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CHAPTER 4

WHEN RESEARCH IS CONCLUDED: ACCESS TO BENEFITS OF RESEARCH BY PARTICIPANTS, COMMUNITIES, AND COUNTRIES

INTRODUCTION [1]

The preceding chapters explored the ethical issues relevant to the design of clinical trials in the context of international collaborative research and the process and content of informed consent—specifically those factors affecting the rights and welfare of research participants prior to and during such a trial. The recommendations that were developed focus on ensuring the ethical soundness of clinical trials that are conducted abroad but subject to U.S. regulations.

This chapter examines the next step in the process: W*hat, if anything, should be provided to participants (and by whom) after their participation in a trial has ended; and what, if anything, should be made available to the host community or the country as a whole at the conclusion of a study that has resulted in a successful product*?

The obligations of *investigators* to *participants* in research have been of central importance in bioethics. Over the years these obligations have become formalized and are now incorporated in government regulations and international and professional guidelines. This matter is so central to the design of ethical research protocols, however, that discussion continues on the possible need to modify and/or add to these obligations as experience accumulates, as circumstances change, as new types of research are being considered, and as our own ethical sensibilities evolve. Until recently, however, relatively little attention has been given to the issue of the post-trial obligations that research sponsors and/or investigators may have to participants. Some countries, such as Canada (1998), the United Kingdom (1999), Uganda (1997), Brazil (1996), and South Africa (1993), have included statements or provisions in their national guidelines that address this issue (see Appendix 3.1). Similarly, international organizations—CIOMS (1993) and UNAIDS (2000), in particular—also have addressed specific aspects of this issue. It is in this spirit that the Commission decided to approach the question of whether there are any post-trial obligations to participants in clinical trials, and if so, the companion question of on whose shoulders such an obligation should fall.

The traditional approach to defining the obligations of sponsors and/or investigators to research participants has focused almost exclusively on issues of justice in the selection of research participants, the voluntary informed consent of participants, and other measures designed to ensure both that participants are not exploited and that risks are minimized during the time of their participation in research. However, in a previous report (NBAC 1998), the Commission went beyond these obligations and addressed the additional issue of post-trial obligations to participants and concluded that post-trial medical follow-up is warranted for research participants with mental disorders. Moreover, the idea that obligations to participants could continue after research is already recognized in several national and international regulations and guidelines as it relates to compensation for research-related injuries to participants (UNAIDS 2000; CIOMS 1993; India 1997; Australia 1998; Brazil 1996).

In general, however, the presumption underlying existing guidelines and regulations has been that any post-trial obligations would fall on other public or private agencies, rather than on sponsors/and or investigators. One problem with establishing post-trial obligations is that they may make it difficult to avoid the "therapeutic misconception," namely that participants are not mistakenly believing that they are entering into a physician-patient relationship (see Chapter 3). Nevertheless, for the reasons outlined below, the Commission decided to consider the ethical appropriateness of recognizing a more general obligation of sponsors and/or investigators to participants and others after the research has been completed.

As discussed in Chapter 1, our focus is limited in two important ways: first, we are only considering the potential obligations of sponsors and/or investigators from developed countries who are carrying out research trials in a developing country. Second, we focus primarily on clinical trials that have demonstrated the efficacy of the experimental intervention for the condition being studied (i.e., have resulted in a successful product). In essence, we are specifically considering potential post-trial obligations only to participants in trials—particularly some Phase II and Phase III trials—that have directly demonstrated the effectiveness of a new intervention and where the research participants are not likely to have any post-trial access to the intervention. If a post-trial ethical obligation cannot be demonstrated in this case, it is not likely to be established for other types of cases. As in previous chapters and throughout this report, we have chosen to focus on understanding what is unique about clinical trials conducted in developing countries and subject to U.S. regulation.

As noted in previous chapters, a salient difference between clinical trials conducted in the United States or in another *developed* country, and research conducted in a *developing* country is the likelihood that people in the host country will have access to any successful outcomes of such research. Although the United States does not guarantee access to comprehensive health care for all of its people—44 million Americans lack public or private health insurance and many insurance plans (including Medicare) do not adequately cover drugs and medical devices—the fact remains that most Americans have access to many of the fruits of biomedical research. Almost every other developed country has a national commitment to universal access to basic health care. The situation is dramatically different in developing countries, where a much larger percentage of individuals live in poverty, and governments typically have little ability to provide for the health care needs of those who cannot afford to pay. Consequently, even after successful demonstration of a new product, the product itself may not be affordable to the government or to most individuals in many developing countries.

The difference between access to health care in resource-poor countries and in developed countries prompts the question of whether industrialized country sponsors of clinical trials should consider arrangements whereby some of the fruits of research would be made available in the host country when the research is concluded. To do so would be one strategy in implementing the ethical requirement discussed in earlier chapters: that research must be responsive to the health needs of the population where the research is carried out. Many researchers from developing countries, for example, expressed the view that the study population or community must benefit as a consequence of the study, and mechanisms to ensure this must be discussed or developed as part of the study proposal.[1] These researchers agreed that some benefit must reach the study population or community, although they varied considerably in the details of what such a principle should require.

Clearly, if all of the risks of research are borne by developing country participants, it seems only fair that benefits of some kind, and perhaps post-trial benefits in particular, should also accrue to those participants and to others in the country where the research is carried out. The discussion that follows considers an answer to the question of whether *those involved in the conduct of clinical trials in developing countries have post-study obligations that differ from those that currently exist when the same research is conducted in, for example, the United States or other developed countries.* In a future report on research oversight and revisions in the

existing regulations, the Commission will address the problem of participants in research in the United States who lack access to a study medication that they continue to need at the end of the trial. For the moment, it is enough to note that the failure of research sponsors to continue to make effective interventions available at the conclusion of clinical trials is simply a description of the existing state of affairs in the United States, not an ethical justification for applying that practice abroad.

There are many reasons why there cannot, however, be a universal answer to the question of what, if anything, participants in a clinical trial should receive once their participation ends or when the trial is over. Several factors must be assessed: What is the basis for the obligation? What should be provided? Who is entitled to receive it? Who is responsible for providing it? What mechanisms should be used to enable this provision? These questions provide the framework for the remainder of this chapter.

This issue must be approached contextually. The circumstances under which clinical trials are carried out vary widely and in a manner that clearly affects the nature of post-trial ethical obligations that may fall on the shoulders of investigators and/or sponsors. It may, for example, make a significant difference whether the health condition being addressed is a local one or one that is widespread. In addition, there are also a wide variety of sponsors and/or investigators whose relationships to the entire enterprise may not only be quite different, but these differences could also affect the nature of any post-trial obligation they might have. The sponsor might be an international pharmaceutical company anxious to develop a new product for the world market, or it might be a government agency or non-profit foundation responding to a request for funds from a group of investigators or the host country itself. Of course, the sponsorship of any one clinical trial could involve these or other combinations of arrangements. In addition, it is no simple matter to decide when a particular trial, or which particular set of trials, has demonstrated the effectiveness of a new intervention. Finally, any post-trial obligations to participants or others may face difficult logistical and practical barriers to fulfilling them.

Despite these difficulties of implementation, the Commission feels strongly that the issue of post-trial obligations should be taken seriously by all those involved in the type of studies considered in this report. It is our view that all parties involved in a particular project should focus on efforts to ensure that an adequate stream of benefits are provided to both the

participants and communities from which they were recruited. We recognize that various contextual factors make it unlikely that any simple rules can be articulated that lays out the precise post-trial obligations of the various parties. Nevertheless, we provide recommendations in this chapter that will point in directions that we believe would help all parties arrive at more equitable arrangements. In almost all situations, however, the following factors may be relevant in assessing the ethical requirements to provide some level of post-trial benefits:

1) Is there a separate arrangement in place to make any successful intervention available to the general population in the country or community where the research is carried out?
2) Has the intervention provided to participants produced a cure for their condition or conferred lasting immunity (e.g., a vaccine), so that they have no further need for treatment following the trial?
3) Is the disease chronic or incurable, thus requiring that participants continue to use the product or else suffer a worsening of their illness and possibly death?

When factors 1) or 2) are fulfilled, there is no need for the research sponsor to provide participants with a needed and successful intervention after the clinical trial has concluded. However, when condition 3) exists and condition 1) does not, it is evident that participants will still need a beneficial intervention and someone to provide it following the completion of a trial.

THE JUSTIFICATION FOR PROVIDING POST-TRIAL BENEFITS TO RESEARCH PARTICIPANTS [1]

There are a number of different reasons that have been offered to justify the claim that participants should be provided with successful products of research they continue to need after their participation in a Phase III trial has ended. The two primary reasons are 1) the special relationship of trust and care between researchers and research participants, and 2) the application of a conception of justice, called "justice as reciprocity."

The Researcher-Participant Relationship [2]

The researcher-participant relationship can be construed as a fiduciary one for the same reason that the physician-patient relationship is held to be a special one of care and trust. At the same time, this metaphor cannot be carried too far, because physician-researchers have potentially conflicting obligations to the research participants, the institution, and the sponsor. Indeed, these conflicts provide much of the rationale for regulations designed to protect human research participants. Nevertheless, many potential participants may think of their involvement in research protocols as, at least in part, being involved in a physician-patient relationship. Indeed, their trust in the medical profession more generally is central to their willingness to participate in research. There is an important aspect of the researcher-participant relationship that arises when individuals are asked by a researcher to participate in a clinical trial involving a disease or condition that affects them directly, and for which they *might* receive an intervention that ultimately proves beneficial to them.

At the end of a trial, participants who have benefited from the experimental intervention and then no longer receive it may experience a loss—one that may be difficult to anticipate at the trial's outset. This possible "existential" loss may not be fully appreciated ahead of time by the potential trial participants, or by the researchers who sought their involvement in the trial. That is, participants who are ill when they enter the research may not be able to fully appreciate how they will feel after their condition has improved, only then to suffer a subsequent deterioration once the trial is completed. This "existential loss" may affect the participant's perception of the trust relationship with the researcher, and therefore effect their involvement in the trial. In our view, because of the nature of this relationship, one of the ways to mediate or reduce the burden of that loss, and sustain the level of trust between investigators and potential participants, is to continue to provide to research participants the intervention they were receiving during the clinical trial and still need once their participation in the trial has ended.

In some ways, the obligation arises from the vulnerability and dependency of both patients and research participants to clinicians and researchers respectively. The general obligation of the fiduciary is to represent the best interests of the beneficiary. Also the obligations flow from the special expertise of the fiduciary. However, whereas in recent years patients (and research participants) in the United States have become better informed, more

involved, and therefore at somewhat less risk as a result of their vulnerability, clinical trial participants in the developing world are generally much more vulnerable. This vulnerability arises from cultural norms as well as educational, economic, and political imbalances. It is for this reason that the responsibilities of researchers to clinical trial participants in the developing world are so important to define.

The issue, of course, is not just whether the participant experiences a loss, but also whether expectations for continued assistance were justified. There is no simple answer to this question, but considerations of how effective the intervention is shown to be or the seriousness and clinical trajectory of the underlying condition are clearly pertinent factors in this respect. The greater and clearer the health benefit to participants, the stronger the obligation should be. Another issue is whether the relationship with the researcher, rather than the drug itself, should continue to be provided. There is considerable evidence that the benefit of being in a clinical trial is the quality of general care provided by the research team, not just the drug. This does not imply however, that the researcher has an open-ended, long-term obligation to provide ongoing care to participants after a clinical trial demonstrates that the intervention is effective. If nothing else, that would preclude them from doing further important studies that they have particular expertise in carrying out.

The importance of building and maintaining trust in international collaborative research cannot be overstated. Although it is necessary to ensure that research is conducted in an ethically appropriate and desirable way, trust is an issue that is infrequently discussed in the context of traditional research ethics and, particularly, in relation to the cross-cultural environment in which international collaborative research is conducted. Trust is not subject to laws or regulations. Rather, it is the foundation for the creation of relationships between individuals involved in working together and the connections and interactions that flow from them. In particular, it has long been recognized that trust lies at the heart of an individual's successful relationship to health care providers. It is this issue of trust that underlies, for example, the willingness of most individuals to share private and rather intimate matters with physicians and other health care providers. It is also this trust in investigators (and possibly in sponsors) that is central to the willingness of individuals to participate in medical experiments. In some situations, the source of this trust emanates both from the experience of potential participants with clinical medicine and/or from their confidence in the effectiveness of government regulations and professional

guidelines, supplemented by, in some cases, the advice of a trusted friend or advisor. In other situations, the source of this trust emanates from the belief (or hope) that research will alleviate their sickness.

Justice as Reciprocity [2]

Justice is a broad concept, embodying several more specific conceptions. In its broadest meaning, questions of justice ask, "what is owed to individuals or groups?" or "what do individuals or groups deserve?" One specific conception of justice is *distributive justice*, which deals with a fair distribution of society's benefits and burdens. In the research context, distributive justice requires that no group or social class undergo the risks and inconveniences of serving as research participants if that group or social class is unlikely to receive some reciprocal benefits for their participation in research.

Justice as reciprocity 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. In particular, something could be owed after the completion of a trial that produces a successful product.

Justice as reciprocity suggests that the value of the reciprocating benefit be commensurate with the contribution; it does not specify the nature of the benefit itself. The suggestion that the benefit should assume a specific form, such as the continuing supply of a needed medication, however, is motivated by the special relationship that exists between the researcher and the participant. Consider the act of providing blood. This may take the form of (a) an exchange for money or (b) free giving with no compensation. The latter is often properly characterized as a gift or a contribution; the former is not so properly characterized, though both can be characterized as consensually providing blood. A society can have room (moral room) for both practices of consensually providing blood. But the meaning and role of the two practices in society are distinct. In many situations, insisting that the form of compensation for participation in a clinical trial include a compensatory (or reciprocal) medical benefit unnecessarily narrows the possibilities. In the situations we are focusing on, however, it seems reasonable to operate on

the presumption that this type of benefit is one additional way to be sure that exploitation is avoided.

On the other hand, the Commission acknowledges that the world is complex enough, with enough variations in local context, that this form of compensation should not be mandatory. There should, however, be a presumption that the form of post-trial benefits for participation in a clinical trial should be a compensatory medical benefit. Although presumptive, this form of compensation can be overridden with the genuine advice and consent of the local representative best able to speak with moral authority for the host community as to what alternative compensatory practices would provide a more appropriate benefit.

Some reject justice as reciprocity as a reason for providing more to research participants beyond not making them worse off during or after a trial than they were before the trial began. They question why one specific type of benefit should be made available to the trial participants following completion of a trial—that of access to the effective intervention. Why would it not be equally satisfactory to offer an alternative benefit, either during or after the clinical trial? To put the question another way, is there an intrinsic connection between doing medical research and providing a benefit in the precise form of the intervention being tested? Justice as reciprocity might be construed more generally, for example, through the provision to the participant, community, or country of some other tangible benefit, such as access to various types of health care other than an experimental drug. Some might maintain that benefits in the form of other kinds of health care (rather than an experimental drug) would satisfy the requirements of justice. Communities in developing countries may need a wide variety of health-related interventions, from oral rehydration for children with diarrhea, to bednets to protect against malaria, to adequate prenatal care for pregnant women. If a primary care clinic has been set up in conjunction with a trial, it may turn out to benefit both the former trial participants as well as others in the community, and thus result in more net benefit than just continuing to provide the experimental drug to the study participants. On the face of it, the best way of deciding on reciprocal health-related benefits to the research participants and the community—which depend on the particular needs and preferences of these people—would be through a process of discussion and negotiation.

An additional question arises about the justice of differentiating between former trial participants and others in the community who are in need of similar medical treatments. Is the

distinction merely arbitrary between former research subjects and their family members, neighbors, and members of the wider community who, because of the selection criteria or study design, were not recruited as research participants? A competing conception of justice, typically referred to as a "formal" presentation of the principle of fairness, is *treat like cases alike, treat different cases differently.* To implement this conception of justice, 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? Or are these cases not exactly alike because participants undertook the risks and experienced the inconveniences of the research?

Similarly, are participants who received a placebo similar to those who received the intervention (because both groups suffer from the illness and undertook the risks of research) or dissimilar (because only the participants who actually benefited would experience a loss if the intervention is discontinued? An additional consideration relates to the study design. If the experimental intervention turns out to be ineffective, and a control group in the study received an established, effective treatment, then members of the experimental group would be denied the benefits that the control group received. This gives rise to the question of whether members of the control group who still need the established, effective treatment after participation ends should continue to receive it. And, as a matter of equity, must those in the experimental group be provided with the established, effective treatment that benefited the control group? There are no easy answers to these dilemmas, and when they arise out of competing ethical principles, the only appropriate recourse is to seek a procedural solution. As suggested below, it is highly desirable for this and similar issues to be decided in advance by prior agreements among the collaborating parties in international research. Consideration should be given to including in these negotiations representatives from the potential research participants' community, since they are the ones most directly affected by the research and its aftermath.

An objection to this entire line of reasoning might be that it is unduly paternalistic for policymakers to determine in advance that certain health benefits should be provided to participants, (or the larger community or country), rather than other benefits the participants may wish to receive. For example, if a country's policymakers must decide between health benefits to their population and other societal benefits, should that determination not be left to their judgment? In this case, the ethical acceptability of this solution depends on the likelihood that a

country has effective political participation across all socioeconomic groups. In some societies it remains the case that those who benefit most from social and economic inequalities also wield disproportionate political power and will influence decisions about tradeoffs to serve their interests as opposed to the interests of participants (Daniels, Kennedy, and Kawachi 1999, 235-236).

We are not persuaded by the objection that it is paternalistic for policy makers to make health policy choices that certain post-trial benefits, if they are realized, should be provided to participants. In the first place, known health benefits are not being determined in advance; rather the possible availability of specific benefits emerging from a successful clinical is discussed and disclosed in advance, and decisions made about how and to what extent this obligation can be realized. In chapter 5 we discuss in more detail the nature of the obligation to provide other indirect benefits that result from research through the mechanism of capacity building. Below we provide our reasons regarding the limitations to the obligation to provide post-trial benefits to communities and countries.

WHAT SHOULD BE PROVIDED TO COMMUNITIES AND COUNTRIES? [1]

We are aware that some national bodies, international organizations, and commentators have urged that those who sponsor and conduct research are under some type of joint and continuing obligation to provide the products of successful Phase III (and certain Phase II) clinical trials to the broader community or country in which the study was conducted. One group of commentators offers the following rationale for the position that successful outcomes of the research should be made available to all inhabitants of the country who would benefit from them.

> 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, Annas, Grodin 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 quinine or chloroquine; yet 20 years after it was studied in Malawi, it has yet to be used there.[2] Other groups have also commented on this issue. For example, the National Consensus Conference that met in Uganda to decide on ethical guidelines for research concluded that researchers must use their best efforts to make interventions found to be successful available to the community following the close of the trial. It was recognized, however, that researchers might not be able to do this because of financial constraints.[3]

The view that successful products of research should be made available is not limited to developing country researchers. When asked if he thought there is an ethical obligation to leave some benefit to the country in which the research is done, Christopher Plowe, a. malaria researcher from the United States, testified that he would have questions about doing a study in Malawi on mefloquine, knowing that it would remain a very expensive and inaccessible drug. A colleague of his in East Africa was concerned that it was taking so long to make a drug available through the industrial sponsor and WHO, that he broke ranks and found a local drug manufacturer in Kenya. The colleague is now arranging for the drug to be sold in Kenya because he thought it was unethical to wait any longer.

A survey of researchers from developing countries conducted for NBAC provides additional support for the view that "something needs to go back" to the study participants and the community at the conclusion of the study. [4] Specific benefits mentioned included medical treatment, health counseling and education, and implementation of the intervention.

> In addition to benefits provided during the research, researchers were asked what benefits accrued to host communities and countries after the research has ended....Of the U.S. researchers, 67 percent had plans to provide the intervention to some developing country residents at the conclusion of the study, while 92 percent of international researchers had such plans. Most often, for both U.S. and international respondents, the intervention was or would be provided to the study population; in some cases it was or would be provided to larger groups such as the study community or the entire country. In the U.S. survey, the interventions being provided to the entire country were more likely to involve funding by the host country government.....
>
> While the majority of international intervention studies had plans in place for distributing successful interventions, many researchers in the U.S. survey commented that this should not be a requirement for projects conducted in developing countries. International respondents were more insistent that such arrangements should be a prerequisite to

conducting research; in the survey, three quarters of the international respondents and half of the U.S. respondents agreed with this principle.[5]

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

The Commission has recommended that arrangements should be in place to continue to provide, on a negotiated basis, needed treatment (including the product) to research participants when their participation in a clinical trial has ended. This leads naturally to a more difficult question: *What, if anything, should be made available to the broader community or host country?* Given that global inequities in wealth and resources are so great, it is unfair and unrealistic to expect governmental or industrial sponsors of successful Phase III clinical trials to seek to redress this particular global inequity when no such requirements exist in other spheres of international relationships. In our view, it is not the purpose of clinical trials to seek to redress these inequities.

We are aware that it may be difficult to distinguish, for purposes of meeting an ethical obligation, between participants in a clinical trial who have a particular condition, and those persons who have the disease but are not involved a particular trial. Indeed, the distinction may appear arbitrary: individuals selected to participate in a clinical trial are part of a larger community (e.g., individuals who may have, or be at risk for a similar disease). In our view, the relevant distinction between these two groups of individuals is that those in a study are being exposed to the risks of the study, while others are not. Moreover, a relationship exists between participants and researchers that does not exist for others. It is this relationship—in particular the responsibilities of trust and care—that gives rise to the obligation to continue to provide a needed intervention to those who have participated in a clinical trial. In addition, as discussed above,

there are important justice considerations that support the argument to provide to participants successful products that arise from clinical trials. We suggested that 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 risks that they are undertaking in that regard. In the context of clinical trials, there is a difference between the contributions made by participants (including accepting the possibility of being harmed by the intervention) as contrasted with those who do not participate in the trial.

WHO SHOULD PROVIDE POST-TRIAL BENEFITS? [1]

We have now described *what* should be provided at the end of a participant's involvement in a clinical trial (established, effective treatment and possibly other related care), and *who* should be entitled to receive these benefits (all participants in the trial). We have also provided our justification for limiting any post-trial benefits to communities and countries in certain ways (e.g., on a negotiated basis). We now turn to an especially difficult problem, namely, *who* should be responsible for providing post-trial benefits? For the most part, we have been referring generally to the obligations of *researchers* and/or *sponsors*. But it is evident that these categories cover a diverse set of individuals and entities, with different responsibilities and authority in the research process, which work together in a wide variety of ways. These differences will influence the nature of the obligations that each party should shoulder.

Obligations of Researchers [2]

While individual researchers do not usually have the resources or authority to directly provide post-trial benefits to participants, they can play a role in helping to assure such arrangements are in place. As described above, their relationship with participants gives rise to obligations of trust and of care as well as their obligations as scientists to conduct sound research. These obligations do not extend to effecting social or health policy in the distribution of resources, but they do extend to an advocacy role of some kind. Thus the basic responsibility of the researcher is to respect the participants by informing them, obtaining meaningful consent,

designing the study in a way that addresses a pressing health care problem, and, we would suggest, assist in putting appropriate post-trial arrangements in place.

We believe, therefore, that the researcher's responsibility also includes looking out for the long-term best interests of the subjects and the community with regard to the intervention being studied. This means discussing with relevant parties the potential for making successful products available to participants and the community and serving as an advocate for such availability if the trial results are positive. It does not mean that the researcher must negotiate directly with the host country government or international agencies, although it may include giving recommendations and serving as a consultant. This advocacy role follows from the researcher's specialized knowledge and expertise about the diseases being studied, his or her understanding of whom might benefit from or be harmed by particular interventions, and their commitment to the research process.

We believe that researchers have some obligations beyond the study itself to raise questions of access to therapies that are proven effective and to encourage negotiations among sponsors and host countries. As discussed above, we do not suggest that researchers are themselves responsible for making new products available. But researchers can fulfill their ethical obligation to act in the best interest of participants by ensuring that the issue of access to effective therapies is considered at each stage of the research process, especially the stages of planning and design. Consideration, therefore, should be given to including them as parties in the negotiations sponsors of research hold with various parties to follow through and ensure the provision of continued treatment for participants who still need it once the research is concluded.

Obligations of Public and Private Research Sponsors, and Others [2]

Given the likely inability of researchers personally to ensure that participants from successful Phase III trials obtain post-trial benefits, we should consider whether that burden would fall most appropriately to the research sponsors Although it is always easy to place obligations on the shoulders of others, there is some support for this general proposition. In focus groups of international researchers conducted in support of NBAC's work, participants expressed a strong belief that effective interventions should be implemented in the host countries, and that U.S. or other foreign sponsors had an obligation to give something back to those countries that

had hosted their research projects. At the same time, U.S. researchers in the companion survey worried that, over time, an absolute requirement to provide a research intervention would be an impediment to finding sponsors willing to support research and thus might be harmful to developing countries. "Furthermore, many [U.S. respondents] stated that funding agencies would never be willing to sponsor research that entailed provision of treatment at the end of the study. But the numerous plans in place to provide post-study interventions demonstrates that in many cases such arrangements are valued and quite feasible."[6]

There are, however, many types of research sponsors, for example, ministries of health in the host country, federal research agencies, private companies, and philanthropies. Each of these sponsors supports research in different ways and for different reasons: thus, the motivations of sponsors are also important considerations. For example, government sponsors are accountable to the citizens for the use of public research funds; they are motivated by a desire to advance and promote the public's health. Their ability to commit support for future benefits is often constrained in various ways, including, for example, by their annual cycle of legislative appropriations. Charities and philanthropies, while motivated by a desire to advance and protect the public's health, may not wish to or be able to take on such a future obligation. Private sponsors may also have an interest in advancing the public's health, but they additionally have an interest in maximizing the benefits to their shareholders, customers, or clients, and may not feel any obligation to provide post-trial benefits. For example, it has been pointed out that if one expects industrial sponsors to provide expensive drugs free of charge after a trial is over, it might curtail the interest that companies might have in developing products specifically for diseases prevalent in developing countries (Nuffield Council 1999, 19). If companies do not see a prospect for a fair return on their investment, either from the market or from government subsidies, they might be less likely to embark on such research endeavors.

Given the variety of possible arrangements that exist in sponsoring international research, it would be difficult to describe in detail all the possible obligations that all sponsors might have. For example, many clinical trials involve multiple sponsors, some of which are U.S. government sponsors and others of which are private companies. Other studies involve multiple sponsors from different countries, where the distinction between "public" and "private" sponsors is not made in the same way as it occurs 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.

This occurs, for example, when philanthropies provide resources in support of HIV/AIDS vaccine research.

There is, however, a set of legitimate expectations and concerns that exist regarding sponsors and their obligations following the completion of a successful clinical trial. We have maintained throughout this report that research should be conducted in developing countries that is responsive to the health needs of those countries. Research of this kind is designed to offer some prospect of benefiting the population from whom participants will be drawn. Accepting the justification for conducting research in developing countries provides strong grounds for accepting the claim that sponsors should be expected to play a significant role in putting in place arrangements to provide some post-trial benefit to the country. One of the ways to deal effectively with these issues is for sponsors to negotiate in advance to make successful products "reasonably available" at the conclusion of a trial.

Making Successful Products "Reasonably Available" [2]

Negotiated agreements that anticipate the effort to make successful products from Phase III trials reasonably available have been difficult to interpret and implement. To date it has proven to be impossible to provide a definition of "reasonable availability" that covers a wide variety of cases, is compelling, and at the same time precise, although some international guidelines have tried to do so. The commentaries under CIOMS *Guideline 8,* "Research involving subjects in underdeveloped communities," and *Guideline 15,* "Obligations of sponsoring and host countries," provide a justification for making products of research available. The key statement appears in Guideline 8:

> As a general rule, the sponsoring agency should ensure that, at the completion of successful testing, any product developed would be made reasonably available to inhabitants of the underdeveloped community in which the research was carried out.
>
> As a general rule, the sponsoring agency should agree in advance of the research that any product developed through such research would be made reasonably available to the inhabitants of the host community or country at the completion of successful testing. Exceptions to this general requirement should be justified and agreed to by all concerned parties before the research begins. (CIOMS 1993, 45).

It is worth noting that Guidelines 8 and 15 are themselves inconsistent in specifying to whom effective interventions should be made reasonably available. Guideline 8 refers to "inhabitants of the underdeveloped community in which the research was carried out," whereas Guideline 15 refers to "the inhabitants of the host community or country." Two separate but related points issue from the "general rule" stated in Guideline 15: 1) How is "reasonably available" to be interpreted? and 2) What should be the nature and content of these prior agreements? Below we will address in more detail the issue of "prior agreements." As for the first question, there has been considerable discussion about the meaning, intent and application of the "reasonable availability" clause in the CIOMS Guidelines. Another international document, the *WHO Operational Guidelines for Ethics Committees that Review Biomedical Research*, makes reference to the availability of successful interventions in connection with the process of ethical review. 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).

In recent years, various provisions relating to obligations concerning access to effective treatments have begun to appear in the ethics guidelines of a few developed and developing countries. We note with interest that the nature, focus, and specificity of these guidelines differ with respect to the obligations to provide post-trial benefits. For example, the guidelines promulgated by the United Kingdom (MRC 1999) and Canada (1998) indicate that access issues should be dealt with prior to the start of research. Neither of these country's guidelines impose any affirmative obligation to make interventions available once a trial is completed. The MRC *Interim Guidelines* state 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 1999, Specific Consideration 9). Canada's *Tri-Council Policy Statement* provides that the Research Ethics Board should examine "the issue of continuing access after the trial" (Canada 1998, Commentary to Article 7.2).

On the other hand, the Ugandan *Guidelines for the Conduct of Health Research Involving Human Subjects* impose an affirmative obligation to make every effort to provide effective investigational treatments to research participants and to the host community. They also make a distinction between the obligations owed to these two groups. The guidelines mandate that "[t]he

investigator must provide assurances that, if the investigational product is found to be beneficial, the investigator will make every effort to ensure its provision, without charge, to participants in the trial following the conclusion of the trial. In addition, the investigator shall make a reasonable effort to secure the product's availability to the local community in which the research occurred" (Uganda 1997, V.D. 4).

Yet another example comes from Brazil, whose National Health Council 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" (Brazil 1996). In addition, "... 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" (Brazil 1997). South African guidelines also make direct reference to the availability of beneficial treatment 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 honoured. 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 (South Africa 1993).

Other documents also address this issue. Indeed, UNAIDS is the first organization to make recommendations that explicitly focus on resolving drug access problems as part of international collaborative research. Not only does the document endorse the notion that planning concerning the availability of the proven intervention must begin prior to 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, as well as to other populations at high risk of HIV infection. 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). It is worth noting, however, that in preparation for the initiation of Phase III HIV vaccine trials in Thailand (which are now underway), and the continued development of earlier phases of vaccine research to be carried out elsewhere, UNAIDS conducted a series of consultations related to HIV/AIDS

vaccine trials. These workshops addressed an array of ethical questions arising out of research sponsored by pharmaceutical companies, UNAIDS, and NIH. Participants in these workshops, held in Uganda, Thailand, Brazil, Geneva, and Washington, D.C., agreed on many ethical aspects of proposed vaccine trials, but they were not able to come up with a precise account of what it means for a product to be made "reasonably available."

Finally, a proposed revision of the *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. The provision states that "[m]edical research is only appropriate if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research" (World Medical Association, 2000). As we discuss more fully in Chapter 5, a defensible justification for providing post-trial benefits to communities may also appropriately follow from policy approaches to enhancing international collaboration through capacity building.

It is clear that, despite the difficulty experienced by many groups to provide a clear and unambiguous definition of the term "reasonable availability," this has not diminished their resolve to focus attention on the basic principle, namely that some type of obligation exists to provide the beneficial intervention to participants in Phase III clinical trials. We also recognize that the length of time participants should receive such treatments will not be the same for all research studies, and therefore cannot be stipulated in general. Similarly, the necessary *services* for providing these products (e.g., nursing, technical experience to provide medications) cannot be anticipated for all studies. Therefore, these issues—the time limit, the nature of the intervention, and the necessary services needed—should be a matter of negotiation with the relevant authorities in the host country, and disclosed as part of the informed consent process.

There appears to be no end to the complexities and uncertainties surrounding the general proposition that proven interventions should be made "reasonably available" in the host country. It is critically important to take account of the views of researchers from developing countries that collaborate with industrialized country sponsors. Authorities from a country's ministry of health, for example, are important, but should not necessarily be the only parties in the process of negotiation. Arriving at the procedural solution may be one of the most practical and acceptable solutions to all collaborating parties.

In Chapter 1, we set 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 in which it is conducted rests also on a conception of justice, which was articulated by the National Commission as the third basic tenet of research ethics. Justice would not be fulfilled when a developed nation conducts or supports research in a resource-poor country if the population from which subjects are recruited is unlikely to benefit from the research results. As stated in the ***Belmont Report***:

> [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, 5).

While this passage does not specifically address international collaborative research, the *Belmont Report*'s conception of justice entails the prospect of successful interventions becoming available to a population that is larger than that of the original study participants, whether the population is a poor group within a wealthy society or the residents of a resource-poor country who are participants in a study sponsored and/or conducted by persons from a developed country. The premise of "responsive-to-needs" thus generates a presumption that if the research leads to the development of therapeutically useful interventions (such as drugs or vaccines), means will exist to afford the population access to these interventions.

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

PRIOR AGREEMENTS [1]

The above discussion leads naturally to the question: in seeking to determine what should be made available following completion of a research project, how to decide which should be presumed to be provided and which should be left for negotiation prior to the trial's initiation? Although no general criterion can be provided for making this distinction, conclusions can be reached on a case-by-case basis, supported by a principled justification.

Kass and Dawson recommend a number of innovative mechanisms for encouraging researchers to engage donors, aid agencies, or service 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.[7]

In recent years there have been efforts to define the arrangements for making products available at the completion of a successful clinical trial. These arrangements are generally referred to as "prior agreements." This term refers generally to arrangements made before research begins that lay out a realistic plan for making the proposed research product or intervention available to the host country after the study is completed. The parties to these agreements usually include some combination of producers, sponsors, and potential users of research products. Industry, academia, and organizations of various kinds are frequently producers and sponsors 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" may appear legalistic and, therefore, confusing. Generally, it is not meant to have any legal connotation in the context of international research ethics and many of these agreements probably will not be legally binding instruments.

There are only a limited number of prior agreements in place in international collaborative research today. Four entities that utilize prior agreements are the World Health Organization (WHO), the leading international health organization in the world; the International Aids Vaccine Initiative (IAVI), an international scientific non-profit 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 products will be made widely available at low cost to both the public sector and 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 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 4.1.)

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

Prior agreements also can be designed to provide a benefit derived from research other than the research product 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 and distribute the drug to its population. Another benefit of this type that will be discussed in Chapter 5 is building research capacity.

The type of benefit that is negotiated will depend on the conditions in, and the capabilities of, the particular host country. Where research is to be conducted in less economically advanced countries, the provision of a benefit in the form of a research product probably would be more appropriate in most cases. The suitability of providing a benefit other than the research product will depend upon the nature of the benefit and the economic and technological state of development of the country in question. Technology transfer makes good sense for countries with strong local pharmaceutical industries, (while building research capacity to one degree or another is applicable to most, if not all, developing country collaborations). 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, Annas, Grodin, et al. 1998) of that country by providing to those communities where the product has been tested affordable access to the product. 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 (Glantz, Annas, Grodin, et al. 1998; del Rio 1998).

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, Annas, Grodin, et al. 1998, 41).

Some Critiques (and Responses) About Prior Agreements [2]

Most stakeholders in the research enterprise probably would agree that, at least in principle, prior agreements are an ethically desirable idea whose 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, IRBs, 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 prior to the commencement of research 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 can help to solve the problem of economic affordability to which factors, such as poverty and high prices, contribute, while a plan for distribution can help address obstacles to availability and inappropriate drug use, such as weak healthcare infrastructure or overprescription by providers.

However, others would contend that it is not feasible to adopt a general requirement that prior agreements to ensure the availability of a proven intervention be negotiated as a condition of the research being approved. Such a requirement has been criticized or could expected to be criticized for the following reasons:

- It is not the prevailing international standard.
- It would create a double standard.
- It would serve only to delay or prevent new drug research in developing countries.
- It would go far beyond the influence one can reasonably expect researchers to have concerning changes in a country's health policy.
- Prior agreements can always be breached.
- Prior agreements are substantively, procedurally, and logistically problematic.

Not the Prevailing International Standard [3]

One 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 limited number of documents. As described earlier in this chapter, these documents include the CIOMS *International Ethical Guidelines*, 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 1999), Canada (1998), Uganda (National Consensus Conference 1997), and Brazil (National Health Council 1987, 1997), the UNAIDS *Guidance Document* (UNAIDS 2000), and the most recent proposed revision of the World Medical Association *Declaration of Helsinki* (WMA, 2000 draft). Such support has manifested itself in two ways. First, these documents all encompass the notion that the ethical acceptability of the proposed research, including issues related to product availability, should be determined before it is underway. Second, a more limited number of them (CIOMS 1993, WHO 2000, National Consensus Conference 1997, National Health Council 1987, 1997), UNAIDS 2000, and WMA, 2000 draft) impose an affirmative obligation to provide successful products to research participants and to the host community.

To consider as part of 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 implementation in the host country and how will implementation occur?

Just because a plan to make research products available to the host country after the trial ends is not the prevailing international standard does not mean it is not an ethical standard to which we should aspire. Little attention has been given in international research ethics to the question of what should be provided to communities and countries where 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.

Creation of a Double Standard [3]

A second criticism of prior agreements is that the adoption of a requirement that prior agreements be negotiated 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, unlike the United States, without prior agreements, the benefits of successful research will not be generally available in developing countries. "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, Annas, Grodin, et al. 1998, 41).

However, others would disagree. There is evidence that 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 competed with multiple facets of access to care, including medication access (Cunningham, Andersen, Katz, 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 knowing full well that only the poor would be recruited as research participants and that the intervention would not be made generally available to the poor (Glantz, Annas, Grodin, et al. 1998).

We do not seek to determine whether a double standard would be, in fact, created if prior agreements were required for research conducted in developing countries. What is more important for our purposes is that simply because the use of prior agreements is not the current ethical standard for research conducted in the United States does not provide adequate justification for not adhering to such a standard elsewhere. Perhaps agreements reached in advance of the start of research conducted in this country is a goal that we should set for ourselves to ensure that research products are made available to those who need them.

From the perspective of justice, we believe that persons enrolled in clinical trials should have access to therapies that are proven effective in the trial. Our report focuses on trials conducted in developing countries because the discrepancies in access are greatest in that context. However, if individuals enrolled in clinical trials in the United States have very little likelihood of gaining access to the therapies studied after the conclusion of the trial, this situation is also ethically unacceptable. Whenever researchers carry out clinical trials in populations with poor access to health care, they should consider in advance the question of access after the trial to therapies proven effective and should seek prior agreements to make therapies accessible.

Delay or Prevention of Research [3]

A third criticism is that by imposing a requirement that prior agreements be negotiated as a condition of research being approved, it will serve only to delay or prevent new drug research in developing countries (Glantz, Annas, Grodin, 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, Annas, Grodin, et al. 1998). Furthermore, the fact that the research is not conducted serves to protect the inhabitants of the country against exploitation as participants in research from which only the industrialized world is likely to benefit.

Unrealistic Influence on Health Policy [3]

A fourth criticism is that the imposition of a requirement for prior agreements as a condition of research being approved "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, what is the likelihood that government policy in a developing country will change as a result of conducting the study so that the intervention will get to the people that need it?[8] Researchers contend that they are powerless to ensure that any interventions supplied to developing countries once a study is over will actually be distributed. 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."[9]

There may be circumstances under which governments and other interested parties are in a better position to commit to making a new therapy available after the conclusion of a pivotal clinical trial that clarifies the probability and magnitude of beneficial effect, safety, and the effectiveness of alternatives. Moreover, the results of the trial may strengthen the position of the host country in negotiating with sponsors, manufacturers, and private philanthropies. The problem, in most instances, is not the inability of researchers to influence national health policy or that developing countries are being told that they must accept prior agreements that they do not want. Rather, it is that accessibility, which includes a component for distribution, is an issue that researchers, sponsors, IRBs, and/or developing countries have either failed to address altogether or simply neglected to address in sufficiently explicit and realistic terms. During their discussions about proposed research, developing country governments should make known to researchers their positions concerning product availability once the research is finished. Assuming that the host country wants to try to ensure that a proven intervention will be made available to its population after the research is completed, a prior agreement can assist in this effort through the development of a plan for distribution.

Potential for Breach of Obligations [3]

A fifth criticism is that researchers and sponsors might breach their obligations under prior agreements to make proven interventions available (Glantz, Annas, Grodin, et al. 1998). Because most of these agreements are not legally binding instruments, developing countries are left without a sufficient remedy upon which to rely. Under these circumstances, they might be reluctant to enter into such agreements. Although failure by a party to an agreement to fulfill its obligations is always a possibility, it does not provide sufficient justification for rejecting the use of prior agreements. A suitable analogy is promise keeping. People make promises and then break them. In doing so, a moral rather than a legal wrong is committed for which there is no remedy. However, this is not a reason to derail the institution of promise keeping as a means of setting up legitimate expectations of the parties in a given situation. Further, the threat of debarment from future research and ostracism by the international research community would, in

many cases, serve as an effective deterrent to an unjustified breach of a prior agreement (Glantz, Annas, Grodin, et al. 1998).

Substantive, Procedural, and Logistical Problems [3]

A final criticism 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 prior to conducting the research. The UNAIDS *Guidance* Document identifies specific issues that need to be addressed 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." 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).

It is easy for some to dismiss the use of prior agreements because of the difficult questions for which there are, as yet, no answers. However, the resolution of critical health problems always requires that parties grapple with complex and challenging issues, and collaborations 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 and/or distribution of drugs in developing countries in a non-research context, such as situations involving purchases by non-governmental organizations (NGOs) or donations by pharmaceutical companies. In both examples, decisions must be made about to whom drugs will be distributed and how. If drugs are purchased by an NGO, it must be determined whether the product will be distributed free of charge or whether the developing country will be responsible for paying a minimal charge. Thus, there is no good reason to believe that these same types of problems in international collaborative research cannot be resolved in a similar fashion.

The process of negotiating such an agreement requires that the parties focus on the expected benefits of the proposed research in a detailed and concrete way by developing a plan for the funding and distribution of the proven intervention. There may be cases where, 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 is completed. The process of developing a plan for funding and distribution would bring that to light and require that the parties deal with the issue of availability. Or it may become apparent in the course of developing such a plan that availability simply cannot realistically be addressed. Such a situation may call for the re-evaluation of the ethical appropriateness of conducting the research.

If these issues are not addressed, then the new proven intervention may not be made available to the country where the research is conducted. For example, if a drug that requires refrigeration is being developed for use in a particular country that lacks refrigerated drug storage capability, a plan for ensuring that the drug will be properly stored must be devised. There is no reason to believe that issues, such as refrigeration, cannot be effectively addressed before the research begins or that it is somehow easier to address them after the study is finished. Ultimately, the parties involved need to reach an understanding about how the country will actually benefit from the proposed research before it begins. This does not mean that the entire population must benefit immediately, but rather, that the parties should be convinced that sufficient numbers will benefit over a reasonable period of time so that a meaningful contribution to the overall welfare of the country is evident.

Finally, the debate concerning the definition of "reasonable availability" has thus far proved unsuccessful in providing a resolution. Arriving at a definition that would satisfy all parties to the debate is a formidable challenge. However, the development of an internationally acceptable standard is a highly desirable goal that should continue to be the subject of discussion. Meanwhile, the use of prior agreements would enable products 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 that process by providing specific examples of the effectiveness or ineffectiveness of various types of arrangements for making research products available.

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 imbalance 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. This new awareness should lead us to the conclusion that we must entertain unique and untested approaches to narrowing the gap

between the developed and the developing worlds. In the late spring and early summer of 2000, substantial commitments by President Clinton, private industry, foundations, and NGOs to combating AIDS indicate an increasing recognition by the developed world that developing countries are unable to successfully address their health needs without its help. Increasingly, efforts in advance of research are being undertaken to make proven interventions and other research benefits widely available in communities and countries where research is conducted. Two organizations have successfully used prior agreements to make products 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 4.1), remain untested, and whether their research products 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 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 4.1 all have been negotiated with the aim of making successful products of research available to communities and countries in which research is carried out. In addition, international documents such as the CIOMS *Guidelines* and the UNAIDS *Guidance* document urge that successful products be made available to a wider segment of the population than the research participants themselves.

CONCLUSION [1]

In this chapter we have considered the question: what, if anything, should sponsors provide to participants after their participation in a trial has ended; and what, if anything, should be made available to the host country as a whole at the conclusion of a study that has provided useful data about a product or intervention? We conclude that at the end of a clinical trial in which a successful product has been found, research participants should be provided with this product. This chapter outlines what sponsors should consider making available, with the understanding

that appropriate host country decision makers are meaningful participants in making arrangements where any potential post-trial benefits are provided to the population.

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Endnotes

[1] See Kass, N., A. Hyder, L. Dawson, and N. Teoh. 2000. "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations." This background paper was prepared for NBAC and is available in Volume II of this report.
[2] Malenga, G. Testimony before NBAC. February 29, 2000. Herndon, VA. Meeting transcript.
[3] Loue, S. Testimony before NBAC. October 21, 1999. Washington, D.C. Meeting transcript, 49
[4] See Kass, N., A. Hyder, L. Dawson, and N. Teoh. 2000. "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations." This background paper was prepared for NBAC and is available in Volume II of this report.
[5] See Kass, N., A. Hyder, L. Dawson, and N. Teoh. 2000. "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations." This background paper was prepared for NBAC and is available in Volume II of this report.
[6] See Kass, N., A. Hyder, L. Dawson, and N. Teoh. 2000. "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations." This background paper was prepared for NBAC and is available in Volume II of this report.

APPENDIX 4.1: PRIOR AGREEMENTS [1]

The World Health Organization [2]

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

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

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

to further utilize it. This type of effort may include the provision by WHO of technical and financial support.

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

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

In addition to commitments relative to quantity, commitments are also sought relative to pricing. Pricing commitments obtained from industry partners by WHO on behalf of public sector agencies may differ depending upon whether the product will be distributed through the private sector. If it is to be distributed through both the private and public sectors, the price at which the product is made available to public sector agencies "shall be (i) preferential compared to the Private Sector price, and (ii) set at the lowest possible level permitting a commercially

reasonable return on combined worldwide sales of the Compound for Distribution in both Public and Private Sectors" (WHO 1999b). The product can be sold in the private sector at whatever price the industry partner chooses. Pricing commitments from industry partners can also take the form of "cost, plus a modest mark-up" or of a maximum price, depending on the circumstances.[3] "Cost, plus a modest mark-up" can be used at any stage of the collaboration, provided the terms can be defined and agreed upon. In contrast, a maximum price commitment can only be used if the development work is at such a point that the parties are able to determine what it will cost to make a product."[4] (Email from David Griffin 7/18/00) If the product will not be distributed through the private sector, availability to public sector agencies shall be "at the lowest possible, commercially reasonable price" (WHO 1999b). Bulk purchase is another mechanism used to ensure availability of products at the lowest cost possible.[5] To a much lesser degree, WHO may receive royalties that are invested in the public interest either to offset the cost of products or to fund further research to meet the needs of developing countries.[6]

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

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

The International Aids Vaccine Initiative [2]

The International Aids Vaccine Initiative [IAVI] is an international scientific non-profit organization founded in 1996 with the single aim of accelerating the development of safe,

effective, accessible HIV vaccines for global use. IAVI's research focus is on vaccines for developing countries. Through the investment of what it calls "social venture capital," IAVI's goal is to develop vaccines that "would be inexpensive to manufacture, easy to transport and administer, stable under field conditions and require few inoculations" (Zonana 1999). IAVI's work is driven by the belief that a vaccine represents the world's best hope to end the AIDS epidemic. A vaccine is scientifically feasible and also would be the most cost-effective way of dealing with the epidemic, which is now global in nature.

In June 1998, IAVI issued a *Scientific Blueprint for AIDS Vaccine Development* (IAVI 1998) that links promising vaccine approaches with countries in which to test them. It seeks to accelerate product development and clinical trials through public-private partnerships between vaccine developers, manufacturers, and those who will test the vaccines. Because it is developing countries where the epidemic is the most severe and the need for a vaccine is greatest, most of IAVI's efforts are focused there. These collaborations seek to ensure that people in developing countries for whom particular vaccines are designed benefit from those vaccines once they are developed.

To date, IAVI has invested about $15 million to create four North-South vaccine development partnerships. It also contributes expertise, "as needed, in areas ranging from project management to regulatory affairs and infrastructure for clinical trials."[9] The first is an academic partnership with the University of Oxford and the University of Nairobi, to develop for East Africa two separate vaccine constructs to be used in combination. The second is an industry/academic/developing country government collaboration, which involves Alphavax Human Vaccines, Inc., a small North Carolina biotechnology firm, and three institutions in South Africa: the University of Capetown, the National Institute of Virology, and the Medical Research Council. The goal of this collaboration is to develop a vaccine to be tested in South Africa (AIDS Vaccine Advocacy Coalition 1999).[10] Both of these vaccines are expected to begin Phase I clinical trials later this year.

In February, 2000, IAVI entered into a third partnership with Targeted Genetics Corporation, of Seattle, Washington, and the Children's Research Institute on the campus of Children's Hospital, in Columbus, Ohio to develop a vaccine for Southern and Eastern Africa that will utilize a vector technology developed by TGC to deliver HIV genes as a form of genetic

immunization. TGC's manufacturing process is based on a cell line originally developed by a researcher at the Institute, which holds the patent to the technology. The vaccine being developed has the characteristic of giving longstanding protection from a single dose and, therefore, may be particularly appropriate for areas where vaccine delivery is difficult. Finally, in May 2000, IAVI entered into its fourth partnership with the Institute of Human Virology. The vaccine under development in partnership with Uganda will be designed to use genetically modified *Salmonella* bacteria as an oral delivery system for DNA. The ease of use and extremely low cost make this a very promising vaccine for large-scale field use. IAVI expects to launch more partnerships later this year.

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

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

IAVI's prior agreements with its industrial partners call for reasonable pricing policies for the public sector in developing countries. The public sector is considered the governments and not-for-profit organizations serving developing countries. In return for financing the early vaccine development, companies agree to make the vaccine available to the public sector in developing countries in quantities reasonable to demand and at a cost of manufacturing plus a

reasonable profit, which is defined. If companies do not do so, IAVI has the right to transfer the intellectual property and background technology to another manufacturer. If the costs of manufacture seem unreasonable, IAVI is permitted under the terms of the agreement to obtain alternative bids for manufacture. If a third party can produce the vaccine for less, the company must match that price or contract the manufacturing from the third party. The vaccine can be sold at the price the market will bear in the developed world and in private markets in the developing world. If its partner is unable to meet its overall obligations under the agreements, IAVI retains the right to choose from several options to ensure global accessibility.

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

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

In addition to the involvement of industry, IAVI believes that international funding from governments is critical to creating the global consortium necessary to ensure that a safe, effective vaccine is developed that will be accessible to the developing country poor. Thus far, IAVI has received financial support from Canada, the United Kingdom, and the Netherlands. Under the

proposed *Vaccines for the New Millennium Act,*[13] the United States would be the fourth country to provide support for IAVI's work.

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

VaxGen [2]

VaxGen, a California-based biotechnology company, developed an AIDS vaccine known as "AIDSVAX" or "gp120." AIDSVAX is the first vaccine candidate in the world to enter Phase III efficacy studies. The company raised money to finance its own trials in an effort to get the vaccine tested as quickly as possible (AIDS Vaccine Advocacy Coalition 1999). Two trials are being conducted on two different vaccines. Each vaccine is designed to prevent a particular strain of the virus prevalent in the country in which it is being tested. The first trial is being conducted in the United States. Between June 1998 and October 1999, over 5,400 participants were recruited, mostly men who have sex with men. Thailand is the site of the second trial. Recruitment of 2,500 participants, all intravenous drug users at high risk of becoming HIV-infected, began in March 1999 and is expected to end sometime in the fall of 2000.

The Thai government, the Bangkok municipal government and Mahidol University have been proactive in working with VaxGen in testing the potential vaccine candidate on the Thai population. Despite the implementation of other interventions, Thailand has one of the fastest growing rates of HIV infections in the world, and the government has made the development of an AIDS vaccine a health priority. Thailand was chosen as a study site for several reasons. One reason is the strong professional relationship that has developed between key individuals at VaxGen and Thai researchers. Another reason is that the strains of the HIV virus present in Thailand are homogeneous, making it easier to test the vaccine. Finally, WHO/UNAIDS selected and supported the building of infrastructure to conduct vaccine trials, and UNAIDS/CDC have supported cohort development over a number of years. The CDC has created a cohort of

injecting drug users from methadone clinics run by the Bangkok Metropolitan Association, who are now being recruited for the vaccine trial.

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

In its discussions with the Thai Ministry of Public Health, VaxGen offered an informal agreement that should there be a licensed product, the country would receive special treatment from the company in making the product available in Thailand (Email from Don Francis). VaxGen has agreed to make a concerted effort to decrease the cost of the vaccine for the country. Or, if feasible, because Thailand has a strong local pharmaceutical industry, arrangements could be made for a bulk shipment of the product with filling and finishing in Thailand.[15] This arrangement was described by one Thai AIDS researcher as a "letter of intent" and the first of its kind in any vaccine trial in the world (IAVI 1999, 7). Discussions about ways of making the product available after completion of the study are ongoing between the parties. Although there is a formal agreement governing the conduct of the Phase III study in Thailand, nothing beyond the "letter of intent" has been requested by the Thai government.

Many of the benefits that will accrue to Thailand as a result of participating in the study take the form of capacity building. The Thais view the transfer of such knowledge and technology as extremely important. Capacity building is occurring in three ways. First, VaxGen is transferring its data management capabilities to Thailand. A complete data center has been established so that the Thais have state-of-the-art hardware and software. VaxGen is teaching the Thai data management unit how to collect, monitor and validate data to comply with international clinical research guidelines. Second, the company has developed a repository of laboratory specimens. Technical know-how is being provided to the Thais about how to store, track, locate, and connect data to specimens. Third, VaxGen is training the Thais in clinical research and good clinical practices relative to conducting Phase III trials. The Thais' experience

has been limited to Phase I and II trials. By engaging in these types of capacity building, the goal is to provide the Thais with the necessary skills and knowledge to enable them to function independently and conduct Phase III clinical trials on their own. Capacity building is occurring as the result of a verbal commitment between VaxGen and the Thais. It is not part of the "letter of intent."

UNAIDS [2]

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

UNAIDS also entered into a preferential pricing agreement with Columbia Laboratories prior to the commencement of UNAIDS-funded microbicide trials in Cote d'Ivoire, South Africa, Benin, and Thailand. If proven successful, it is expected that the product will be made available by Columbia Laboratories, its manufacturer, to all trial participants at no cost until it is registered in the markets in the countries where the research is conducted. After that time, it will be available at a reduced price in the private sector of all developing countries. [16]

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[1] Griffin, P.D. Testimony before NBAC. January 13, 2000. Washington, D.C. Meeting transcript.
[2] Email communication between P. David Griffin, WHO, and Alice Page, NBAC. July 18, 2000.
[3] Email communication between P. David Griffin, WHO, and Alice Page, NBAC. February 11, 2000.
[4] Email communication between P. David Griffin, WHO, and Alice Page, NBAC. July 18, 2000.
[5] Griffin, P.D. Testimony before NBAC. January 13, 2000. Washington, D.C. Meeting transcript.
[6] Griffin, P.D. Testimony before NBAC. January 13, 2000. Washington, D.C. Meeting transcript.
[7] Griffin, P.D. Testimony before NBAC. January 13, 2000. Washington, D.C. Meeting transcript.
[8] Griffin, P.D. Testimony before NBAC. January 13, 2000. Washington, D.C. Meeting transcript.
[9] http://www.iavi.org (last accessed: 6/22/00)
[10] http://www.iavi.org (last accessed: 6/22/00)
[11] Berkley, S. Testimony before NBAC. January 13, 2000. Washington, D.C. Meeting transcript.
[12] Berkley, S. Testimony before NBAC. January 13, 2000. Washington, D.C. Meeting transcript.

[13] Legislation introduced into the Senate: S.2132.IS by Kerry and the House: H.R.3812.IH by Pelosi.
[14] Berkley, S. Testimony before NBAC. January 13, 2000. Washington, D.C. Meeting transcript.
[15] Email communication from Donald Francis, Vaxgen, to Alice Page, NBAC. November, 17, 1999.
[16] Email communication from Julian Fleet, UNAIDS, to Alice Page, NBAC. May 17, 2000.

CHAPTER 5
ENHANCING INTERNATIONAL COLLABORATIVE RESEARCH

INTRODUCTION [1]

In previous chapters of this report, we have discussed and made recommendations regarding matters relating to the ethical design and conduct of clinical trials in developing countries that are sponsored by U.S. organizations and subject to U.S. regulations. For the most part, these recommendations have been specific to issues that arise in the design, conduct, and aftermath of the trials themselves. We expressed the view that research participants not only should be no worse off as a result of their participation in a clinical trial conducted in a developing country, but that there is an obligation to provide to these participants (and perhaps others) the benefits that follow from the completion of a successful trial once the trial is ended. We have already noted that it is important that sponsors and/or investigators from developed nations carrying out clinical trials in developing countries take steps to ensure that participants are not exploited. Likewise, it is important to ensure that the host country itself is not exploited, since there is always a concern that such exploitation may arise when there is a large gap in the power and wealth of the parties involved. Under these conditions, it is often asserted, for example, that the rich and powerful will appropriate an unjustified share of the fruits of the collaboration and in the process accumulate an even more compelling ethical obligation to redistribute resources from themselves to their poorer partners.

Quite aside from the equity of particular collaborations between partners with very different resource capabilities, there always lurks in the background of such activities the nature of the ethical obligation, if any, of rich nations to transfer resources to poor nations. For some observers, such an ethical obligation arises either out of a simple desire to relieve poverty and distress or because one believes that the wealth of the richer countries is unearned and, therefore, undeserved. This report does not address any of the issues related to the general obligations of rich nations in the arena of international distributive justice, despite the overwhelming importance of these issues. We acknowledge the issue only to be sure that when we consider the ethical concerns that accompany the interaction of nations in biomedical research we do not

overburden the discussions by conflating our more general ethical obligations with those that arise in the specific context of collaborative biomedical research. While these two sets of obligations are not independent, discussion of the issues can be clarified by separating, to the extent possible, the nature of these obligations.

One of the unique features of international collaborative research is the degree to which economically more prosperous countries have the opportunity to both enhance mutual trust and encourage future collaboration by leaving the host community or country better off as a result of the collaboration. The type of benefit that could be realized as a result of the collaboration might depend on the health conditions, the state of economic development, and the scientific capabilities of the particular host country. As discussed in Chapter 4, the provision of post-trial benefits to participants and/or others in the form of successful research products is one option. The suitability of providing a benefit other than the research product will depend on the nature of the benefit being considered and on the economic and technological state of development of the country in question. In most cases, efforts to help build local research capacity are another viable option. These two options are not, of course, mutually exclusive. But no matter what form the benefit takes, the ultimate goal of providing it is to improve the welfare of the people in the host country.

While we were not persuaded that there is a specific obligation to provide the successful products of a particular clinical trial to all citizens of a country (as opposed to those who were in the clinical trial), it is our view that there might be additional opportunities to provide long-lasting benefits to communities and countries by taking steps that would enhance future or ongoing international research collaboration.

In this chapter we discuss ways to enhance collaborative international research through three routes: 1) assisting in building the capacity to conduct research, including infrastructure development, training, and education; 2) assisting in building the capacity to conduct the necessary scientific and ethical review of clinical trials; and 3) clarifying where appropriate and revising when needed the U.S. regulatory requirements for research conducted abroad. These three routes are related, but they are not dependent on one another. Moreover, progress in each of them may take different forms. For example, capacity building to conduct research involves the issue of what investigators can do within a clinical trial to enhance the ability of host country

researchers to conduct research (e.g., training and education), as well as what funders can provide in the way of research infrastructure (e.g., equipment) to enable future research to proceed. This contrasts with the idea of building capacity to conduct the necessary scientific and ethics review of studies, which often involves a particular type of training. In addition, any clarification to or revision of U.S. research regulations will require a clear understanding of the scope of existing regulations, particularly with respect to the issuance of assurances of protections to non-U.S. entities and the determination of equivalent protections.

CAPACITY BUILDING IN THE CONDUCT OF RESEARCH [1]

In preparing this report there was considerable sentiment expressed to NBAC for the importance of capacity building. We heard from several individuals who conduct research in developing countries that capacity building in those countries is a central tenet of their work. For example, one expert noted that training and capacity building help to provide mechanisms for strengthening relationships with the local collaborators, as well as for leaving behind lasting benefits in the communities where the research is carried out.[1] Similarly, respondents in a survey conducted for NBAC also confirmed that capacity building should be integral to any study. Authors Kass and Hyder wrote, "Researchers should conceive of their role as facilitating host countries' capacity to eventually conduct most of their research independently, and should aim for such capacity development to be one of the most significant benefits a study can provide."[2]

Such sentiments are consistent with guidelines and other policy statements from several national and international bodies. These documents include provisions pertaining to the responsibilities of industrialized-country sponsors of research in developing countries, including assistance in building local and national capacity for designing and conducting trials and for their scientific and ethical review, and for implementing the results of the research following the trial. For example, in our review of national and international guidelines (see Appendix 3.1), we found that two developing countries have provisions in their guidelines that directly address capacity building. In Brazil, Section III.3.s of Resolution No. 196 states that "...Studies sponsored by external organizations must also respond to training needs in Brazil." South African guidelines state, "While studies are in progress ... the opportunity should be taken to train local health workers in skills and techniques that can be used to improve health services ... When the study

team departs it leaves something of value, such as the ability to monitor diseases or mortality rates." In addition, both the 1993 CIOMS *International Ethical Guidelines* (CIOMS 1993) and the UNAIDS *Guidance Document for Preventive HIV/AIDS Vaccine Trials* (UNAIDS 2000) address this topic. In a departure from the way research in developing countries has been carried out in the past, a consensus has emerged that a true partnership should be forged, rather than an approach in which industrialized country sponsors dictate the terms of the research.

In the arena of capacity building, UNAIDS has developed a list of mechanisms for capacity building in the context of HIV vaccine research that can be adapted to other areas of international research (2000, 16). These mechanisms include

- Scientific exchange, and knowledge and skills transfer between sponsor countries and institutions, host countries, and communities
- Capacity building programs in the science and ethics of vaccine development
- Development of national and local ethics review capacity
- Information and education program support to affected communities from which research participants are drawn
- Early involvement of affected communities in the design and implementation of research protocols (see also Chapter 2)

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

Exhibit 5.1.: Examples of Building Research Capacity

- The Fogarty International Center at the National Institutes of Health (NIH) sponsors international research and training programs aimed at building research capacity in the poorest nations of the world where the need is the greatest. These grants allow institutions in the United States to work in partnership with colleagues in the developing world to conduct research and, in the process, build a cadre of young foreign investigators positioned to address the scientific challenges in the most crucial areas, including HIV/AIDS, emerging infectious diseases, bioethics, medical informatics, population and health, environmental and occupational health, maternal and child health and others.[3] The Center's activities follow from the many activities of "international cooperation" described in the U.S. Public Health Service Act (Sec 307.[242] (a)).

- The International AIDS Vaccine Initiative (IAVI) has formed several wide-ranging partnerships to accelerate the development and testing of preventive AIDS vaccines that would be appropriate for use in various parts of the developing world. (See also Appendix 4.1). One of these partnerships is with the Ugandan Ministry of Health. Ugandan scientists will be collaborating with IAVI on the development and testing of an orally administered AIDS vaccine under development at the University of Maryland Biotechnology Institute. The vaccine's development is being funded by IAVI. The Ministry of Health in Uganda and IAVI also intend to work together to support on-going efforts in Uganda to further build clinical trial infrastructure and prepare sites for trials of a range of preventive AIDS vaccines. Both organizations are also committed to strengthening the capacity of Ugandan scientists to play an active role in vaccine research and development, and to collaborating with other U.S. and European groups working on vaccine development in Uganda.

- The Rockefeller Foundation created the International Clinical Epidemiology Network (INCLEN) in 1980 to improve the health of populations by bringing the science of public health epidemiology to bear on the practice of medicine. INCLEN identifies medical schools in the developing world to train mid-level faculty in the disciplines of clinical epidemiology, biostatistics, health social science, and clinical economics; support those faculty members (and the Clinical Epidemiology Units [CEU] that they formed) through mentorship, continuing education, logistical support, and ongoing linkages with colleagues around their regions and the world; and thereby help those who had been trained establish themselves as productive and influential teachers and researchers, as well as clinicians, administrators, and policymakers. INCLEN has trained nearly 500 faculty members at the Masters level since 1980, and 83 percent remain affiliated with 56 CEUs, located in 24 countries (Global Forum for Health Research website).

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

CAPACITY BUILDING IN THE CONDUCT OF SCIENTIFIC AND ETHICS REVIEW [1]

Of particular importance to the concerns of this report is the adequacy of procedures in host countries for conducting scientific and ethical review. Ultimately, such a capacity provides a better opportunity for enhancing collaboration in international research. In Chapters 2, 3, and 4 we made recommendations addressing specific aspects of ethics review relevant to the assessment and approval of clinical trial protocols. In this section, we focus on enhancing the capacity of developing countries to conduct these reviews themselves.

Scientific and ethical review procedures are well established in many countries and agencies that sponsor international collaborative research, but these procedures are at different stages of evolution in developing countries where clinical trials are carried out. For example, in our review of national and international guidelines, all, with the exception of the Nuremberg Code and that of China, explicitly state that prior ethical and/or scientific review by an independent body is required (see Appendix 3.1).

A survey of U.S. and international researchers conducted for NBAC revealed several important findings regarding oversight and review of research in host countries. For example,

- Nearly all (91 to 96 percent) of the studies described by U.S. respondents were reviewed by a U.S. IRB, and these respondents also reported that most studies were also reviewed by an IRB in the host country.
- In contrast, researchers from various host countries reported that significantly fewer (55 percent) of studies funded by U.S. sponsors were reviewed by a U.S. IRB.
- U:S. researchers often expressed frustration that U.S. IRBs did not appear to understand or appreciate the realities of life in developing countries, thus imposing requirements on investigators that were inappropriate and unrealistic.
- The vast majority of both U.S. and host country researchers felt that the host country investigators sometimes or always relied on U.S. research regulations for guidance, while77 percent of host country researchers and 64 percent of U.S. researchers felt that the use of appropriate international guidelines was better than relying on U.S. rules and regulations.

- Most respondents (85 percent of the host country researchers and 77 percent of U.S. researchers) felt that local review should be required for all studies conducted in developing countries.

It is now generally recognized that research involving human participants should be conducted only after prior approval by an appropriate ethical review body that has assessed the research according to established criteria. The need for independent review of proposed research, carried out by an unbiased committee comprised of individuals with relevant knowledge of medical science and research ethics cannot be overemphasized. When domestic research is sponsored or conducted in accordance with U.S. research regulations, an IRB is empowered to make these assessments. We found, however, that ethical review committees are still not well established in some countries where international collaborative research is conducted. With the increasing amount of U.S.-sponsored research conducted in collaboration with other countries, there is a need to enhance the efficiency of those efforts without compromising the protection of research participants.

VARIATION IN NATIONAL AND INTERNATIONAL GUIDELINES [1]

In developing recommendations for enhancing international collaborative research, and to more fully understand what provisions existed regarding international collaborative research, NBAC staff prepared a detailed comparison of relevant international laws, regulations, and guidelines from 17 countries and 7 international organizations. (A summary of the analysis appears in Appendix 3.1 and the complete analysis is published in Volume II of this report.)

Seven documents developed by international organizations describe general principles and guidelines for the ethical conduct of research, while the remaining 17 national documents set forth the laws, regulations, or guidelines specific to the country in question. These documents were selected from both developed and developing countries, and represent a breadth of geographical and cultural diversity. This analysis focused on ascertaining features of U.S. research regulations that might be absent from other national and international documents, and

conversely, determining if issues appear in international documents that are absent from the U.S. regulations. Exhibit 5.2 lists the sources of the 24 documents.

Exhibit 5.2: National and International Guidelines Reviewed by NBAC

- Australia – National Statement on Ethical Conduct in Research Involving Humans (1999)
- Brazil – Resolutions 196/1996, 251/1997, and 292/1999 (1996-1999)
- Canada – Tri-Council Policy Statement, Ethical Conduct for Research Involving Humans (1998)
- China – Guidelines on Ethical Review of Medical Research (1998)
- Council for International Organizations of Medical Sciences (CIOMS)/ World Health Organization (WHO), International Ethical Guidelines for Biomedical Research Involving Human Subjects (1993)
- Council for International Organizations of Medical Sciences (CIOMS), International Guidelines for Ethical Review of Epidemiological Studies (1991)
- Council of Europe – Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine (1997)
- Declaration of Helsinki (1996)
- Denmark – Act on a Scientific Ethical Committee System and the Handling of Biomedical Research Subjects (1992)
- Finland – Decrees 785/1992, 494/1998 and 986/1999 (1992-1999)
- France – Law on the Protection of Persons Whom Medical Experiments are Performed (1994)
- India – Indian Council of Medical Research (ICMR) Consultative Document on Ethical Guidelines on Biomedical Research Involving Human Subjects (1997)
- International Conference on Harmonization (ICH) – Harmonized Tripartite Guideline, Guideline for Good Clinical Practice (1996)
- Netherlands – Law Regarding Medical-Scientific Research on Humans (1998)
- Nuremberg Code (1947)
- South Africa – Guidelines on Ethics for Medical Research (1993)
- Thailand – Rule of the Medical Council on the Observance on Medical Ethics (1995)
- Uganda – Guidelines for the Conduct of Health Research Involving Human Subjects (1997)
- United Kingdom – Guidelines for Good Clinical Practice in Clinical Trials (1998)
- United Kingdom – Interim Guidelines for Research Involving Human Participants in Developing Societies, Ethical Guidelines for MRC-Sponsored Studies (1999)
- United States – Food and Drug Administration (FDA) (2000)
- United States – Common Rule (2000)
- United States – Agency for International Development (USAID) (2000)
- UNAIDS – Ethical Considerations in HIV Preventive Vaccine Research (2000)

At the very least, these documents begin to explain why researchers collaborating on a common project may find it difficult to comply with the respective guidelines required of them in their own country. At worst it may indicate that if the lack of consistency among guidelines is not addressed, serious and unnecessary difficulties may arise in international research, possibly preventing important research from going forward. This calls for an examination of whether to broaden the U.S. regulations to include some of these provisions, which is addressed in the final section of the chapter. Nonetheless, since there must be some mechanism in place to provide ethics review before research is conducted in another country, it is in the interests of all parties to develop such a capacity in the host country.

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

Recommendation 5.2: Sponsors and researchers should assist in building the capacity of ethics review committees in developing countries to conduct scientific and ethical review of international collaborative research.

HOW THE CURRENT U.S. ETHICS REVIEW SYSTEM WORKS [1]

In examining how the current process for protecting human subjects works, it is important to understand the procedures established by DHHS and, in particular, the role of the Office for Human Research Protections (OHRP) in DHHS-conducted or sponsored research.

The Federal Policy for the Protection of Human Subjects (45 CFR 46, Subpart A), also known as the Common Rule, establishes detailed requirements regarding the form and substance of IRBs, including membership (45 CFR 46.107), functions and operations (45 CFR 46.108), requirements for review of research (45 CFR 46.109), criteria for approval of research (45 CFR 46.111), authority to suspend or terminate research (45 CFR 46.113), and record-keeping

obligations (45 CFR 46.115); the elements and documentation of informed consent (45 CFR 116, 46.117), and the authority of the institution within which an IRB resides to approve or disapprove research (45 CFR 112). DHHS also requires entities that conduct research to comply with additional protections for research involving fetuses, pregnant women, and human in vitro fertilization (Subpart B), prisoners (Subpart C), and children (Subpart D) (45 CFR 46).

DHHS and its lead research agency, NIH, have the most extensive experience with the Common Rule because they conduct or sponsor more human subjects research than any other federal agency. In addition, DHHS sponsors and conducts research in the United States and in other countries. The procedures followed by DHHS can be compared with those of the U.S. Food and Drug Administration (FDA) and with the U.S. Agency for International Development (USAID).

The U.S. Food and Drug Administration (FDA) [2]

FDA, while an agency of DHHS, operates under separate human subject protection regulations (21 CFR Parts 50 and 56) issued under different authorities in the Federal Food, Drug, and Cosmetic Act (FDC Act) and Public Health Service Act. FDA sponsors comparatively little human research, but regulates all human research involving human drugs, biologics, and medical devices that is performed in the United States or relied upon in support of U.S. marketing approval for such products. DHHS-funded research studying those products would be subject to both DHHS and FDA regulations. The FDA regulations are congruent with the Common Rule in most respects, but include some differences based on FDA's particular statutory authorities and regulatory mission. In contrast to DHHS regulatory focus on institutions receiving DHHS funds, FDA regulations focus on the sponsors developing the products, the investigators performing the research studies, and the IRBs reviewing the research.

U.S. Agency for International Development (USAID) [2]

USAID, like DHHS, is a federal agency that adheres to the Common Rule. USAID sponsors research in the United States and in other countries, but does not conduct any research

of its own. It has codified the Common Rule to set standards fir USAID-supported research conducted in the United States or in other countries (22 CFR 225). The regulations are oriented primarily toward biomedical research, but cover other types of research, including survey research/demographic data collection, epidemiologic research, operational or operations research, research on diagnostic tests, and education research, where the principal issue generally "is protection of privacy rather than direct physical harm" (USAID 1996).

Safeguarding the rights and welfare of human subjects is the primary responsibility of the organizations to which USAID awards support. Its regulations and procedures emphasize "practicality, flexibility, and common sense" (USAID 1996). USAID recognizes three essential "pillars of protection": (1) review by a properly constituted ethical committee or IRB; (2) a meaningful assessment of risk/benefit by the IRB; and (3) a meaningful informed consent procedure. USAID "recognizes that foreign countries may often present special situations." In our view, these pillars correspond exactly with the substantive ethical standards discussed in Chapter 1. USAID will accept legitimate foreign procedural systems as long as they are determined to provide protection "at least equivalent" to its policy. Substantive application of the "three pillars" will generally satisfy this requirement.

USAID supports research in foreign countries in three ways. The first provides support to a U.S.-based institution conducting research in another country. If the institution has a DHHS-approved multiple project assurance (MPA) or single project assurance (see below), it may be applied to USAID-sponsored research. If not, the institution must obtain an assurance from USAID. The foreign institution can then rely on review by the IRB of its U.S. partner with an assurance. USAID encourages, but does not require, that a host country IRB also review the research.

Reliance on the assurance held by Johns Hopkins University was the method by which approval was obtained from USAID for a project conducted in collaboration with colleagues at Nepal Netra Jyoti Sangh (NNJS)(see Exhibit 5.3). In this type of situation, USAID trusts and relies heavily on the judgment of the U.S.-based IRB to protect human research participants. Although USAID may be familiar with the institution's MPA, it does not examine each new project or protocol. The second mechanism by which USAID supports research in other countries is through funding research conducted by international organizations or institutions,

including WHO, UNICEF, the United Nations Development Programme (UNDP), and certain non-U.S.-based non-governmental organizations (NGOs). Finally, USAID directly supports host country governments or NGOs.

In the last two cases, standards for human participants protections can be met if the organization, institution, or country simply agrees to be bound by a USAID assurance. It can also be met if institutions adhere to standards that afford "at least equivalent protections" to human participants. "At least equivalent" determinations can be made in two ways. First, USAID has determined that "research supported through or adhering to the standards established by United Nations agencies" is considered to afford "at least equivalent" protections (USAID 1996). This is the mechanism upon which USAID most frequently relies. It is based on USAID's familiarity with U.N. agency standards and review processes, and its trust in those agencies to protect research participants.

Second, USAID has developed a procedure for making its own "at least equivalent" protection determinations. As previously described, USAID recognizes three essential "pillars of protection" that will generally satisfy the "at least equivalent" protection requirement. "In assessing equivalency, the general concept should be whether protection under the system is for all practical purposes the same when viewed *in toto* and not whether any specific component (e.g., the precise make-up of the IRB equivalent) is identical." A justification memorandum must be prepared that describes how the alternative system provides the three "pillars of protection" (USAID 2000). The *in toto* standard used by USAID differs significantly from what OHRP would generally require under the same circumstances (e.g., full compliance with U.S. regulations). However, this mechanism has never been invoked by USAID.

DIFFICULTIES POSED BY FEATURES OF U.S. REGULATIONS AND THEIR IMPLEMENTATION [1]

The studies commissioned by NBAC in support of this report (see Volume II) provide a number of examples of difficulties encountered by researchers in implementing U.S. regulations or policies in other countries. U.S. researchers who work in other countries and their host country collaborators complain about the apparent rigidity of some U.S. regulations and the perceived inflexibility with which the Office for Protection from Research Risks (OPRR) has implemented

them. The researchers pointed to inordinate delays in being able to begin their work, as well as to requirements that are either financially or administratively impossible for many developing countries to fulfill. These difficulties are discussed below. Some difficulties stem from procedural and administrative aspects of the U.S. research regulations or their implementation in the past by OPRR, which some researchers have been found to be unnecessarily rigid. For example, developing country researchers surveyed in a study conducted for NBAC repeatedly expressed the need for flexibility in adapting the procedures specified in U.S. regulations for application in their countries.[4]

A case study (see Exhibit 5.3) provides an example of some of the difficulties faced by researchers, sponsors, and developing countries in achieving appropriate levels of review, suggesting that there may be ways in which U.S. regulations could be made more flexible without lowering the substantive ethical standards embodied in the U.S. regulations.

Exhibit 5.3: Difficulties with the Assurance Process in a Study in Nepal

In Nepal a large, community-based randomized trial was designed to provide zinc supplementation to children age two weeks to three years and then measure change in total mortality as the primary endpoint. Sectors of approximately 20 to 40 households were to be randomized to receive either 10 milligrams per day of zinc or placebo to all children within the specified age group. A total of 48,000 child-years of observation were required to detect a 20-percent reduction of mortality. Every six months all children receive routine vitamin A supplementation through the national vitamin A deficiency control program. The specific aim of the study is to determine if zinc supplementation can reduce child mortality over and above that attributable to vitamin A supplementation.

The study followed 3 community-based trials of micronutrient supplementation to children and women conducted over the past 12 to 14 years, all performed by the same research group at Johns Hopkins University in collaboration with colleagues at the Nepal Netra Jyoti Sangh (NNJS). These previous studies were funded primarily by USAID. The ethical review process included IRB review and approval by the Committee on Human Research at Johns Hopkins University and by the National Health Research Council (NHRC), the organization in Nepal that reviews all health research projects for appropriateness and compliance with ethical principles. The Johns Hopkins University IRB requires approval by the local IRB prior to granting its final approval.

The funding source for the proposed zinc supplementation trial was NIH's National Institute of Child Health and Human Development (NICHD). Johns Hopkins University has a Multiple Project Assurance (MPA) with NIH. Because NNJS, the local collaborating Nepalese agency,

did not have an MPA, they were required under 45 CFR 46 to submit documentation needed in order to obtain a Single Project Assurance (SPA) from the former OPRR. The SPA must be signed by the NNJS and the NHRC, the local IRB. The U.S. researchers felt that the language of the SPA document was unnecessarily prescriptive, for example, by specifying the exact composition of the local IRB, outlining the procedures that should be used at its meeting and in its decision-making process, and dictating its record keeping and reporting responsibilities to the U.S. government. As a result, the NHRC rejected the document and its senior members expressed irritation that the U.S. government would meddle in the internal affairs of a Nepalese government agency that was complying with the principles set forth in the *Declaration of Helsinki*.

The problem was eventually resolved through a process whereby an alternative SPA document was drafted by the U.S. researchers and approved by the NHRC. OPRR then suggested some proposed revisions, which the NHRC accepted. The revised document is now back at OHRP awaiting final approval. According to one U.S. researcher, despite its resolution, this situation has unnecessarily generated bad feelings in Nepal.

Equivalent Protection [2]

Both U.S. and foreign researchers participating in DHHS-conducted or sponsored research at international collaborative sites must adhere either to the provisions of 45 CFR 46 or to procedures that are "at least equivalent" to those provided for in the regulations. They must *also* adhere to an ethical guideline accepted in the United States, most commonly the *Belmont Report* (National Commission 1979), but others, including the *Declaration of Helsinki,* have been accepted by DHHS.

As mentioned above, a provision in the regulations permits a foreign institution to deviate from the specific procedures for protecting human subjects delineated in 45 CFR 46 as long as the procedures with which it agrees to comply provide "at least equivalent" protections (45 CFR 46.101(h)). That provision states that:

> When research covered by this policy takes place in foreign countries, procedures normally followed in foreign countries to protect human subjects may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration ... issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a Department

or Agency head determines that the procedures prescribed by the institutions afford protections that are at least equivalent to those provided in this policy, the Department or Agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy.

With respect to FDA, foreign research involving FDA-regulated products is not subject to FDA regulation unless a study sponsor elects to bring it under FDA's regulatory control. The sponsor may conduct the research under an investigational exemption (Investigational New Drug (IND) for human drugs and biologics or Investigational Device Exemption (IDE) for medical devices) issued by FDA. Where the sponsor elects to conduct the study under an IND or IDE, FDA human subject protection regulations (21 CFR Part 50 for informed consent, and 21 CFR Part 56 for IRBs) apply just as if the study were to be conducted in the United States. Alternatively, a sponsor may conduct a foreign study without an IND or IDE, and then submit a product approval application that relies on the data from the foreign study.

Where the foreign study supporting an approval application is not conducted under an IND or IDE, the study must comply with either the requirements of the *Declaration of Helsinki* or the laws and regulations of the country in which the research is conducted, whichever provides greater subject protection. The human subject protection provisions for such foreign research not conducted under an IND or IDE are imposed through the product review portions of the FDA regulations. The FDA regulations relating to foreign human drug and biologic data from studies not conducted under an IND appear in the regulations at 21 CFR §312.120. The New Drug Application (NDA) regulations at 21 CFR §314.106 impose additional requirements where an NDA relies solely on foreign data in support of a marketing application. For medical devices, the Pre-Market Approval (PMA) regulations at 21 CFR §814.15 impose requirements equivalent to the requirements for drugs and biologics.

Many U.S. researchers, as well as those from developing countries, have observed that difficulties arise when U.S. research regulations are "exported" to other countries. Some have even expressed the view that there is a perception that these regulations are being "imposed" on other countries.[5] In comments made by researchers participating in an NBAC-sponsored survey a U.S. researcher invoked the distinction between ethical principles and specific procedures in the following comment: "The principles of U.S. ethical review should be applied overseas but not the specifics."[6] Others expressed a preference for using international guidelines instead of U.S.

rules. One U.S. researcher said: "It would be good to have international standards that at least match the extent of the U.S. requirements, since these would be more appropriate to the international setting."[7]

Another view expressed a preference for using guidelines from the host countries: "National guidelines in developing countries should take precedence over U.S. regulations when the study is initiated by researchers in the developing country and the role of U.S. researchers is merely to provide technical assistance and expertise as in the collection and analyses of samples...Alternatively, international guidelines should be instituted based on international consensus. Having international guidelines would expedite the IRB approval process since researchers in all countries would be operating under the same set of rules."[8]

In his commissioned paper for NBAC (see Volume II), Bernard Dickens wrote:

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

In our view, the issue that Dickens raises is significant, and supports the distinction we have emphasized earlier in this report: that substantive ethical principles or standards are more fundamental and subject to less negotiation than are matters of procedure. Any given set of substantive ethical standards and principles may give rise to more than one set of appropriate procedures to implement these standards. So long as a procedure (for example, obtaining informed consent without documenting the signatures) is consistent with the ethical standard, the particular procedures themselves should be seen as less consequential. In contrast, if a tension arises because of disagreement regarding the substantive ethical principle or standard, problems will arise for which no mere procedural solution is adequate.

As of June 2000, OHRP is the agency responsible for making determinations of equivalent protection for DHHS. However, to date, OHRP has neither (a) provided criteria for determining what constitutes equivalent protections, nor (b) actually made such determinations.

In lieu of having developed a process for making equivalent protections determinations, in the past OPRR relied on its standard mechanism for negotiating assurances with foreign institutions to ensure that human subjects are adequately protected. In response to questions asked by NBAC, an OPRR official wrote that: "There is no established process by which requests for "equivalent protections" determinations are made. Requests to OPRR to accept an institution's procedures for protecting human subjects are generally made by investigators which, in turn, are invariably addressed in the process of negotiating an assurance."[9] The same official testified that "Typically what happens is that we very delicately negotiate an assurance that spells out those protections without actually citing the U.S. regulations. In other words, what we have done is negotiate an assurance on a case-by-case basis that incorporates those national protections without a formal declaration of equivalence."[10]

OHRP does not, however, have the authority to make determinations of equivalent protection on behalf of non-DHHS agencies, although its authority to negotiate assurances affords it a certain amount of influence. Other agencies that are signatory to the Common Rule have the authority to negotiate assurances, and also to make determinations of equivalent protection. It would seem that U.S. agencies who sponsor or conduct research in other countries have the authority to determine whether foreign guidelines or regulations provide protections to human participants equivalent to those provided in U.S. regulation, however, no criteria exist for agencies to implement this authority, nor does there appear to be any incentive to do so. Indeed as Dickens observed:

> Accordingly, it may be an act of faith for a Department or Agency head to determine that institutional procedures in some foreign countries 'afford protections that are at least equivalent to those provided in this policy' as required by 45 CFR 46.101(h). Ultimately, confidence may have to be placed in foreign institutions' conformity with substantive rules of ethical conduct for protection of human subjects of research, and not on the procedures that they use.[11]

Given the breadth of experience within U.S. agencies—particularly DHHS and USAID—we would expect that this situation could be remedied quickly. It is appropriate for OHRP to both coordinate this activity and be responsible for developing further guidance.

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

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

Assurances [2]

The function of OHRP's current assurance practice is the regulation and oversight of institutions that conduct federally funded research involving human participants both domestically and in other countries. An assurance is "[a] legally binding written document that commits a public or private entity to compliance with applicable federal minimum standards for the protection of human subjects prior to engagement in department or agency conducted or supported research."[12] The assurance document can be described as a pledge or commitment by the institution seeking the assurance to conduct research ethically and in accordance with 45 CFR 46. An approved assurance is a prerequisite to both federally conducted or sponsored research. It is important to note that although DHHS generally provides support to institutions in the form of a grant, assurances also are required if support is provided in a non-financial form. For example, if a federal employee collaborates in research, even though no federal funds are

provided, this constitutes agency support sufficient to bring the institution under the Department's jurisdiction and renders it subject to 45 CFR 46.

OHRP has two main types of assurances: multiple project assurances (MPA) and single project assurances (SPA). It has created a third type of assurance, the cooperative project assurance (CPA), which is used for research conducted under the Cooperative Protocol Research Program (CPRP). CPRP research involves multiple sites and multiple protocols where the studies are similar (e.g., oncology trials) and under joint institutional sponsorship. There is also a variation of the CPA, the international cooperative project assurance (ICPA), which is used for research conducted in other countries. The regulations authorize DHHS to approve an institution's assurance for "Federalwide use." When DHHS has approved such an assurance, all other Common Rule signatory agencies must accept the assurance if it is "appropriate for the research in question" (45 CFR 46.103(a) (1999)). If another Department accepts the DHHS assurance for "Federalwide" use, the institution must provide any reports required under the regulations to both OPRR/OHRP and the supporting agency.

Most DHHS funding for human participants research goes to institutions with MPAs. MPAs are "approved for universities and other major research centers that conduct a substantial number of studies and have demonstrated a willingness and the expertise to comply with human subjects requirements" (GAO 1996, 8). The MPA allows the IRB to review and approve research without additional OHRP involvement, subject to any restrictions OHRP may place on the assurance relative to the types of research that the IRB may review. An institution with an approved MPA may review various types of research projects for a specified period of time, generally three years with renewal every five years thereafter. The types of research that may be reviewed by the institution's IRB depend upon the composition of the IRB.

Research conducted under a CPRP may be reviewed by an institution with an MPA without the need for additional assurances (e.g., a CPA). Most MPA institutions agree to abide by DHHS regulations for all research they fund or conduct, not just research that is federally funded.

The former OPRR reported to NBAC that it had not approved an MPA for any foreign institution. It has been suggested that OPRR/OHRP grant more MPAs to foreign institutions and to other countries. "There is no apparent reason why more foreign MPAs cannot be granted.

OPRR should give serious consideration to issuing MPAs to those foreign institutions (or countries) where multiple SPAs are negotiated" (Wichman, Smith, Mills, et al. 1997).

An institution with an approved SPA may review research studies described specifically in the SPA. Generally, a SPA is limited to similar or closely related research studies conducted under a single grant, cooperative agreement, or contract. In the past, OPRR reviewed the research project (which may include several protocols) and the proposed informed consent form. The SPA is usually used for institutions that do not conduct a large number of DHHS-funded research studies. If a foreign institution without an MPA wishes to conduct research with DHHS support, that institution must have an assurance. An SPA is also used when institutions with an MPA conduct research in collaboration with other sites that do not have MPAs. Each collaborative site that is engaged in research is required to have an approved assurance, and if the site does not have an assurance that supports the research, the SPA is used. Thus, when an MPA institution plans to conduct research in another country, the foreign performance site will generally be required to negotiate a SPA, such as the local collaborating agency. Such an SPA also requires that reporting of problems be directed to the U.S. government instead of allowing local laws and procedures to respond first. Currently, OHRP has about 1,475 SPAs from foreign institutions.[13] [note: update before press]

An institution with an approved CPA for domestic institutions may review all CPRP research that is also reviewed and approved by OHRP or an institution whose IRB is approved by OHRP. Like a SPA, a CPA limits the authority of the institution in its review of research. If the institution is engaged in other non-CPRP research, it must obtain a separate SPA. If an institution has an MPA, it does not need a CPA in order to participate in CPRP research. Recently, OPRR/OHRP approved CPAs submitted by sites in other countries, thereby allowing foreign institutions to participate in CPRP research. Such research is conducted pursuant to an ICPA. In order for an ICPA to be approved by OHRP, a foreign body, such as a Ministry of Health, must assure compliance by each of its members and meet minimum IRB requirements. In addition, the foreign IRB that approves the research must have knowledge of the local population from which the research participants are drawn.[14] An institution with an approved ICPA for foreign institutions has the same authority and responsibilities as institutions with CPAs. About 270 foreign institutions have ICPAs.

In addition to assurances, which are used to bind institutional recipients of federal support, OHRP uses similar documents for hybrid situations or individual recipients. Inter-Institutional Amendments (IIAs) are used to assure compliance by a performance site that does not have an IRB, but which is affiliated with an MPA institution. The IIA essentially allows employees affiliated with an institution with an MPA to conduct research under the MPA without having to obtain an SPA. In practice, this applies primarily to domestic research since only one foreign institution currently holds an MPA. The Non-Institutional Investigator Agreement (NIA) is used for individuals not affiliated with an institution who are engaged in research that is part of a CPRP. The NIA allows investigators to become involved in research with OHRP's approval of this document. The Agreement for an Independent Investigator (AII) is used in non-CPRP research (OPRR/OHRP, Types of Documents). It is "for use by investigators who are participating in an [D]HHS conducted or supported research project when acting in their own name independent of any hospital, clinic, or other facility."[15]

Criticisms of the Single Project Assurance Process [3]

OPRR/OHRP's assurance process has been criticized because it requires foreign institutions to follow U.S. procedures. According to a survey of international researchers using SPAs, "there needs to be an increased acceptance by OPRR of ethical guidance and standards of practice in other countries" (Wichman, Smith, Mills, et al. 1997, 5). Clarification of what constitutes "at least equivalent" protections, and flexibility in its interpretation, especially with respect to procedural matters, was also suggested. Documentation does not always assure compliance; in the end, there must be some level of trust by OHRP in the researchers and the local IRB. Other comments from researchers about how to improve the current process for protecting research participants in international collaborative research almost uniformly suggested the need for greater flexibility. One individual urged that other countries' institutions should choose the composition of the IRB. Another said: "Why is it that the country's or institution's IRB must be approved on every occasion [SPA]? It is stupid and embarrassing to have to demand this. Approve the Board and let them get on with the job." And still another researcher said: "My single experience has been very negative – to the point where my

collaborators almost pulled out." Wichman and her colleagues from whose study the above quotations were found, observed that:

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

Many researchers who were interviewed or provided testimony to NBAC were also highly critical of the SPA process. In an NBAC-sponsored survey, of those interviewed, 49 percent of us researchers in the survey recommended eliminating SPAs, and 65 percent of those who obtained them did not find them valuable in ensuring host country review. [16] They found it to be burdensome, irrational in its structure, and of questionable merit in achieving the goal of protecting research participants. Christopher Plowe testified to the burdens and peculiar nature of the assurance process. He commented on the complex situation that results from the way SPAs are granted. Since SPAs are defined by projects based on the funding mechanism, and not the research protocol, researchers need to obtain multiple SPAs for a single study protocol in cases where there are multiple funding sources. Moreover, when a funding source changes for the same protocol, researchers again have to obtain a new SPA. This imposes a burden on both the U.S. researchers and their local collaborators. Plowe noted that this is difficult to explain to the IRB in other countries. The IRB members complain that they have already reviewed a particular study and wonder why they have to review that same study again.

A different mechanism from the current one was proposed to NBAC for certifying foreign IRBs, that is, certification not based on funding source, but rather on some type of standing recognition of an IRB in another country, once it has been determined that the IRB is properly constituted. This might represent a certification process analogous to that used for MPAs.[17]

A particular feature of the SPA process is a determination by OHRP that research ethics committees be constituted in precisely the way stipulated by the U.S. regulations. Several researchers commented that this procedural requirement is unduly rigid. [18] However, one respondent added that if that composition fails to address a key ethical concern, such as local

community input and review, then it should be incumbent on the researchers to ensure that those concerns are addressed through other mechanisms, for example, the establishment of a community advisory board. In the NBAC-sponsored survey, 83 percent of U.S. researchers and 92 percent of international researchers commented that U.S. regulations should not dictate the composition of host country IRBs. One researcher states that U.S. regulations dictating the composition of host country IRB should not prevail, and suggested that there should be international guidelines.[19]

OHRP's Proposed Revisions to the Assurance System [3]

Federal regulations (45 CFR 46.103(a)) require all institutions engaged in research involving human subjects and supported by DHHS to provide OPRR (now superceded by OHRP) with a written Assurance of Compliance with the regulations.[20] However, many researchers have criticized the current assurance process as being difficult to understand and implement. OHRP is proposing a new assurance process that stresses a cooperative approach to protecting human research participants.

In September 2000 OHRP informed the Commission that the current assurance system was being revised,[21] based on a draft plan circulated to relevant federal agencies. The proposal would eliminate the assurance documents now in place and replace them with either a Federalwide Domestic Assurance or a Federalwide International Assurance, covering all federally supported human research Under the new system, all current assurance documents[22] would be eliminated and replaced with a single, web-based assurance. This new assurance would cover all federally supported research involving human subjects. When applying for a renewal of its assurance an institution would access OHRP's website, view the terms of assurance, and provide information to OHRP on-line. Only the signature page committing the institution to the terms of assurance would be forwarded to OHRP in hard copy. An institution may decide to keep or establish its own IRB(s), rely on the IRBs of another institution, or use an independent IRB. Foreign institutions would be permitted to cite the ethical principles of the *Declaration of Helsinki,* the National Commission's *Belmont Report,* or other relevant international research guidelines as an alternative to the DHHS regulations. Under all assurances, institutional

personnel (i.e., assurance signatory official, senior IRB administrator or contact person, IRB chairperson and members, and research investigators) would be required to complete training on guidelines or regulations pertaining to the protection of human research subjects. OHRP will provide a basic education module through its website to facilitate such training. To ensure that institutions are in compliance with the assurance, OHRP plans to expand educational activities, review institutional procedures for protecting human subjects, increase the number of announced and unannounced site visits, and develop both a web-based and a telephone information service.

We are encouraged that OHRP intends to take these steps to revise and simplify the current assurance process. However, it will be important to monitor the success of this new policy, especially when seen in the light of our concerns about the way in which equivalent protection determinations have been made in the past.

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

Problems Related to Documentation of Informed Consent [2]

We have noted in other chapters in this report that two types of ethical requirements—substantive and procedural—must be carefully considered before research proceed with human participants. We have maintained, however, that while differences in the host country may permit (indeed, may require) that some accommodation be made in the *procedures* used to protect human participants in research, the same cannot be said regarding compromise of certain *substantive ethical standards and principles*. For example, Chapter 3 discussed examples of difficulties researchers in some countries encounter arising from the U.S. requirements for documentation of informed consent. To summarize briefly, those difficulties include: the reluctance of participants in some countries to sign documents or provide a thumbprint; the prevalence in some parts of the world of illiterate or sub literate populations, making written

consent documents irrelevant to their comprehension; and the amount of detail and sheer length of some consent forms, rendering them unlikely to be read or understood by participants and undermining their trust in the researchers. We have recommended that the provisions of 45 CFR 46 requiring written, signed consent documents for all research involving more than minimal risk (with those already noted as exceptions in 45 CFR 46) be modified to allow for waivers of one or both of these requirements, that researchers must provide adequate justifications for requests for such waivers, and that a mechanism be established to audit and make publicly known the results of such audits. Similar modifications would be needed to the provisions of FDA's informed consent regulations at 21 CFR Part 50.

Problems Related to IRB Functions [2]

Other difficulties beyond those emanating from the need for written, signed consent documents have been identified. In some cases, the sheer amount of time required to obtain approvals is a barrier to research. One researcher complained about delays of more than two years, which undermined effective collaboration with local scientists.[23] There may be good reason for the perceptions of delay in the review process, including, most obviously, that some countries—and the research institutions within them—lack the capacity to establish and maintain a system of ethical review. But it is equally obvious that knowledge, expertise, and creative ideas abound, and would benefit from being harnessed. This is why, for example, the *UNAIDS Guidance Document* (2000) and the recent WHO *Operational Guidelines for Ethics Committees that Review Biomedical Research* (2000) recommend that collaboration between sponsors and host countries, and with other international organizations and experts can enhance the capacity for developing countries to provide independent and competent review.

The Commission heard other suggestions in this regard. For example, in their report to NBAC, Kass and Hyder recommend that the process of ethical review could be streamlined based on a study's level of risk.

> There may be cases where reviews are hastened to meet a deadline or a waiver granted after preliminary review (for secondary data analysis or extremely low risk studies), but all studies, irrespective of topic and method, need to be reviewed. The notion that studies

> pertaining to social sciences, especially anthropological sciences, and those involving qualitative research methods need not be reviewed must be negated. Some of the most sensitive issues of human interactions are raised in such studies, and risks arising from breaches of confidentiality, particularly in certain countries, can be literally life threatening. Rather than determine whether review should occur based on a study's discipline or method, IRBs should streamline their review based on the level of risk. Riskier studies ought to be subjected to more rigorous and detailed reviews, and should similarly require more justification from researchers, and then more thorough consent processes and a higher threshold of participant understanding. Studies also need to be reviewed independent of the source of funding. Donor agencies – private, international, national, non-governmental – all are within the purview of ethical reviews. Therefore, bilateral agencies working within countries fund research and such studies need to be reviewed as well."[24]

A specific problem area confronted by IRBs in other countries is that of conforming to U.S. regulations and OPRR/OHRP procedural requirements, as already noted above. Patricia Marshall's report to NBAC cites the comments of a physician-researcher from Lagos, Nigeria. In addition to having to "fight with Washington" to change the consent form, this investigator was frustrated with the administrative aspects of the process, including the amount of paperwork and committee negotiations.[25]

In addition to having to make the required changes in consent forms, several physicians expressed concerns about the possibility of overlooking some of the suggested modifications for consent forms because of the routing back and forth between U.S. and host researchers and their IRBs, in addition to the U.S. funding agency. One Nigerian physician described a situation in which he received IRB approval for conducting a study from his own institutional IRB. He went on to explain, "We sent it to (our colleagues in the U.S.) who sent it to NIH. They looked at the original consent (not ours) and they wanted modifications on the original." The U.S. investigators modified the consent form and sent it back to their Nigerian colleagues who, according to the investigator, "gave it to the (local) IRB who approved it and sent it back to NIH." In situations like this, the physician questioned whether all of the modifications would finally make it into the consent form actually used with patients because it would have gone through so many iterations and levels of review.[26] Another researcher questioned whether the "procedural minutiae" actually succeed in protecting research participants. The researcher maintained that money and time could be better spent on site visits that could observe the

consent process and the procedures for protecting confidentiality, as well as to get feedback from participants.[27]

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

> "...for any given project there are multiple IRB clearances. Each IRB meets once a month at different times. Each IRB uses different presentations and consent forms. Each IRB has a different set of rules. Some accept oral consent. Others written consent. Others written consent with witnesses, without witnesses. And depending on who the witnesses are, each IRB responds with different comments that must be addressed, a different time period for approval and, therefore, different time for yearly renewal." [28]

Moreover, the need for approval of a protocol and informed consent documents in the case of multiple IRBs gives rise to the question: what should be done when IRBs disagree? Pape further observed that there is no mechanism for resolving such conflicts and no understanding on the part of one IRB of how the other operates. [29] This lack of familiarity on the part of IRBs with the situation in countries where research is conducted was noted by another researcher, who said that the U.S. IRB has essentially no experience with conditions and realities of life, medical care, and research in developing countries. [30]

Problems When Studies are Sponsored by Multiple Countries [2]

Problems with the ethics review process in international research go beyond those of whether different review committees make different determinations about a particular protocol. The problem is that any project in which a U.S. institution receives federal funds (regardless of the number and location of other sponsor or research sites) must be submitted to and approved by a U.S. IRB with which the researcher is affiliated. Some view this as the United States imposing its culture and values on other countries. This may be too simplistic a view, however. We noted in Chapter 4 some of the complexity in assigning obligations to the diversity of research sponsors for providing any post-trial benefits to participants or countries. Similarly, when there are multiple sponsors, determinations of which ethics review committee (and how many ethics review committees) are required poses additional complexities. NBAC heard testimony that

countries such as Australia, Canada, the United Kingdom, and others in western Europe have their own regulatory rules and agencies, and their institutions would be unlikely to be able to delegate approval of studies to U.S. IRBs, even though local review processes and principle are similar to those under the U.S. regulations.[31]

Several of the researchers who provided testimony to NBAC offered suggestions to remedy the problems arising from multiple IRBs from the various countries involved in the collaboration, and from the poor communication that currently exists between or among them. Additional suggestions came from respondents to the surveys conducted by consultants. Some of these suggestions included:

- Seeking ways to increase communication among multiple IRBs responsible for review of U.S.-sponsored research conducted in other countries, perhaps via an annual meeting between the chairs of IRBs from collaborating countries or visits between the chairs of each IRB.[32]
- Compulsory coordination among investigators and local IRBs.[33]
- Seeking input from local IRBs or community members in the host country in designing the consent process prior to review by a U.S. IRB; moreover, the U.S. IRB should be flexible and receptive to such proposals.[34]
- Design of consent forms in the host country by the local investigator, followed by approval by the local IRB, rather than have the documents and approval emanate from the United States.[35]
- Delegating resolution of differences and conflicts to the host country.
- Including on U.S. IRBs that review developing country protocols members with experience working or living in developing countries.[36]

We are aware that these (and other possible proposals) to reduce the burden of multiple IRB review have yet to be comprehensively assessed. We encourage sponsors, researchers, and review committees to consider these approaches. In our view, the principle of prior independent review of research is a central and unarguable one. We also believe that when research is conducted by multiple sponsors, agreement should be reached in advance about the number of

ethics review committees necessary to ensure that appropriate consideration has been given to the rights and welfare of human participants. Given the breadth and scope of international research, we are persuaded that efforts to encourage transnational research (including methods of efficiently reviewing such studies) should be enhanced.

The substantive ethical standard that research involving human participants cannot proceed with the prior approval of an independent committee competent to conduct such a review is foundational. We recognize however, that the number of such committees a particular clinical trial may face varies depending on the country, the funding source, and the guidelines being used. Where research subject to U.S. research regulations is sponsored and/or conducted in other countries, prior ethics approval ethics review must occur by a U.S. IRB, and by an appropriately constituted review committee in the host country. For purposes of U.S.-based researchers (where U.S. institutions receive financial support) and where U.S. institutions are subject to U.S. regulations, we remain convinced that both a U.S. IRB and a local ethics review committee in the host country is required. This requirement may be seen as a minimum. Clearly, where clinical trials are supported by multiple sponsors (including several sponsors from the United States or other countries), ethics reviews may be conducted in accordance with the guidelines and procedures already established in those settings. In such cases, coordination and communication between and among review committees should be fostered.

Recommendation 5.6: Clinical trials conducted in developing countries and subject to U.S research regulations must meet prior approval by an independent ethics review committee in the country where the research will take place, as well as by a U.S. IRB. Researchers should include in the research protocol plans for facilitating communication between or among IRBs in the United States and with review bodies in the collaborating countries.

Recommendation 5.7: When research is supported by a U.S. organization or entity that is not subject to U.S. research regulations, researchers are encouraged to comply with Recommendation 5.6 above. Researchers should include in the research

protocol plans for facilitating communication between or among IRBs in the United States and with review bodies in the collaborating countries.

Lack of Resources as a Barrier in Some Countries [3]

Difficulties of IRBs in resource-poor countries in complying with U.S. regulations may stem from lack of funds to carry out their responsibilities. In some cases, local IRBs have requested overhead or operational costs for studies done in collaboration with U.S. researchers. Some investigators interviewed by Marshall suggested that regulatory agencies in the United States should make a greater investment in the IRBs of host countries through training and the provision of materials and resources[37]. This suggestion raises concerns about the intermingling of the ethics and the finances, a situation that is problematic because protocols could be delayed for monetary reasons rather than because of ethical concerns. Since NIH does not provide financial support to subcontracting institutions in other countries, and the World Health Organization pays no overhead, "what you end up doing is trying to bargain by offering to train personnel, provide equipment, provide services, or trying to somehow imbed the equivalent of overhead in your budget and deal with it that way.[38]

One researcher noted that foreign IRBs have no budget and asked why they should use their time to meet U.S. OPRR/OHRP regulations when no funds are provided for salary, secretarial, courier service, office maintenance, and other necessities.[39]

We recognize that the experiences of those who testified before us or responded to surveys conducted on our behalf may not be generalizable to all countries. However, we are persuaded that these issues likely do arise for researchers (and ethics review committees) in other countries. Indeed, we have recognized in previous reports (NBAC 1998; NBAC 1999) that there are costs to providing protection to human subjects in research, and researchers and institutions should not be put in the position of having to choose between conducting research and protecting subjects. Therefore, one means to enhancing international collaborative research is to make available the resources necessary to conduct such reviews.

Recommendation 5.8: Federal agencies and others that sponsor international research in developing countries should provide financial support for the costs

(administrative and operational) of compliance with requirements for oversight of research involving human participants.

Difficulties Related to Enforcement and Compliance [2]

Even where published guidelines or regulations exist, they cannot serve as adequate protection for research participants unless they are properly implemented and enforced. For example, researcher Sana Loue testified that there is no infrastructure in Uganda that has oversight and enforcement authority over the operation of research ethics committees. This is the case both for IRBs at the institutional and national levels. The situation is further complicated by a controversy between the National Drug Authority, the Uganda National Council of Science and Technology, and the Ministry of Justice regarding exactly who should assume responsibility for that oversight function.[40] Loue said that consequences of violating the Uganda ethical guidelines for research include prohibition of ever conducting any research in Uganda, the termination of a specific research project, and the temporary suspension of a research project pending further investigation. She surmised that the framers of the Uganda guidelines contemplated that the media would act as an enforcement mechanism, in that through the media violations would come to the attention of whatever enforcement authority is put in place, as well as to research participants themselves.

Another potential problem for enforcement and redress in some countries may stem from the absence of a requirement for signed consent forms. Developing country researchers surveyed in the project conducted by Kass and Hyder generally agreed that the IRB process is useful in improving the quality of the research, but some were skeptical of the effectiveness of the IRB system as a mechanism to protect human rights.

BUILDING AND MAINTAINING TRUST [1]

Chapter 4 describes the relationship between researchers and participants as one of trust. Although it is necessary to ensure that research is conducted in an ethically appropriate and desirable way, it is an issue infrequently discussed in the context of traditional research ethics and, particularly, in relation to the cross-cultural environment in which international

collaborative research is conducted. Trust is not subject to laws or regulations. Rather, it is the foundation for the creation of relationships between individuals involved in research and the connections and interactions that flow from them. An international collaboration may consist of researchers from many countries and sponsors from varying disciplines, institutions, communities, and countries, all of whom bring very different viewpoints and perspectives to the research at hand. The relationships and, ultimately, the level of trust established between individuals, institutions, communities, and countries is determined by complex, and often contradictory, social, cultural, political, economic, and historical factors.

CONCLUSIONS [1]

In this chapter we identified two ways in which additional benefits can flow to host countries, through building capacity to conduct research, and through building capacity to conduct scientific and ethics review. In addition, we identified ways in which U.S. regulations might be made more flexible to accommodate some of the barriers to successful collaboration without lowering the substantive ethical standards embodied in the U.S. regulations. We recognize, however, that establishing the means to enhance international collaborative research must go beyond regulations (King, Henderson, and Stein 1999). It is essential therefore, for sponsors, the countries from which they come, and researchers engaged in such important work to enhance these collaborations.

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[1] Plowe, C. Testimony before NBAC. February 29, 2000. Herndon, VA. Meeting transcript, 107.

[2] See Kass, N., A. Hyder, L. Dawson, and N. Teoh. 2000. "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations." Part F, pg. 6. This background paper was prepared for NBAC and is available in Volume II of this report.

[3] Keusch, G.T. Letter of Welcome, Fogarty International Center. http://www.nih.gov/fic/about/welcome.html(6/22/00)

[4] See Kass, N., A. Hyder, L. Dawson, and N. Teoh. 2000. "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations." This background paper was prepared for NBAC and is available in Volume II of this report.

[5] See Kass, N., A. Hyder, L. Dawson, and N. Teoh. 2000. "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations." This background paper was prepared for NBAC and is available in Volume II of this report

[6] From data collected for Kass, N., A. Hyder, L. Dawson, and N. Teoh. 2000. "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations." Question J9, p. 32.

[7] From data collected for Kass, N., A. Hyder, L. Dawson, and N. Teoh. 2000. "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations." Question J9, p. 30.

[8] From data collected for Kass, N., A. Hyder, L. Dawson, and N. Teoh. 2000. "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations." Question J9, p. 31.

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

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[14] http://www.grants.nih.gov/grants/oprr/humansubjects/assurance/icpa-nci.htm (6/26/00)

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[16] From data collected for Kass, N., A. Hyder, L. Dawson, and N. Teoh. 2000. "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations." Question J9, p. 31.
[17] Plowe, C. Testimony before NBAC. February 29, 2000. Herndon, VA. Meeting transcript, 113-119.
[18] From data collected for Kass, N., A. Hyder, L. Dawson, and N. Teoh. 2000. "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations." Question J9, p. 31.
[19] From data collected for Kass, N., A. Hyder, L. Dawson, and N. Teoh. 2000. "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations." Question J8.
[20] The other 16 agencies and departments which are signatories to the Common Rule must accept these approved assurances.
[21] E. Greg Koski, Ph.D, Director, Office for Human Research Protections. Testimony before NBAC, September 13, 2000. Washington DC. Meeting Transcript
[22] This includes the Multiple Project Assurance (MPA), Cooperative Project Assurance (CPA), Single Project Assurance (SPA), Inter-Institutional Amendment (IIA), Cooperative Agreement (CA), Agreement for an Independent Investigator (AII), and Non-Institutional Investigator Agreement (NIA).
[23] From data collected for Kass, N., A. Hyder, L. Dawson, and N. Teoh. 2000. "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations." Question J8.
[24] See Kass, N., A. Hyder, L. Dawson, and N. Teoh. 2000. "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations." This background paper was prepared for NBAC and is available in Volume II of this report.
[25] See Marshall, P., 2000, "The Relevance of Culture for Informed Consent in U.S. Funded International Health Research." p. 31. This background paper was prepared for NBAC and is available in Volume II of this report.
[26] See Marshall, P., 2000, "The Relevance of Culture for Informed Consent in U.S. Funded International Health Research." p. 32. This background paper was prepared for NBAC and is available in Volume II of this report.
[27] From data collected for Kass, N., A. Hyder, L. Dawson, and N. Teoh. 2000. "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations." Question J8
[28] Pape, J.P. Testimony before NBAC. February 29, 2000. Herndon, VA. Meeting transcript, 33.
[29] Pape, J.P. Testimony before NBAC. February 29, 2000. Herndon, VA. Meeting transcript, 35.
[30] See Kass, N., A. Hyder, L. Dawson, and N. Teoh. 2000. "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations." Part E, p. 6. This background paper was prepared for NBAC and is available in Volume II of this report
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[40] Loue, S. Testimony before NBAC. October 16, 1999. Washington, D.C. Meeting transcript, 38