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CHAPTER 3
VOLUNTARY, INFORMED CONSENT[1]

INTRODUCTION [1]

The requirement to obtain voluntary, informed consent from human participants before they are enrolled in research is fundamental in research ethics. This requirement is reflected in all published national and international codes, regulations, or guidelines pertaining to research ethics, including those in many developing countries such as Uganda, India, and Thailand (See also Appendix 3.1). It also appears in a major international human rights instrument, the International Covenant on Civil and Political Rights, to which the United States is a party. Article 7 of this covenant provides that "no one shall be subjected without his free consent to medical or scientific experimentation" (United Nations 1966).

The requirement for freely granted and informed consent to participate in research reflects one or more substantive ethical principles, such as respect for persons, human dignity, or autonomy. However, it is possible to respect persons and their dignity or autonomy and to affirm the requirement to obtain voluntary, informed consent, while at the same time allowing for modifications in the particular procedures for obtaining consent, such as those stipulated in the U.S. policy for the protection of human subjects in research (45 CFR 46.117c). In this chapter we thus distinguish the ethical standard or requirement of voluntary informed consent from its underlying principle(s) and distinguish both from the various procedures that have evolved to realize them. The underlying ethical principles generate the informed consent requirement or standards, and the various procedures employed are methodologies for meeting the standard and sustaining our commitment to the underlying ethical principles.

Despite the ethical centrality of voluntary, informed consent and its underlying principle(s), problems of interpretation and application exist for researchers, review committees, and others. Many of these problems are common to countries with a great deal of experience in biomedical research—usually developed countries—and developing countries who usually have less experience in conducting or collaborating in biomedical research. However, some problems in the process and documentation of informed consent in international collaborative research appear especially difficult to resolve in cases where the nations involved do not share common

cultural values, attitudes, and ethical commitments. For U.S. sponsors of international research it is important, therefore, to address prominent issues that have been identified concerning the application of U.S. research regulations for informed consent in settings where culture and custom are different from those that provide the basis for U.S. regulations.

The main questions that this chapter addresses are:

1) If cultural factors create a barrier to complying with the substantive ethical standard of informed consent, is it permissible to depart from that standard if the research could not otherwise be carried out?

2) How can investigators obtain informed consent in settings where potential research subjects have a belief system that lack the concepts and explanatory features of modern medical science and technology?

3) How can voluntary participation be ensured in settings where community leaders may exert pressure on the entire community to enroll in a proposed clinical trial?

4) If cultural differences between the United States and other countries make it difficult or impossible to adhere to U.S. federal regulations that stipulate particular procedures for obtaining informed consent from individual participants, how should this problem be handled?

5) In what ways should the United States modify its informed consent regulations to adapt to various cultural circumstances in other countries without compromising the substantive ethical standard of informed consent?

In responding to these questions, we remain convinced that U.S. sponsors of research abroad should adhere to internationally agreed-upon ethical standards of voluntary, informed consent in conducting research even in the face of cultural diversity. It should be possible to remain sensitive to cultural differences without departing from these standards. Nevertheless, we need to acknowledge that disagreement still exists about this claim. For example, one commentator has argued that "[i]t is 'ethical imperialism' at its worst to assume that the informed consent requirement, which does indeed serve one (only one) moral principle in the Western setting, is in itself such a universal ethical standard" (Newton 1990, 11). This same commentator contends that growing doubt surrounds the value of individualism and individual rights, so "the investigator might better stick to the research and accept the local assessment as to adequate protection of individual rights" (Newton 1990, 11).

Exactly the opposite position is stated by two other scholars: "Appeals to cultural sensitivity...are no substitute for careful moral analysis. We see no convincing arguments for a general policy of dispensing with, or substantially modifying, the researcher's obligation to obtain first-person consent in biomedical research conducted in Africa." Ijsselmuiden and Faden add that defenders of such a policy "have relied on limited and often dated anthropologic literature that does not reflect the rapid cultural changes brought about by colonialism and independence, warfare, and urbanization" (Ijsselmuiden and Faden 1992, 833). We are persuaded by this latter view, which supports the application of the substantive ethical principles and standards embodied in the U.S. as well as international research regulations regarding informed consent of research participants wherever research governed by U.S. regulations is carried out in other countries.

The recommendations developed in this chapter generally focus on the three traditional elements of informed consent (Faden and Beauchamp 1986): 1) disclosing information to potential research participants (see Exhibit 3.1); 2) ascertaining their understanding of what has been disclosed; and 3) ensuring their voluntariness in agreeing to participate in research.[2] Obtaining adequately informed, fully voluntary consent from individual research participants is a necessary requirement in preventing exploitation. There should be no disagreement that using human beings as means to the ends of others, without their knowing and freely granted permission, constitutes exploitation and therefore is unethical.

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

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

(1) a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
(2) a description of any reasonably foreseeable risks or discomforts to the subject;
(3) a description of any benefits to the subject or to others which may reasonably be expected from the research;
(4) a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
(5) a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) for research involving more than minimal risk [as defined in 45 CFR 46.102(i) (1999)], an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
(7) an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
(8) a statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled (45 CFR 46.116(a) (1999)).

In addition to the basic information listed above, the U.S. regulations require that participants be given other information that may affect their participation in research, depending on the nature of the project itself. The U.S. regulations list six such additional disclosures (45 CFR 46.116(b)).

THE ETHICAL STANDARD OF INFORMED CONSENT [1]

During its deliberations, the Commission reviewed the various definitions of informed consent used in the U.S. Code of Federal Regulations (45 CFR 46 (1999)), the World Medical Association's *Declaration of Helsinki* (WMA 1964, as amended 1996), CIOMS (CIOMS 1993), and the International Conference on Harmonization Harmonized Tripartite Guideline, Guideline for Good Clinical Practice (ICH 1996). We adopted the following definitions as the clearest and most appropriate for the purposes of this report.

Informed Consent: A process by which an individual voluntarily expresses his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to his or her decision to participate. This definition is adopted from the International Conference on Harmonization, Harmonized Tripartite Guideline, Guideline for Good Clinical Practice, GCP Guideline 1.28 (ICH 1996). An important feature of this definition is that it focuses on the *process* of obtaining consent rather than on the *documentation* of that process, for example, in a written, signed, and dated consent form.

In an ethically sound consent process, a member of the research team provides information to the potential subject, ascertains that the subject understands the information provided, and the subject voluntarily agrees to participate. In the documentation of the process of informed consent it is essential that the potential participant signs or otherwise indicates his or

her agreement to participate. In many settings it is also required that the person obtaining the consent signs the consent form or other related documents, and a witness (or person designated by the participant) attests to the process. It is always essential to make a distinction between the consent *document* and the consent *process* and not allow the document itself to constitute the informed consent process.

Substantive Standard of Informed Consent: This phrase refers to the requirement to obtain voluntary, informed consent and reflects the principle that competent individuals are entitled to choose freely whether to participate in research. This definition was adopted from the CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Guideline 1, Commentary, para. 2, p. 13 (CIOMS 1993). Broadly speaking, voluntary, informed consent protects the individual's freedom of choice, respects the individual's personhood, dignity, or autonomy, and reduces the chances of exploitation.

Objections to this substantive ethical standard are rarely, if ever, voiced even in parts of the world where the culture places less emphasis on individual rights and freedom of choice than is common in Western and most industrialized countries. In sharp contrast, however, various objections often arise about the necessity of certain procedures for obtaining and documenting informed consent; for example those stipulated in U.S. research regulations and other documents, such as the ICH Harmonized Tripartite Guideline for Good Clinical Practice.

As already noted, it is important to distinguish *substantive ethical principles and standards,* from the procedures that implement them. Although procedures are important, they can often be modified without compromising ethical principles or standards. Examples of procedural aspects of the informed consent process and its documentation include requirements that the informed consent documents be in writing and signed by the research participant; that the consent form be signed by the person obtaining consent or by the principal investigator; and that there be a witness to the signing of consent forms. Other examples of procedures that are not always central to meeting the substantive ethical principles and standards of voluntary informed consent are the involvement of family members in the consent process or obtaining a community leader's permission before approaching individuals in the community. Although it is necessary—and not always easy—to determine which procedural aspects are ethically required and which might be altered or waived altogether, procedural requirements should be viewed as less fundamental than matters of substantive ethical standards or principles.

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

CULTURAL BARRIERS RELATING TO DISCLOSURE REQUIREMENTS [1]

Requirements for disclosure of information in the context of research usually exceed the requirements for disclosure in therapeutic contexts. In the United States, the requirements for disclosure of information to potential participants in research are quite specific and detailed, as is evident from the elements listed in Exhibit 3.1. Among different nations, major social and cultural variations exist regarding the appropriate disclosure of medical information to patients in therapeutic contexts. These different views regarding disclosure in the clinical context will inevitably affect judgments about the amount and kind of information that should be disclosed in the research context. Below three principal types of disclosure are discussed: 1) disclosure of diagnosis and risk; 2) disclosure of the use of placebos and randomization; and 3) disclosure of alternative treatments. In addition, we consider a fourth type of disclosure—the disclosure of any post-trial benefits, since this issue becomes central in Chapter 4.

Disclosure of Diagnosis and Risk [2]

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

Kass and Dawson describe a similar situation in their report to NBAC: "...in some developing country settings, a diagnosis of cancer would never be revealed directly to the patient but rather to members of the patient's family."[5] Although this observation appears to be related only to clinical care, and not research, in fact, the conversations cited in these reports occurred in the context of discussion about their research participation. Similarly, different cultures have quite different attitudes toward the disclosure of risks in the *clinical context*, and some hold that it is not always appropriate to disclose to patients the full reality of their situation. For example, Nigerian researchers indicated to one of our consultants that consent documents attached to certain research protocols included information that potential participants might not only find extraneous, irrelevant or culturally inappropriate, but unduly alarming. These researchers called particular attention to the emphasis placed on explaining the potential risks to study participants, noting that in the United States there is much greater interest in communicating the possibility of harm to research participants than in their own country. One physician noted that, given Nigerian cultural norms, that disclosing all possible risks would unnecessarily alarm potential research participants associated with the research.[6] Based on such observations, some people believe that, at least in some cultures, it would be impossible to enroll research participants by adhering to the basic elements of disclosure as presented in 45 CFR 46.116(a).

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

Diversity in the practices of disclosing information in the clinical context does not alter the requirements for certain disclosures in the research context.

On the other hand, there certainly are good reasons for continuing to study these matters in more detail with an aim to learning about how cultural variations affect the meaning and effectiveness of the consent process and the use of particular consent documents. In our view, it is critical to find innovative and culturally responsive ways to disclose information to potential participants. Furthermore, we heard testimony from both U.S. and developing country researchers who have succeeded in adhering to this standard,[7] even though doing so often takes more time and effort than researchers typically expend in the informed consent process. Even in cultures in which a diagnosis of serious illness is not normally revealed in the treatment context, researchers can often find ways to overcome this barrier to disclosure in the research setting.

Disclosure About Placebos and Randomization [2]

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

Disclosure of Alternative Therapies [2]

Love and Fost (1997) describe a struggle in one U.S. IRB that reviewed a proposal for a randomized clinical trial of adjuvant treatment for breast cancer to be conducted in Vietnam. The investigator "found himself uncertain about the application of American standards of informed consent in the Vietnamese setting" (Love and Fost 1997, 424). After consultation with Vietnamese and cultural experts, he concluded, "American standards would not be acceptable to Vietnamese physicians, political leaders in Vietnam, or the vast majority of Vietnamese patients" (Love and Fost, 1997, 424). One key reason for this unacceptability is a particular characteristic of medical practice in Vietnam, in which patients do not participate in their medical decisions and look to their physicians to tell them the appropriate treatment. As a result, the researcher contended that it was necessary to withhold from potential subjects any information that would convey the treating doctor's uncertainty, specifically, information about alternative therapies and the use of randomization to determine the subject's proposed treatment (Love and Fost 1997, 425)."

Again, we do not find that these cultural differences are adequate to forego the requirement to make disclosures about alternative therapies available to potential participants were they to choose not to enter a clinical trial.

Disclosure About Possible Post-Trial Benefits [2]

The basic disclosure requirements for satisfying the informed consent provisions in U.S. research regulations (see Exhibit 3.1) focus on information a potential participant needs to understand in order to decide whether to participate in a study. Of the eight basic requirements, one focuses on potential benefits: "a description of any benefits to the subject or to others which may reasonably be expected from the research" (45 CFR 46.116(a)(1)). Traditionally, such a disclosure has been required to ensure that potential participants understand whether there is any possibility that the intervention itself might benefit them while they are enrolled in the study itself. There is, however, no specific mention of any post-trial benefits. As noted in Chapter 1, and discussed more specifically in Chapter 4, access to health care services can be an important element in assessing whether all appropriate ethical obligations to research participants have

been met, including possible post-trial benefits to participants. In any case, potential participants should be informed of the potential benefits, if any, that they may be entitled to prior to deciding on their participation. Since this information must be disclosed as part of the consent process, and would be listed in a consent form, IRBs should require investigators to make these disclosures.

In summary, we have concluded that cultural differences do not justify withholding of information from potential research participants regarding disclosure of diagnosis and risk, placebos and randomization, alternative therapies, or possible post-trial benefits.

Recommendation 3.2: Researchers should develop culturally appropriate ways to disclose information that is necessary for adherence to the substantive ethical standard of informed consent, with particular attention to disclosures relating to diagnosis and risk, placebos and randomization, alternative therapies, and post-trial benefits. Researchers should describe in the protocol and justify to the IRB the procedures they plan to use for disclosing such information to participants.

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

Recommendation 3.4: NIH, CDC, and other U.S. departments and agencies should support research that specifically addresses the informed consent process in various cultural settings. In addition, those U.S. departments and agencies that conduct international research should sponsor workshops and conferences where international researchers can share their knowledge of the informed consent process in these settings.

OTHER CULTURAL BARRIERS RELATING TO INFORMED CONSENT PROCESS [1]

There are additional barriers to the informed consent process more generally that can arise in a different cultural setting. These include the ability of potential participants to understand the scientific and technical aspects of research protocols given the culture and belief system within which they live, and the influence and involvement of others in the consent process.

Understanding the Information Provided in the Consent Process [2]

In some cultures, potential research subjects have a belief system that lacks the concepts and explanatory features of modern medical science and technology. A daunting challenge to the possibility of obtaining informed consent arises when people do not understand or accept scientific explanations of health and disease.[9] Marshall's report quotes one physician: "...what I worry about is whether we are really informing them. We are talking to a society that does not believe in the germ theory of disease so it's difficult to explain." The researcher went on to give an example of the widely pervasive belief system than a person's death is a result of sorcery rather than a lethal infection.[10] In noting that he had encountered a cultural belief that spirits cause epilepsy, Alfred Sommer, Dean of the Johns Hopkins School of Hygiene and Public Health, told NBAC "we do not want to fight a belief system. We simply say we have this pill. We believe it is safe. We think it may reduce the recurrence of the following thing. We would like you to take it."[11]

Despite such potential barriers to adequate understanding, researchers are often be able to devise creative measures to overcome these barriers if they are willing to devote the time and effort to do so. An example appears in the report by Kass and Hyder: "...the concept of immunology, an immune response, that there's something in your blood that's going to attack bacteria and viruses which you also don't have a concept for....[H]ow much can someone really focus on the consent form when they have this whole new idea that there's this battle going on in their bloodstream?...When we go and translate, we try to use, for example immune cells, we talk about people who guard houses...it's a particular kind of watchman. So you have a particular kind of watchman in your blood...."[12]

A number of studies bear out this point. For example, even in countries with very low literacy rates (e.g., 30 percent for men and 10 percent for women in Senegal) one group found that "widespread illiteracy is not a barrier to comprehension, especially since informed consent is more an interactive process than one that depends on reading" (Preziosi, Yam, Ndiaye, et. al. 1997). However, the authors of this study did conclude that understanding abstract scientific concepts, such as double-blinding and randomization, can be difficult (Preziosi, Yam, Ndiaye, et. al. 1997). To help explain these complex issues, researchers turned to explanations that were understandable to the community involved: "To illustrate the principle of randomization and the possibility that one of the vaccines might fail, the presenters used a familiar agricultural example: the evaluation of fertilizers or of seed varieties on randomized plots, a procedure familiar to farmers in the area" (Preziosi, Yam, Ndiaye, et al. 1997).

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

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

Translation and back translation of a written consent form are not always an adequate mechanism to ensure that it conveys appropriate information. Jean Pape, a researcher from Haiti who is also on the Cornell University faculty, described the complexity of this process.[14] His research group is ready to begin HIV vaccine trials in Haiti. They need approval from their own IRB in Haiti, as well as from the IRB at Vanderbilt University, one of the collaborators, and by the IRB at Cornell University Medical School. To be understandable to participants, the consent form had to be in Creole. Yet the document also had to be in French, the language of the Haitian researchers. Because the consent form had to be reviewed by the Cornell IRB, a translation in English was also required. Pape said that the back translation of a consent form "does not guarantee that volunteers have really understood the objective of the study, the risks and advantages, and their voluntary participation,"[15] a difficulty reported in another study in Nigeria.[16]

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

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

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

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

Involvement of Others in the Informed Consent Process [2]

Several possible barriers exist to the individual choice by potential participants in research. Among those barriers identified by Kass and Hyder,[19] who administered questionnaires and conducted focus groups with non-U.S. researchers, were the following: deference to physician/health personnel; low economic status of potential subjects; low level of awareness or education; limited decision-making power for women; community leaders' disapproval; family disapproval; and cultural customs that prohibit "refusing a guest" (rules of traditional hospitality). We discuss a subset of these barriers in this section—those pertaining to the involvement of community leaders and family members in the consent process.

Community Leaders [3]

In some cultures, investigators need to obtain permission from a community leader or village council before approaching potential research subjects. Yet it is important to distinguish permission to enter a community for the purpose of conducting research from individual informed consent. Reports by NBAC consultants all noted the role of community leaders or elders as an integral part of the process of recruiting subjects. Although their reports typically use

the terminology of "consent" to refer to the community's permission or a leader's authorization for the researchers to approach individual subjects, we reserve the term 'consent' to refer to the permission or authorization given by the individual being recruited as a research participant.

The need to obtain permission from a community leader (who is sometimes a village chief) before approaching individuals need not compromise the ethical standard requiring the individual's voluntary informed consent to participate in research. Gaining permission from a community leader is no different, in many circumstances, from the common requirement in this country of obtaining permission from a school principal before involving pupils in research, from a nursing home director before approaching individual residents, or from a workplace supervisor before initiating a research screening program. An ethical problem arises only when the community leader exerts pressure on the community in a way that compromises the voluntariness of individual consent. NBAC consultant reports describe both types of situation (see Exhibit 3.2). (These reports are available in their entirety in Volume II of this report.)

Exhibit 3.2: Involvement of Community Leaders in Informed Consent

- There are very positive informed consent stories where you would never go first to the individual. You can approach the individual after you have explained the research to the chief or local leader. Then they explain the informed consent process to their people without exerting the pressure. The best evidence of the effectiveness of this approach is when people refuse to participate. "That's a good sign. They are able to refuse."[20]

- In contrast, in some settings, the head of the village, or a group of elders makes a collective decision for the village. If they make the decision in favor of participating in the trial, virtually everyone will participate. The people in the community people are then extremely reluctant to withdraw from the trial because of the collective nature of community activities.[21]

- In other settings there can be found authorization by a community leader that is compatible with individuals' right to refuse and authorization in a context in which the chief's word is law. One physician described "two levels" of consent or permission: "One is community and the other is individual....When you leave (the Chief), the Chief is expected to open households so there is really another level of consent (in between)...the Chief and council, the household head, then the individual."[22] In answer to the question, "then how will the community respond?" the physician said that most of the time the members agree to participate. "You are likely to get approval." At the same time, there is

some uncertainty on the part of the physicians interviewed about the extent to which individual agreement to participate is voluntary.[23]

- "Regarding whether the community leaders should be asked to approve the study depends on 1) whether you are working in a healthy community, and 2) on the level of corruption of the community leaders. I have been conducting a study in [a] Nigerian city since 1987. There, we have 'laid low', trying to avoid the gaze of the community leaders and state or national politics. Had we been noticed there, the tremendous corruption would have destroyed the study. However, working in a Nigerian village would be an entirely different matter. In that situation, a study could not be conducted without the approval and active support of the community leaders."[24]

- An American researcher conducting malaria studies in Mali and in Malawi noted the difference between the two settings. In Mali the study was conducted in a remote rural area, in which community leaders were heavily involved. In contrast, the Malawi study took place in a large city with an established health care system and a better educated population. In this latter setting, "community consent" at the national or institutional level is very removed from individuals and the local community, and it seems likely that consent by community leaders would not have an undue impact on the decisions of individuals. In addition, in an urban context, it is more difficult to identify appropriate spokespersons for the larger community, especially as individuals in urban areas tend to associate themselves with many different kinds of communities.[25]

Nevertheless, recruitment procedures in some cultures involve community leaders or tribal chiefs whose authority does not allow individual members of the community to refuse to participate in research for which the leader has granted permission. Further, in some settings, it is not a local community leader or village chief, but the central government that mandates the participation of individuals in research.[26]

The question then arises whether there are some countries in which U.S. researchers ought not engage in international collaborative research. In our view, if the political system in a country, or the local situation, makes it truly impossible for individuals' consent to be voluntary, and that fact is known in advance, then it would be inappropriate for U.S. researchers to choose such settings because they could not adhere to the substantive ethical standard of informed consent.

Recommendation 3.8: When culture or custom requires permission of a community leader before researchers may approach individual subjects, researchers should be

unwilling. The Ugandan group did not view the concept of autonomy as entirely alien to their culture when applied to the research context. It thus seems possible, in some cases, to respect the autonomy of the individual and at the same time respect the cultural practice of involving the family. Uganda also provides a good example of recent political changes that have affected informed consent in the research context (see Exhibit 3.3).

Exhibit 3.3: New Uganda Guidelines for Informed Consent

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

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

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

SOURCE: S. Loue. Testimony before NBAC. October 21, 1999. Washington, D.C. Meeting transcript.

Researchers in other countries also have reported on their efforts to involve the family in ways that do not undermine the standard of individual consent. Marshall reported for example,

sensitive to such local requirements. However, in no case may permission from a community leader or council replace the requirement of individual voluntary informed consent.

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

Family Members [3]

In some cultures it is customary, though not required, for other members of a potential subject's family to be involved in the informed consent process. In most instances the need to involve the family is not intended as a substitute for individual consent but rather, as an additional step in the process.[27]

An example of a multi-step process involving the family is described by Loue and colleagues (1996) in their report on a workshop in Uganda that addressed the problem of acquiescence by another family member in order for an individual to participate in research. Family members must be consulted before individual subjects can be enrolled. The situation in Uganda is further complicated by the simultaneous existence of customary or traditional practices, as noted above, and modern civil law. The modern law states that an 18-year-old male living at home has the legal right to make his own decision, but customary law dictates that the son must first obtain his father's permission. Ugandan women are even further restricted by the need to obtain their partner's permission before they can agree to serve as research participants.

Participants in the Ugandan workshop arrived at a compromise solution between the conflicting demands of customary law and the standard of informed consent in research. The group recommended a 48-hour waiting period between the time researchers solicit potential subjects' participation and the time subjects sign a consent form. During that period, potential subjects may confer with family members, if they wish, before deciding finally whether to participate. A family member could ask the researcher questions about the research that might arise in the course of a family discussion. The workshop group agreed, however, that another family member could not volunteer an individual as a research subject if that person was

involvement of family or community members. Involving others ranges from providing written information sheets for potential participants to take home and discuss with their spouse to community meetings to present information about the research and obtain community consensus. When the potential subject wishes to involve family members in the consent discussion, the researcher should take appropriate steps to that end.

Consent by Women [3]

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

Much research is directed at conditions that affect both women and men. Yet it is important not to neglect research that affects only women. In reality, without involving the husband in the consent procedures, it may be impossible to conduct some research on common, serious health problems that affect only women. In such cases, the likely consequence would be the denial of subsequent health benefits to all women in that country. The prospect of denying such a substantial benefit to all women in a particular culture or country calls for a narrow exception to the recommendation 3.11 presented below that researchers should use the same procedures in the consent process for women and men. This exception involves obtaining the permission of a husband in addition to the woman's own consent. In order to justify such an exception, researchers must provide evidence that 1) it would be impossible to conduct the research without obtaining permission of women's husbands, in addition to their own consent; 2)

that in Nigeria cultural norms require the permission of a woman's husband before she may enroll in research. A Nigerian physician involved in a breast cancer study noted that cancer patients often need the approval of the husband to participate in research. However, the physician also emphasized that in such cases the woman's individual consent is still essential. Indeed, most investigators have developed strategies that accommodate and encourage discussion regarding study participation with family members.[28]

Recommendation 3.10: When a potential research participant wishes to involve family members in the consent process, the researcher should take appropriate steps to accommodate this wish. In no case, however, may a family member's permission replace the requirement of individual informed consent.

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

The practice of bypassing the individual, as often happens in the case of women or elderly persons,[29] quite clearly departs from the ethical principle, as stated in the CIOMS guidelines, that "competent individuals are entitled to choose freely whether to participate in research" (CIOMS 1993). However, potential subjects may also choose to involve others, such as family members, in the consent process. Involving family or community members in the informed consent process need not diminish, and might even enhance, the individual's ability to make his or her own choices and to give informed consent (or refusal). Empirical studies provide examples of family and/or community involvement in the informed consent process. In the Gambia, for example, many parents sought the advice of health workers, friends and family, and traditional or religious leaders before enrolling their children in research. However in all cases one of the child's parents made the final decision (Leach, Hilton, Greenwood, et al. 1999). Interestingly, in the Gambia, traditional or religious leaders were involved in making the decision in only one percent of cases (Leach, Hilton, Greenwood, et al. 1999).

These examples show that it is often possible to obtain individual informed consent while at the same time preserving cultural norms, which may require and/or benefit from the

failure to conduct this research would deny its potential benefits to women in the country; and 3) measures to respect the women's autonomy to consent to research are undertaken to the extent possible.

Recommendation 3.11: Researchers should use the same procedures in the informed consent process for both women and men.

INDUCEMENT TO PARTICIPATE IN RESEARCH [1]

A fundamental principle of research ethics is the requirement that participation be voluntary, that is, "free of coercion and undue influence" (National Commission 1979). However, among the most difficult requirements to ensure is the voluntariness with which participants consent to enroll in a study. Pressure from a community leader, the power and authority of the medical professionals who serve as investigators, and the fear of loss of health benefits to which people are otherwise entitled may compromise individuals' freedom to refuse to participate in research. The provision of medical care and treatment during a study may constitute an incentive for individuals to enroll in a study, but it should not be construed as a coercive offer that would unduly compromise the voluntariness of participation.

It is generally easier to determine when coercion is present than it is to specify when a study design constitutes an undue inducement or influence. One definition states that "undue influence...occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance" (National Commission 1979, 6). Discussions of undue inducements have traditionally focused on monetary payments to research subjects, and address the question of whether any amount of money is an acceptable inducement and, if so, at what point the acceptable inducement becomes "undue" (Dickert and Grady 1999; Macklin 1981; 1982).

Other aspects of research design that may pose a problem of undue influence have received considerably less attention. As the CIOMS *Guidelines* acknowledge: "It may be difficult to distinguish between suitable recompense and undue influence to participate in research...Someone without access to medical care may be unduly influenced to participate in research simply to receive such care" (CIOMS 1993). This situation is likely in many developing

countries, where a large number of people have little or no access to medical care and treatment even for ordinary illnesses, a concern expressed to NBAC in testimony.[30]

It is necessary, then, to decide the answer to a threshold question: Can the very offer to participate in research constitute an undue inducement to people in resource-poor countries who have little or no access to medical care and treatment? (Bernstein 1999). Even a placebo-controlled trial offers such individuals a 50 percent likelihood (in a two arm trial) of receiving an intervention that, although unproven, may be beneficial. If the solution to this fundamental problem is to forgo biomedical research entirely in such places, it might make those populations worse off than they would be if research goes forward. This consideration requires us to review the ethical consequences of *not* conducting research and to determine whether those consequences outweigh the ethical problems alleged to exist in conducting the research. But we can avoid having to attempt such balancing if we can distinguish properly between inducements that are acceptable and those that constitute undue influence.

No hard and fast criterion can be stipulated for making this distinction. However, one approach is to consider possible determinants of the motivation to participate in research, in general, according to the following rough schema. People may, for example

(a) act out of egoistic self-interest, where there is a potential benefit to them.

(b) act out of rational or enlightened self-interest, where there is potential benefit to others as well as to themselves, and some risk to themselves.

(c) act out of pure altruism, where they expect no benefit to themselves but expect benefit to others, and accept some risk to themselves.

(d) refuse to act because of perceived high risk or great inconvenience, only agreeing to undergo the risk when offered considerable material reward;

(e) act because of fear or threat of worse consequences from failing to act in a certain way than from agreeing to do so.

All of these situations apply to some extent to the context of research. Situation (b) is the standard presupposition in clinical research. Prospective subjects weigh the risks and benefits, recognizing that there may be some risk to themselves but also some possible benefit, and that the research as a whole may provide benefits to others. Situation (c) is the standard one for research not designed to provide direct benefit to subjects, but, for example, to determine the safety of drugs in Phase I studies, to discover basic physiological mechanisms, or to arrive at

baseline data. Situation (d) captures the idea of "undue inducement" where people make a rational refusal based on perceived risk but then only agree to take the risk when provided with a considerable material reward. Situation (e) is the paradigm of coercion: in hierarchical groups, in coercive settings, or under threat, individuals agree to participate in research because they fear the consequence of refusal. In this situation, their participation is coerced, not voluntary. Situation (e) therefore, is ethically prohibited.

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

It might be objected that this definition is embedded in a document created in the United States, a wealthy, industrialized country, and therefore is irrelevant to resource-poor countries. The reply to this objection is twofold.

First, poor people exist in every country, and participation in a clinical trial is often the only way that uninsured individuals in the United States have access to some medical care. Yet no one could reasonably maintain that the poor or uninsured should be excluded from participation in research, or that it would be ethically acceptable to deny to them medical benefits in a study that they could not otherwise obtain outside the trial.

Second, the problem does not lie in the definition of "undue inducement," but rather, in the difficulty of determining just when an offer—admittedly an inducement—becomes *undue*. Those who argue that participation in research does constitute an undue inducement for poor people in developing countries would have to maintain that offering high quality medical care and treatment the participants would not otherwise receive is unwarranted and inappropriate. However, as we have argued, the provision of medical care or treatment that would not otherwise

be available to research subjects should not, in principle, be construed as an undue influence to participate. This conclusion is supported by developing country researchers surveyed in one of the projects commissioned by NBAC.[31] We conclude that the potential benefits of participation in research may be an inducement for people in developing countries who lack access to medical care; nevertheless, it does not sufficiently diminish their voluntariness so as to make their consent ethically invalid.

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

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

As in any ethical dilemma, this one requires a weighing of moral considerations in order to determine which alternative is more acceptable. An appeal to certain ethical principles offers some insight. Since the well accepted principle of nonmaleficence (National Commission 1979; Beauchamp and Childress 1994) requires that harm to subjects be minimized,[32] this principle refers to a circumstance in which voluntariness may be somewhat diminished. However, the principle of nonmaleficence[33] could never be used to justify coercion of research subjects, which would entirely preclude their voluntary participation. We conclude that in this situation it is more acceptable to allow the possibility of somewhat diminished voluntariness of participation than to run the risk of harm to participants in the control arm who are denied an established, effective treatment for their disease, a position consistent with other guidelines, including those of the Medical Research Council in the United Kingdom (Medical Research Council 1999).

The Therapeutic Misconception: Some Misconceptions [2]

One barrier to understanding the relevant, important aspects of any proposed research is what has been called the "therapeutic misconception" (Appelbaum, Roth, and Lidz 1982; Churchill, Collins, King, et al. 1998; King 1995). This phrase refers to the belief that the purpose of a clinical trial is to benefit the individual patient rather than to gather data for the purpose of making a contribution to scientific knowledge. The trust patients have in their physicians in the clinical setting relies on an important feature of the physician-patient relationship—physicians should choose the most appropriate treatment for the individual patient. To apply that same concept to the research setting is to fall prey to the therapeutic misconception, which surfaces even where subjects have received complete information (ACHRE 1996, Ch. 16). In short, this misconception rests on a confusion between the aims of research and the aims of individualized medical treatment of patients.

The therapeutic misconception is widespread in all cultures and parts of the world, developed as well as developing. It is evident in empirical studies from a wide range of countries, including the United States, Brazil, Chile, Sweden, the Netherlands, and the United Kingdom. For example, in a study conducted in a clinic in Brazil, all of the women who were interviewed said that they entered the study because they "thought that the contraceptive being offered would be good for them" (Hardy, Osis, Bento et al. 1998).

International collaborative research requires adherence to internationally accepted standards, one of which is disclosure of all relevant information necessary for volunteers to make a reasoned decision whether to participate, even if patients do not receive similar disclosures in the clinical practice of medicine. The examples cited earlier in this chapter—disclosures about diagnosis, and disclosures about placebos and randomization—rest on customary medical practice in countries or communities where research was being proposed. But even if it would be inappropriate to force a non-customary process on physicians in the practice of clinical medicine in their own country, research is not medical practice. To withhold relevant information from potential research subjects who are unfamiliar with the research enterprise is to actively promote the therapeutic misconception and thereby fail to enable the participants to understand the distinction between clinical practice and research.

A different sort of complication arises from the language itself in some parts of the world.

One American respondent to the study conducted by Kass and Dawson stated the following: "In many African languages, there is no word for 'research' or 'science.' The word used is generally the same as the word for 'medicine.' There is no concept of an experiment, placebos, etc., and despite the best translation of the most simply worded consent form, many adult subjects still have no understanding of the difference between being a research subject and receiving medical treatment." The researcher went on to say: "This should not be a reason to exclude these people from research; in fact they are often the population who will benefit most from the research and the only population in whom the studies can be done, e.g., persons at risk of naturally acquired malaria or other tropical diseases."[34]

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

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

DOCUMENTATION OF INFORMED CONSENT [1]

The distinction between the process of obtaining informed consent and the consent form that documents this process is a critical one. Working outside the U.S. requirements for documentation of informed consent (45 CFR 46.117 (1999)) can often pose a barrier to research that otherwise conforms to the substantive ethical standard for informed consent. Problems arise,

for example, from the need for written, signed consent forms and from the amount of information typically provided on U.S. consent forms for a complex biomedical study. In some developing countries, the requirement that informed consent be documented on a written form signed by the research subjects is thought to be inappropriate. One obvious circumstance is that of illiterate subjects, who may be able to understand information presented orally but who find a written form on which they are required to make their mark totally useless. Moreover, in some cultures people distrust any "signing process." This distrust is common even in countries with a high literacy rate, such as Argentina and other Latin American countries, where people have lived under oppressive regimes and fear that signing a document could put them in jeopardy. NBAC heard several examples that illustrated both of these situations, some of which are provided in Exhibit 3.4.

Exhibit 3.4: Examples of Documentation of Informed Consent Requirements

Sugarman and colleagues provided two examples in which requiring a signed informed consent document was especially problematic: "...in one project involving many illiterate subjects, although thumbprints might be considered to be an appropriate means of documenting individual informed consent, local investigators did not use such an approach because it too closely related to past police tactics and were believed to frighten potential research participants. In another setting, where guerilla warfare was ongoing, the use of written informed consent posed a risk to participants because these documents linked them to particular institutions."[35]

The Ugandan *Guidelines for the Conduct of Health Research Involving Human Subjects* reject a requirement for written informed consent. This stems from Uganda's past experience of torture and persecution of individuals found to be associated with particular enterprises, and recognizes the sensitivity to individuals' reluctance to sign a piece of paper that attaches their name to an enterprise. Individuals who do not wish to sign may put an "X" in place of a signature.[36] This is a good example of how procedural requirements can be made sufficiently flexible to reflect social and cultural sensitivities.

Jean Pape, a Haitian researcher, discussed the complexity of the consent forms. He said the forms are clearly too lengthy, and over the past 22 years he has found them to be more and more complicated, stating "They appear to be more concerned about legal implications for sponsor agencies than concern with the welfare of the volunteers. We cannot read them to volunteers because the only time a volunteer had a document like this read to him was when he was in a court of law and had to sign some kind of papers. So this is changing the trust relationship that we have with our participants and, therefore, we have to explain it step-by-step."[37]

Grace Malenga said of consent forms used in Malawi that providing too much information is likely to scare off patients. "You start asking questions or telling them to sign...some papers and immediately...they will look at them, some of them have actually withdrawn." Some people were willing to participate until they were asked to sign a piece of paper.[38]

Nigerian researchers pointed to the length and complexity of informed consent documents and the need for written consent as obstacles for those attempting to obtain consent from potential study participants.[39] In Marshall's study for NBAC, investigators agreed that individuals may have some anxiety about writing their signature or placing their thumbprint on a formal document because of uncertainties about whether the document could be used against them. One investigator noted: "Even if they use a thumbprint, they (can) get suspicious. They can't read so they wonder why (you need their thumbprint). It's a big fear...the issue (has to do with) government documents. (It's threatening) because they don't know what they are signing or what they might be 'giving away.'"[40]

At the same time, there is some evidence that researchers can overcome many of the barriers to participants' understanding of lengthy, complicated consent forms by devoting more time and effort to the consent process. Several empirical studies of informed consent carried out in developed countries describe a fairly elaborate, multi-stage consent process aimed at overcoming these barriers. Studies conducted in Chile, the Netherlands, and Switzerland, found that researchers could overcome these barriers to the informed consent process with three separate preparatory sessions with potential participants (Sánchez, Salazar and Tijero 1998; Rodenhuis, Van den Heuvel, Annyas, et al. 1984; Tomamichel, Sessa, Herzig, et al. 1994). For example, in approving protocols, IRBs may waive documentation of informed consent through a signature or a thumbprint, provided that the researchers give adequate justification for the waiver and ensure adherence to the substantive ethical standard of informed consent. It is our view that in such cases the justification, while important, must also pass public scrutiny. We would encourage a process by which these waivers were audited by a competent body.

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

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

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

CONCLUSIONS [1]

It is evident that cultural barriers in some countries prevent the informed consent process from being carried out in precisely the same way the U.S. research regulations stipulate. However, investigators can, for the most part, overcome these barriers without violating the substantive ethical standard that requires them to obtain individual and voluntary informed consent from competent research participants. One mechanism for overcoming or addressing problems in a culturally sensitive way, without compromising ethical standards for obtaining voluntary informed consent, is to work collaboratively with the community in which the research will be carried out. This process involves members of the community before, during, and after the research is conducted. Informing and educating the local community well in advance of the research can aid in recruiting volunteers, and help to find ways to ensure that recruitment is noncoercive. Such a process of community education and consultation is important in protecting the rights of potential subjects during recruitment, promoting their understanding, and providing additional information about the study when relevant and necessary.

Based on studies commissioned for NBAC and testimony presented at meetings, we found no evidence in developing countries of opposition to the requirement for voluntary, individual informed consent. Instead, there is considerable evidence that researchers, community representatives, and others in those countries are eager to respect the rights of individuals who become research participants. Indeed, the surveys conducted by Kass and Hyder lend considerable support to the view that developed and developing country researchers view the requirement to obtain voluntary, informed consent as a leading ethical standard.

Adherence to this ethical standard requires that researchers disclose relevant information, that they take steps to ascertain that potential participants understand what they have been told, and that they ensure that each individual's consent is voluntary. Nevertheless, some customs and traditions indicate the need to modify some of the specific procedures related to the process and documentation of informed consent as stipulated in the U.S. regulations. Those procedures should be made sufficiently flexible to be adapted to the context in developing countries. The requirements of written consent and the participant's signature, mark, or thumbprint on consent forms are procedures that an IRB should be allowed to waive when researchers provide adequate justification for such waivers.

Every competent adult should be able to decide freely whether to participate in research, a position adopted in previous NBAC reports (NBAC 1998; NBAC 1999). Those who wish to cede that decision to another ought to be able to do so, but the initial choice is still theirs. We know, however, that personal and local circumstances complicate such a choice. In reality, there are many obstacles to achieving the ideal state of affairs. Nevertheless, adherence to these customs need not compromise the ethical standard of informed consent. In some circumstances, researchers should be afforded greater flexibility in the means they use to inform participants about research and in the methods of documenting consent in international collaborative research. In addition, potential subjects may wish to involve family members in their decision to participate, and researchers may need to obtain a community leader's permission before approaching individuals in the recruitment process.

Thus, our recommendations recognize the roles of families and community leaders, as well as the complications of customs that preclude full disclosure of medical details to patients themselves. These recommendations represent only the first steps toward eventually reaching a

state of affairs in which every competent individual, in whatever context, voluntarily makes his or her own decision about participation in research based on adequate information.

References

Advisory Committee on Human Radiation Experiments (ACHRE). 1996. *Final Report*. New York: Oxford University Press.

Appelbaum, P.S., L.H. Roth, and C.W. Lidz. 1982. "The Therapeutic Misconception: Informed Consent in Psychiatric Research." *International Journal of Law and Psychiatry* 5(3-4) : 319-329.

Beauchamp, T.L., and J.F. Childress. 1994. *Principles of Biomedical Ethics*, 4th ed. New York: Oxford University Press.

Bernstein, N. 1999. "For Subjects in Haiti Study, Free AIDS Care Has a Price." *New York Times* June 6.

Bevan, E.G., L.C. Chee, S.M. McGhee, and G.T. McInees. 1993. "Patients' attitudes to participation in clinical trials." *British Journal of Clinical Pharmacology* 35: 204-207.

Churchill, L.R., M.L. Collins, N.M.P. King, S.G. Pemberton, and K.A. Wailoo. 1998. "Genetic Research as Therapy: Implications of 'Gene Therapy' for Informed Consent." *The Journal of Law, Medicine & Ethics*. 26(1) : 38-47.

Code of Federal Regulations. *Title 45 Public Welfare.* Department of Health and Human Services, NIH, OPRR. Washington, D.C.

Council for International Organizations of Medical Sciences (CIOMS). 1993. *International Ethical Guidelines for Biomedical Research Involving Human Subjects.* Geneva: CIOMS.

Dickert, N., and C. Grady. 1999. "What's the Price of a Research Subject? Approaches to Payment for Research Participation." *New England Journal of Medicine* 341(3): 198-203.

Faden, R.R., and T.L. Beauchamp. 1986. *A History and Theory of Informed Consent*. New York: Oxford University Press.

Hardy, E., M.J.D. Osis, S.F. Bento, A.L. Jiménez, and C.R. Carnevalli. 1998. *Informed Consent and Fertility Regulation in Brazil.* Final Report. Campinas, São Paulo, Brazil. Unpublished.

Ijsselmuiden C.B., and R.R. Faden. 1992. "Images in Clinical Medicine." *New England Journal of Medicine* 326(12): 830-844.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). 1996. *ICH Harmonised Tripartite Guideline* Guideline

for Good Clinical Practice. Geneva: ICH Secretariat, International Federation for Pharmaceutical Manufacturers Association.

King, N.M.P. 1995. "Experimental Treatment: Oxymoron or Aspiration?" *Hastings Center Report* 25(4): 6-15.

Leach, A., S. Hilton, B.M. Greenwood, E. Manneh, B. Dibba, A. Wilkins, and E.K. Mulholland. 1999. "An evaluation of the informed consent procedure used during a trial of a *Haemophilus influenzae* type B conjugate vaccine undertaken in The Gambia, West Africa." *Social Science & Medicine* 48: 139-148.

Loue S, Okello D, Kawuma M, 1996. "Research Bioethics in the Ugandan Context: A Program Summary." *Journal of Law, Medicine & Ethics* 24: 47-53.

Love R.R., and N.C. Fost. 1997. "Ethical and Regulatory Challenges in a Randomized Control Trial of Adjuvant Treatment for Breast Cancer in Vietnam." *Journal of Investigative Medicine* 45(8): 423-431.

Macklin, R. 1982. "Beyond Paternalism." *IRB: A Review of Human Subjects Research* 4(3): 6-7.

Macklin, R. 1981. ""'Due' and 'Undue' Inducements: On Paying Money to Research Subjects." *IRB: A Review of Human Subjects Research* 3(5): 1-6.

Medical Research Council of the United Kingdom. 1999. *Interim Guidelines- Research Involving Human Participants in Developing Societies: Ethical Guidelines for MRC-sponsored Studies*. United Kingdom: MRC.

National Bioethics Advisory Commission. 1998. *Research Involving Persons with Mental Disorders that May Affect Decisionmaking Capacity*. 2 vols. Rockville, MD: U.S. Government Printing Office.

National Bioethics Advisory Commission. 1999. *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*. 2 vols. Rockville, MD: U.S. Government Printing Office.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Washington, DC: Department of Health, Education, and Welfare.

National Consensus Conference. 1997. *Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda*. Kampala, Uganda: National Consensus Conference.

Newton, L. 1990. "Ethical Imperialism and Informed Consent." *IRB: A Review of Human Subjects Research* 12(3): 10-11.

Preziosi, M.P., A. Yam, M. Ndiaye, A. Simaga, G. Simondon, and S.G.F. Wassilak. 1997. "Practical experiences in obtaining informed consent for a vaccine trial in rural Africa." *New England Journal of Medicine* 336(5): 370-373.

Rodenhuis, S., W.J.A. Van den Heuvel, A.A. Annyas, H.S. Koops, D.T. Sleijfer, and N.H. Mulder. 1984. "Patient motivation and informed consent in a Phase I study of an anticancer agent." *European Journal of Cancer and Clinical Oncology* 20(4): 457-462.
Sánchez. S., G. Salazar, and M. Tijero. 1998. *Final Report of the Project Decisions and Perspectives of Women Who Participate in Contraceptive Clinical Trials.* Instituto Chileno de Medicina Reproductiva. Santiago, Chile. Unpublished.

Tomamichel, M., C. Sessa, S. Herzig, J. de Jong, O. Pagani, Y. Willems, and F. Cavalli. 1995. "Informed consent for phase I studies: evaluation of quantity and quality of information provided to patients." *Annals of Oncology* 6(4): 363-369.

United Nations. General Assembly. 1996. *International Covenant on Civil and Political Rights.* Res 2200A(XXI) at 52, UN Doc A/6316, 999 U.N.T.S. 171. New York: UN.

World Medical Association (WMA). 1964. The Helsinki Declaration: World Medical Association Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects (amended: 29th World Medical Assembly, Tokyo, Japan, October 1975; 35th World Medical Assembly, Venice, Italy, October 1983; 41st World Medical Assembly, Hong Kong, September 1989; and 48th General Assembly, Somerset West, Republic of South Africa, October 1996). Ferney-Voltaire, France: World Medical Association, http://www.wma.net/e/policy/17-c_e.html.

[1] The material in this chapter benefited from reports prepared by several consultants to NBAC, articles published in the literature, and two unpublished studies provided to NBAC by researchers from South America (Hardy, Osis, Bento, et al. 1998; Sánchez, Salazar, and Tijero 1998). The consultants' reports are: Sugarman, J., B. Popkin, F. Fortney, and R. Rivera, 1999, "International perspectives on protecting human research subjects." Marshall, P., 2000, "The Relevance of Culture for Informed Consent in U.S. Funded International Health Research." and Kass, N. and A. Hyder, 2000, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations." These background papers were prepared for NBAC and are available in Volume II of this report.

[2] The basic elements of disclosure in the informed consent process presented in the Federal Policy for the Protection of Human Subjects are listed in Exhibit 1. References in this chapter to the basic elements of disclosure in informed consent are to the eight requirements found in this policy.

[3] See Sugarman, J., B. Popkin, F. Fortney, and R. Rivera, 1999, "International perspectives on protecting human research subjects."; Kass, N. and A. Hyder, 2000, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations."; Marshall, P., 2000, "The Relevance of Culture for Informed Consent in U.S. Funded International Health Research." These background papers were prepared for NBAC and are available in Volume II of this report.

[4] See Sugarman, J., B. Popkin, F. Fortney, and R. Rivera, 1999, "International perspectives on protecting human research subjects." p. 10. This background paper was prepared for NBAC and is available in Volume II of this report.

[5] From data collected by Kass, N., and L. Dawson, 1999, Preliminary Focus Group Report. *For* Kass, N. and A. Hyder, 2000, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding

U.S. Human Subjects Regulations." p. 9. This report was used to write the background paper prepared for NBAC that is available in Volume II of this report.

[6] See Marshall, P., 2000, "The Relevance of Culture for Informed Consent in U.S. Funded International Health Research." p. 18. This background paper was prepared for NBAC and is available in Volume II of this report.

[7] Plowe, C. Testimony before NBAC. February 29, 2000. Herndon, VA. Meeting transcript; Pape J.P. Testimony before NBAC. February 29, 2000. Herndon, VA. Meeting transcript.

[8] See Sugarman, J., B. Popkin, F. Fortney, and R. Rivera, 1999, "International perspectives on protecting human research subjects." pp. 17. This background paper was prepared for NBAC and is available in Volume II of this report.

[9] See Kass, N. and A. Hyder, 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.

[10] See Marshall, P., 2000, "The Relevance of Culture for Informed Consent in U.S. Funded International Health Research." p. 34. This background paper was prepared for NBAC and is available in Volume II of this report.

[11] Sommer, A. Testimony before NBAC. September 16, 1999. Arlington, VA. Meeting transcripts, 214.

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

[13] See Marshall, P., 2000, "The Relevance of Culture for Informed Consent in U.S. Funded International Health Research." p. 17. This background paper was prepared for NBAC and is available in Volume II of this report.

[14] Pape, J.P. Testimony before NBAC. February 29, 2000. Herndon, VA. Meeting transcript.

[15] Pape, J.P. Testimony before NBAC. February 29, 2000. Herndon, VA. Meeting transcript, p. 32.

[16] See Marshall, P., 2000, "The Relevance of Culture for Informed Consent in U.S. Funded International Health Research." p. 15. This background paper was prepared for NBAC and is available in Volume II of this report.

[17] Plowe, C. Testimony before NBAC. February 29, 2000. Herndon, VA. Meeting transcript, p. 151.

[18] Pape, J.P. Testimony before NBAC. February 29, 2000. Herndon, VA. Meeting transcript.

[19] See Kass, N. and A. Hyder, 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.

[20] From data collected by Kass, N., and L. Dawson, 1999, Preliminary Focus Group Report. *For* Kass, N. and A. Hyder, 2000, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations.". This report was used to write the background paper prepared for NBAC that is available in Volume II of this report.

[21] From data collected by Kass, N., and L. Dawson, 1999, Preliminary Focus Group Report. *For* Kass, N. and A. Hyder, 2000, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations."p.8. This report was used to write the background paper prepared for NBAC that is available in Volume II of this report..

[22] See Marshall, P., 2000, "The Relevance of Culture for Informed Consent in U.S. Funded International Health Research." p. 34. This background paper was prepared for NBAC and is available in Volume II of this report.

[23] See Marshall, P., 2000, "The Relevance of Culture for Informed Consent in U.S. Funded International Health Research." p. 22. This background paper was prepared for NBAC and is available in Volume II of this report.

[24] From data collected by Kass, N. and L. Dawson, 1999. *For* Kass, N. and A. Hyder, 2000, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects

Regulations."Q. J8, . p.1

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

[26] See Kass, N. and A. Hyder, 2000, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations."p.8. This background paper was prepared for NBAC and is available in Volume II of this report.

[27] Sugarman and colleagues state that "investigators in one country repeatedly noted that patients who might be asked to enroll in a medical study would be skeptical of an investigator who did not involve the family in the decision making process." See Sugarman, J., B. Popkin, F. Fortney, and R. Rivera, 1999, "International perspectives on protecting human research subjects." p. 9. This background paper was prepared for NBAC and is available in Volume II of this report.

[28] See Marshall, P., 2000, "The Relevance of Culture for Informed Consent in U.S. Funded International Health Research." p. 28. This background paper was prepared for NBAC and is available in Volume II of this report.

[29] See Kass, N. and A. Hyder, 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.

[30] Plowe, C. Testimony before NBAC. February 29, 2000. Herndon, VA. Meeting transcript, 106

[31] See Kass, N. and A. Hyder, 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.

[32] This same principle is implicit in 45 CFR § 46.111(a)(1) (1999), stating that in reviewing research, IRBs must determine that risks to subjects are minimized.

[33] While the *Belmont Report* defines the principle of nonmaleficence as part of the principle of beneficence, and Beauchamp and Childress define nonmaleficence as distinct from beneficence, both sources maintain that nonmaleficence requires that harms be minimized.

[34] See Kass, N. and A. Hyder, 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.

[35] See Sugarman, J., B. Popkin, F. Fortney, and R. Rivera, 1999, "International perspectives on protecting human research subjects." p. 11. This background paper was prepared for NBAC and is available in Volume II of this report.

[36] Loue, S. Testimony before NBAC. October 21, 1999. Washington, D.C. Meeting transcript, 28-29, 40.

[37] Pape, J.P. Testimony before NBAC. February 29, 2000. Herndon, VA. Meeting transcript, 35.

[38] Malenga, G. Testimony before NBAC. February 29, 2000. Herndon, VA. Meeting transcript, 67.

[39] See Marshall, P., 2000, "The Relevance of Culture for Informed Consent in U.S. Funded International Health Research." p. 24. This background paper was prepared for NBAC and is available in Volume II of this report.

[40] See Marshall, P., 2000, "The Relevance of Culture for Informed Consent in U.S. Funded International Health Research." p. 26. This background paper was prepared for NBAC and is available in Volume II of this report.

APPENDIX 3.1 - ENHANCING INTERNATIONAL COLLABORATIVE RESEARCH

1. What procedural requirements articulated in the United States regulations are absent from other documents?

Continuing IRB review

The documents listed below are the only ones that have language that addresses continuing IRB review.

<table>
<tr><td>Canada

Article 1.13(a)
"Ongoing research shall be subject to continuing ethics review."</td><td rowspan="2">South Africa

Chapter 13
"It is recommended that:
• Research Ethics Committees should require investigators in charge of approved research projects to submit a brief report of progress at least annually.
• Investigators should be requested to send copies of any published reports to the Research Ethics Committee.
• Ways in which patients and health workers may approach the Research Ethics Committee when there is concern about the conduct of research should be made known."</td></tr>
<tr><td>UNAIDS

Guidance Point 15
"A plan for monitoring the initial and continuing adequacy of the informed consent process and risk-reduction interventions, including counseling and access to prevention methods, should be agreed upon before the trial commences."</td></tr>
<tr><td>United States
Food and Drug Administration

21 CFR § 56.103
"Any clinical investigation which must meet the requirements for prior submission ... to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB ..."</td><td>United States
Common Rule and USAID

45 CFR § 46.103(b) and 22 CFR § 225.103(b)
"... the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB ..."</td></tr>
</table>

2. What substantive ethical principles or standards articulated in other documents are absent from the United States federal regulations?

Written informed consent is not always required

Under U.S. regulations, an IRB may waive any or all of the requirements for informed consent; a waiver usually is granted for research that is considered *minimal risk*. However, these documents have language that permit alternatives to written informed consent.

Declaration of Helsinki	**Canada**
Principle I.9 "... The physician should then obtain the subject's freely-given informed consent, preferably in writing."	Article 2.1(b) "Evidence of free and informed consent by the subject ... should ordinarily be obtained in writing. Where written consent is culturally unacceptable, or where there are good reasons for not recording consent in writing, the procedures used to seek free and informed consent shall be documented."
France	**United Kingdom (1999)**
Title II, Article L. 209-9 "... Consent shall be given in writing, or, if it cannot be given in writing, shall be witnessed by a third party ... independent of the investigator and or the sponsor."	Specific Consideration 8 "... A permanent personalised record of consent should be retained, although this need not necessarily be in the form of a signature."

Providing adequate access to health care

CIOMS/WHO (1993)	**Council of Europe**
Commentary for Guideline 15 *"... sponsors should also provide facilities and personnel to make necessary health-care services available to the population from which research subjects are recruited ..."*	Article 3 "Parties, taking into account health needs and available resources, shall take appropriate measures with a view to providing ... equitable access to health care of appropriate quality."
ICH	**Uganda**
Principle 4.3.2 "During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events ... related to the trial."	V.D.(3) "The investigator must provide adequate and safe medical or dental care ... to participants during the clinical trial ... and must ensure that the appropriate medical care and follow-up procedures are maintained after the trial for a period of time ..."

3. What categories articulated in other documents are absent from the U.S. regulations?

Level of treatment provided to research participants

Declaration of Helsinki	**Australia**	**Canada**
Principle II.4 "... every patient ... should be assured of the best proven diagnostic and therapeutic method."	Principle 12.2(b) "An HREC must consider all aspects of the design of a clinical trial and be satisfied that there is a scientifically valid hypothesis being tested which offers a realistic possibility that the interventions being studied will be at least as effective as standard treatment."	Article 7.4 "The use of placebo controls in clinical trials is generally unacceptable when the standard therapies or interventions are available for a particular patient population."
CIOMS/WHO (1993)	**ICH**	**United Kingdom (1999)**
Commentary on Guideline 14 *"... as required by the Declaration of Helsinki ... 'every patient – including those of a control group, if any --- should be assured of the best proven diagnostic and therapeutic method.' Therefore, if there is already an approved and accepted drug for the condition that a candidate drug is designed to treat, placebo for controls usually cannot be justified."*	Principle 2.1 "Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement."	Specific Consideration 6 "The Helsinki principle ... – ... best proven diagnostic and therapeutic method ... - should take into account of the available and feasible health care in the particular developing country (The fact that a treatment tested in a trial may not currently be affordable to the local population should not in itself necessarily be a reason to preclude the study on ethical grounds ...)"
South Africa (1993) Chapter 11 "Where the administration of effective treatment is important for the future well-being of the patient, it is ethical for a controlled trial to be undertaken only if, at the outset, the investigator does not know whether the trial treatment is more or less effective than the standard treatment with which it is to be compared (or than no treatment at all in the case of a placebo-controlled study) ... Withholding effective treatment for a limited, stipulated period, whether or not it is substituted by a placebo, can sometimes be acceptable in order to validate a technique of measurement or confirm the sensitivity or discrimination of a therapeutic trial design. This can only be acceptable if no long-term harm to the patient can reasonably be foreseen by the applicant and the Research Ethics Committee."		

Providing research results to participants

Australia	**Brazil**	**CIOMS (1991)**
Principle 1.18 "... Normally, research results should be made available to research participants."	Resolution 196/1996 – III.3.n "... When it is ... beneficial to foster or encourage changes in practices or behaviors in the interest of a community, the research protocol must include, whenever possible, provisions to communicate such benefits to the individuals and/or communities."	Principle 13 "Part of the benefit that communities, groups, and individuals may reasonably expect from participating in studies is that they will be told of findings that pertain to their health ... Research findings and advice to communities should be publicized by whatever suitable means are available ..."
India	**South Africa**	**UNAIDS**
General Principle 2 "...The principles of informed consent and voluntariness are cardinal principles to be observed throughout the research and experiment, including its aftermath and applicative use so that research subjects are continually kept informed of any and all developments in so far as they affect them and others."	Chapter 12 "In studies which involve any sustained co-operation on the part of the patient it is good practice to make arrangements to inform participants of the outcome of the research in broad terms, and to combine this with a letter of thanks or a small gift in the case of children."	Guidance Point 2 "... other knowledge and benefits resulting from HIV vaccine research should be made available as soon as possible to all participants in the trials in which it was tested ..."
United Kingdom (1998)	**United Kingdom (1999)**	
Principle 5.4.8 "... Where feasible, trial participants should also be notified of progress with the trial and the eventual outcome of the trial."	Specific Consideration 9 "In anticipation of any beneficial results of therapeutic research, there should be normally discussion in advance with relevant parties in the developing society about the dissemination of those results to study participants and local inhabitants, and about subsequent availability of the relevant product to local inhabitants."	

U.S. regulations only have a statement that prohibits the inclusion of exculpatory language in the informed consent.

Australia	**Brazil**	**CIOMS/WHO (1993)**
Principle 12.7 "An HREC must be satisfied ... arrangements exist to ensure adequate compensation to participants for any injury suffered as a result of participation in the trial."	Resolution 196/1996 – V.5 "The researcher, the sponsor, and the institution must assume full responsibility for providing comprehensive care to the research subjects, as regards complications and injury resulting from foreseen risks." Resolution 196/1996 – V.6 "Research subjects that suffer any type of injury resulting from their participation in the research, regardless of such injury having been foreseen in the terms of consent, or not, have the right to receive comprehensive medical care, as well as indemnity." Resolution 196/1996 – V.7 "Under not circumstance will the research subject be required to waive his/her right to indemnity for injury resulting from the research ..."	Guideline 13 "Research subjects who suffer physical injury as a result of their participation are entitled to such financial or other assistance as would compensate them equitably for any temporary or permanent impairment or disability."
India		**Netherlands**
Specific Principle 4.1 (drugs etc.) "Research subjects who suffer physical injury as a result of their participation are entitled to financial or other assistance to compensate them equitably for any temporary or permanent impairment or disability ... The sponsor ... should agree, before the research begins, to provide compensation for any physical injury for which subjects are entitled to compensation."		Article 7.6 "... The injured party who has no insurance in place ... has toward a governmental service, institution, or company the rights which he would otherwise have in accordance ... with regard to the insurer."
South Africa	**Uganda**	**UNAIDS**
Chapter 14 "In the event of any significant injury, the patient should be entitled to receive compensation regardless of whether there may or may not have been negligence or legal liability on any other basis." Chapter 19 "In the event of injury sustained by a patient/volunteer during the course of a clinical trial, compensation should be paid without the patient/volunteer having been required to prove *mala fides*, negligence or incompetence."	V.E.(6) "The sponsor is responsible for providing compensation or indemnity in the event of trial-related serious injury, disability, or death ..."	Guidance Point 9 "The nature, magnitude, and probability of all potential harms resulting from participation in a HIV preventive vaccine trial should be specified in the research protocol as fully as can be reasonably done ... including compensation for injury related to the research, and referral to psycho/social and legal support, as necessary."

Successful products made reasonably available to participants and communities

Brazil	**CIOMS/WHO (1993)**
Resolution 196/1996 – III.3.p "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." Research 196/1996 – III.3.s "Research involving human subjects ... must ... submit evidence, in case of research conducted abroad or with external cooperation, of commitments and advantages to the research subjects and to Brazil, which will result from the implementation of the research ..." Resolution 251/1997 – IV.1.m "... 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 given."	Commentary to Guideline 8 *"If any product is to be developed ... clear understanding should be reached ... about what the community is to expect and what can or cannot be provided during and at the close of the research. Such understanding must be reached before the research has begun, to ensure that the research is truly responsive to the priorities of the community ... As a general rule, the sponsoring agency should ensure that, at the completion of successful testing, any product developed will be made reasonably available to inhabitants of the underdeveloped community in which the research was carried out ..."* Commentary to Guideline 15 *"... the sponsoring agency should agree in advance of the research that any product developed through such research will be made reasonably available to the inhabitants of the host community or country at the completion of successful testing ..."*
Canada	**South Africa**
Commentary to Article 7.2 *"The REB should also examine (1) the issue of continuing access after the trial, (2) the treatments ... or, (3) if impossible, the provisions taken to ensure adequate replacement."*	Chapter 11 "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."
UNAIDS	**United Kingdom (1999)**
Guidance Point 2 "Any 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 ..." Commentary to Guidance Point 2 *"At a minimum, the parties should begin this discussion before the trials commence ..."*	Specific Guideline 9 "In anticipation of any beneficial results of therapeutic research, there should normally be discussion in advance ... about subsequent availability of the relevant product to local inhabitants."

	Uganda V.D.(4) "The 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."

Equivalent protections (harmonization of standards)

<table>
<tr>
<td>Brazil

Resolution 196/1996 – III.3.s
"... The protocol must comply with the requirements of the Declaration of Helsinki and include ... an authorization issued in the country of origin. The Committee for Ethics in Research will require compliance with its own ethical parameters ..."

Resolution 292/1999 – II
"In all research [coordinated abroad or with foreign participation], it is mandatory: to set forth the responsibilities, rights, and obligations through an agreement of the parts involved (in the research)."

Resolution 292/1999 – VII
"In preparing the (research) protocol, special attention must be given to the presentation of ... approval document issued by the Committee on Research Ethics or equivalent institution in the country of origin that will promote or also execute the project."</td>
<td>CIOMS (1991)

Principle 48
"... the initiating agency should submit the study protocol to ethical review, in which the ethical standards should be no less exacting than they would be for study carried out in the initiating country; the ethical review committee in the host country should satisfy itself that the proposed study meets its own ethical requirements."

ICH

Introduction
"The objective ... is to provide a unified standard for the European Union, Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions."</td>
</tr>
<tr>
<td>India

IV. Issues related to national and international collaborative research (Human Genetics Research)
"International collaborative projects should not only [follow] the guidelines for collaboration but make sure that the investigations should follow ... international standards, Declaration of Helsinki or Nuremberg Code. Written descriptions of the specific procedural implementation of such policies that have been adopted by the collaborating institutions in their own countries are required."</td>
<td>Uganda

I.A.(3)
"... if the procedures required in the foreign country provide at least the equivalent protection as those provided by these rules, the substitution of the foreign country's procedures may be approved [but] is not ... required by these rules."</td>
</tr>
</table>

Research and review of research in other countries

Australia	**Brazil**	**Canada**
Principle 1.21 "Where research is conducted in an overseas country under the aegis of an Australian institution or organization, the research must comply with the requirements of this Statement as well as the laws and guidelines of that country."	Resolution 196/1996 – III.3.1 "Research involving human subjects ... must ... respect the cultural, moral, religious, and ethical values, as well as the mores and habits, when research involves communities."	**Article 1.14** "Research to be performed outside the jurisdiction or country of the institution which employs the researcher shall undergo prospective ethics review both (a) by the REB within the researcher's institution; and (b) by the REB, where such exists, within the legal responsibility and equivalent ethical and procedural safeguards in the country or jurisdiction where the research is to be done."
CIOMS/WHO (1993) Guideline 8 "Before undertaking research involving subjects in underdeveloped communities, whether in developed or developing countries, the investigator must ensure that ... the proposals for the research have been reviewed and approved by an ethical review committee that has among its members or consultants persons who are thoroughly familiar with the customs and traditions of the community."	**India** B.I Ethical considerations for specific areas – Drug trials (drugs etc.) *"The proposed trial should be carried out, only after approval of the Drugs Controller General of India ... The guiding principles should be followed irrespective of whether the drug has been developed in this country or abroad or whether clinical trials have been carried out outside India."*	**South Africa** Chapter 1 "The basic ethical assumption in medical research is the autonomy of the individual within the broader context of human relations. The social and cultural environment should be taken into consideration in all circumstances. Patients should be treated as human beings in the context of their social, political, economic and religious environments. Assessments of patients and healthy volunteers in research programmes should be made within the context of the family and cultural system. Research programmes should treat people as part of a community while simultaneously respecting their individual autonomy. This is of paramount importance for medical research in an African context."
UNAIDS Guidance Point 5 "To ensure the ethical and scientific quality of the proposed research, its relevance to ... and its acceptance by the affected community ... community representatives should be involved in an early and sustained manner in the design, development, implementation, and distribution of results of HIV vaccine research."	**United Kingdom (1999)** Specific Consideration 7 "Local ethical review of research proposals is required to judge the ethical acceptability of research in accordance with the customs and traditions of the particular community ..."	