

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

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

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

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

Current Challenges to Host Country Ethics Review

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

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

The Need for Multiple Ethics Reviews

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

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

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

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

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

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

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

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

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

Challenges of Multiple Review

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

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

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

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

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

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

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

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

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

Lack of Resources as a Barrier to Ethics Review

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

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

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

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

Equivalent Protections

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

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

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

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

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

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

Starting in June 2000, OHRP became the agency responsible for making determinations of equivalent protections for DHHS. However, to date, OHRP has not provided criteria for determining what constitutes equivalent protections or made any such determinations about other countries' guidelines. In lieu of having developed a process for making equivalent protections determinations, OPRR in the past relied on its usual process for negotiating assurances with foreign institutions to ensure that human participants are adequately protected. In response to questions from NBAC, an OPRR official wrote that "[t]here is no established process by which requests for 'equivalent protections' determinations are made. Requests to OPRR to accept an institution's procedures for protecting human subjects are generally made by investigators which, in turn, are invariably addressed in the process of negotiating an assurance."[32] The same official testified before NBAC that "[t]ypically what happens is that we very delicately negotiate an assurance that spells out those protections without actually citing the U.S. regulations. In other words, what we have done is negotiate an assurance on a case-by-case basis that incorporates those national protections without a formal declaration of equivalence."[33]

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

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

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

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

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

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

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

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

The Need for Uniformity in Application

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

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

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

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

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

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

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

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

Building Host Country Capacity to Review and Conduct Clinical Trials

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

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

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

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

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

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

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

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

Exhibit 5.1: Examples of Building Research Capacity

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

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

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

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

Variation in National and International Guidelines

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

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

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

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

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

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

Exhibit 5.2: National and International Guidelines Reviewed by NBAC

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

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

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

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

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

Conclusions

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

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

Notes

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

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

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

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

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

6 Ibid., 115–117.

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

8 Public Law 717, 75th Congress.

9 Public Law 184, 78th Congress.

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

11 See Kass and Hyder, 76.

12 Ibid., 77.

13 Ibid., 159.

14 Ibid., 209.

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

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

17 Ibid., 159.

18 See Kass and Hyder, 51.

19 Ibid.

20 Ibid.

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

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

23 Ibid.

24 See Kass and Hyder, 147–149.

25 See Marshall, 32.

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

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

28 Ibid., 13, 210.

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31 Ibid., 30.

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

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

34 See Dickens, 6.

35 Ibid., 3.

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

37 See Kass and Hyder, 222.

38 Ibid., 67.

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43 See Kass and Hyder, 209–210.

44 Act No. 503 of 24 June 1993.

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

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

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