Chapter Four

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

Introduction

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

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

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

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

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

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

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

Obligations to Research Participants

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

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

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

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

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

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

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

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

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

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

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

The Researcher-Participant Relationship

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

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

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

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

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

Justice as Reciprocity

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

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

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

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

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

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

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

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

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

What Should Be Provided to Communities and Countries?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Who Should Provide Post-Trial Benefits?

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

Obligations of Researchers

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

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

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

Obligations of Public and Private Research Sponsors and Others

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

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

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

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

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

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

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

Prior Agreements

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

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

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

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

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

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

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

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

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

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

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

Some Critiques (and Responses) Concerning Prior Agreements

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

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

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

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

Delay or Prevention of Research

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

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

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

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

Substantive, Procedural, and Logistical Problems

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

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

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

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

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

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

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

Not the Prevailing International Standard

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

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

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

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

Unrealistic Influence on Health Policy

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

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

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

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

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

Creation of a Double Standard

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

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

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

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

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

Potential for Breach of Obligations

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

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

Exhibit 4.1: Vaccine Initiatives Timeline 2000–2001

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

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

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

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

Exhibit 4.1 continued

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

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

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

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

HIV/AIDS Drug Cost Reduction Initiatives

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

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

Bill and Melinda Gates Foundation Research Initiatives

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

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

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

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

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

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

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

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

Conclusions and Recommendations

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

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

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

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

Notes

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

2 Ibid., 98.

3 Ibid., 39–40.

4 Ibid., 43.

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

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

7 See Kass and Hyder, 39–40.

8 Ibid., 40–41.

9 Ibid., 41.

10 Ibid., 155.

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

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

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

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

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