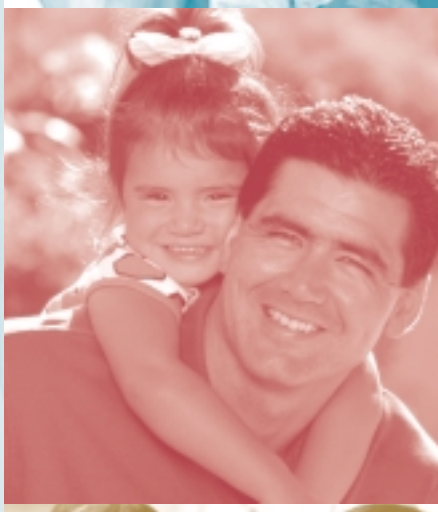
Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries



VOLUME II

COMMISSIONED PAPERS AND STAFF ANALYSIS

Bethesda, Maryland
May 2001

The National Bioethics Advisory Commission (NBAC) was established by Executive Order 12975, signed by President Clinton on October 3, 1995. NBAC's functions are defined as follows:

a) NBAC shall provide advice and make recommendations to the National Science and Technology Council and to other appropriate government entities regarding the following matters:

   1) the appropriateness of departmental, agency, or other governmental programs, policies, assignments, missions, guidelines, and regulations as they relate to bioethical issues arising from research on human biology and behavior; and

   2) applications, including the clinical applications, of that research.

b) NBAC shall identify broad principles to govern the ethical conduct of research, citing specific projects only as illustrations for such principles.

c) NBAC shall not be responsible for the review and approval of specific projects.

d) In addition to responding to requests for advice and recommendations from the National Science and Technology Council, NBAC also may accept suggestions of issues for consideration from both the Congress and the public. NBAC also may identify other bioethical issues for the purpose of providing advice and recommendations, subject to the approval of the National Science and Technology Council.

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THE CHALLENGE OF EQUIVALENT PROTECTION

Commissioned Paper
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1. Introduction

Title 45 of the Code of Federal Regulations Part 46 (45 CFR § 46) addresses the protection of human subjects of biomedical and behavioral research, including "research conducted, supported, or otherwise subject to regulation by the Federal Government outside the United States" § (46.101(a)). Part 46 regulates the process of review of research proposals through Institutional Review Boards (IRBs) and substantive rules required to be observed on such general matters as informed consent and such special matters as research involving prisoners, children, and pregnant women. Part 46.101 provides in paragraph (g) that the policy on protection of human subjects "does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research."

§ 46.101(h) provides that:

> [w]hen research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly (sic) Declaration (Declaration of Helsinki amended 1989[1]) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a Department or Agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the Department or Agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy….

This intention to accommodate studies the policy covers that are conducted in a foreign country therefore depends on a determination that "the procedures prescribed by the institution" afford human subjects at least equivalent protections to those provided in the policy.

The reference to "procedures" repeats the policy's recognition that "procedures normally followed" in foreign countries "may differ from those set forth in this policy." This raises the issue of whether equivalent protection is focused only on matters of institutional review procedures, where the equivalent structure and functioning of an IRB are required, or whether equivalence must extend beyond the process of review to include the substance of the proposal to be reviewed, including, for instance, subjects' informed and voluntary consent and appropriate acquisition and research use of fetal tissues.

The example provided suggests the latter. The Declaration of Helsinki is established and periodically revised by the World Medical Association (WMA), described in the policy as the World Medical Assembly, perhaps confused with the World Health Organization's governing body, the World Health Assembly. Most recently revised in 1996, the Declaration of Helsinki is modestly entitled only as "Recommendations guiding physicians…" and, in contrast to the WMA Declaration of Geneva, which "binds physicians," provides in its Introduction that "[i]t must be stressed that the standards as drafted are only a guide to physicians all over the world," and that physicians "are not relieved from criminal, civil and ethical responsibilities under the law of their own countries."

The procedural content of the Declaration of Helsinki is rudimentary. In its Basic Principles, Article 1.2 requires that a research protocol:

> should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

Departmental and Agency heads responsible for determining equivalent protection must therefore look beyond the claim of a foreign institution that its review procedure conforms to the Declaration of Helsinki. Compliance with the Declaration's guiding recommendations and an accordingly constituted independent review committee's comments and guidance may be satisfied by procedures falling far short of the composition and standards of operation expected of IRBs bound by the policy in the Federal Regulations.

The contrast may be mitigated to some degree by the substantive provisions of the Declaration of Helsinki. These address conformity with generally accepted scientific principles, the requirement of prior animal studies, qualifications and supervision of research personnel, prior risk-to-benefit assessment, subjects' voluntary and adequately informed consent, protection of vulnerable subjects and, for instance, preservation of privacy and confidentiality. Since the policy illustrates equivalent protection through "the procedures prescribed by the institution" by reference to the Declaration of Helsinki, whose procedural provisions are undeveloped, the conclusion may be drawn that equivalence addresses substantive principles of ethical conduct of research with human subjects, and not only the process of the review itself.

Considerably closer to the Federal Regulations is review under the drug industry's International Conference on Harmonization (ICH) Guideline for Good Clinical Practice, operative since January 1997. The objective of the Guideline is to provide a common standard for the European Union, Japan, and the United States to facilitate the mutual acceptance of clinical trial data by regulatory authorities. The Guideline was developed with consideration of additional countries including Australia, Canada, and the Nordic countries. Its provisions closely reflect those of the Federal Regulations, and points of departure are so relatively minor that requirements of equivalent protection may easily appear to be satisfied.

The introduction to the Declaration of Helsinki and its Basic Principles cited above both make explicit reference to the obligation to obey research host countries' laws. The Federal Regulations are similarly subject to legislative provisions and judicial and quasi-judicial interpretation in the United States. It is therefore relevant in an approach to equivalence briefly to consider as a model the body of countries' domestic laws that governs matters materially affected by the laws of foreign jurisdictions, called Conflict of Laws or Private International Law.

2. The Legal Model

The modern preoccupation with globalization, particularly in the field of commercial interaction and enterprise, has deeply historical roots. The historic law of commerce, the *lex mercatoria*, in England also known as the Law Merchant, was a code of rules covering foreign trade and traders that was declared to be of universal application. It constituted an international trade law similarly applied in mercantile courts throughout medieval Europe, and its concept has survived to modern times.[2] Similarly, commonly observed maritime customs were founded on Byzantine principles that were well established by the twelfth century and quite uniformly applied by maritime courts of the north and east Mediterranean and North Atlantic coasts. In England, the Law Merchant was absorbed into the Common law during the seventeenth and eighteenth centuries, adding to Anglo-Saxon customary law, the Common law, an enduring capacity to resolve within its own doctrines on conflict of laws disputes involving alien and internationally recognized legal principles.

An initial issue is the respect given to judgments of other countries' courts of law. A key approach is acceptance of the propriety of other countries' legal procedures, such as the Continental inquisitorial trial process, which differs from the Common law's adversarial process. Similarly, when, for instance, English law made 10 or more years' practice at the Bar a precondition to judicial appointment, and 5 or more years' experience on the High Court bench a legal condition of elevation to appellate courts, judgments of Continental courts were recognized whose judges, immediately on graduation from schools of law, had directly entered the judicial

branch rather than the practicing or administrative branch of the legal profession. Countries do not enforce other countries' criminal or tax laws, but widely recognize foreign marriage laws. When, for instance, English law required parental consent for the marriage of adolescent girls, Scottish law did not. Accordingly, elopements of legal minors for marriage in Scotland were common, particularly to the first village on the main road crossing the border, Gretna Green. However, only marriage in monogamous form is recognized, excluding matrimonial relief in marriages celebrated in polygamous form even when no second or later spouse exists. Although U.S. states are constitutionally required to give other states' legal processes full faith and credit,[3] such as the liberal laws in Nevada on marriage and divorce, a current challenge is recognition of same-sex marriages legally recognized in Hawaii.

When another jurisdiction's laws involve issues of judicial procedure, they may not only prevail but be unreviewable in another jurisdiction's courts, except on human rights grounds; but rulings on matters of substance, such as polygamous marriage, are reviewable and may not prevail. Whether an issue is of procedure or substance is a matter of classification according to each jurisdiction's own domestic law. Jurisdictions usually attempt to accommodate and apply others' substantive rules. For instance, Common law jurisdictions divide property into real property and personal property. Land itself is real property ("real estate"), but a lease over land is personal property ("personalty"). Continental Civil law derived from Roman law divides property into movable and immovable property, the latter including real estate and leasehold interests in land. When, for instance, a Common law court is administering an estate including interests in foreign land, it applies the law of the jurisdiction where the land involved is situated, treating leasehold interests according to the foreign law on immovable property rather than its own domestic law on personal property.

Countries are more easily disposed to accept substantive rules of other countries that are culturally and/or religiously compatible. Hence, Gretna Green marriages are acceptable in England, but foreign marriages monogamous in fact but celebrated in polygamous form are not. Difficulties concern recognition of divorces, for instance, in Islamic ("tallack") and Jewish ("get") religious form where they are claimed as allowing subsequent nonbigamous marriages in Common law jurisdictions.

Some principles are considered of universal application, binding among all nations ("erga omnes") that no jurisdiction can violate, tolerate to be violated elsewhere, or agree with another state to allow to be violated. One is that forced or otherwise involuntary marriage is not recognized. Another is that, since persons cannot profit from their own wrongs, a person acquitted of murder in his own country because of the defense of "honor" that excuses killing, for instance, an adulterous wife or a fornicating sister or daughter, cannot inherit the victim's assets located in a country that does not allow this defense.

3. The Model Applied to Research Ethical Review Procedures

The legal distinction between matters of process and of substance may be applied to determinations of equivalence in protection of human subjects of research. The policy under Federal Regulations may be satisfied where a country's equivalent of an IRB does not satisfy the criteria of membership or function laid out in 45 CFR § 46.107 and § 46.108 respectively, provided that the substantive rules of subject protection are applicable. For instance, in countries with few experts in a particular area, some of whom are principal investigators, no review committee may be capable of constitution whose member with relevant expertise does not have a conflict of interest. Other members may want not only that person's information, permissible to be given under § 46.107(e), but also that person's advice and judgment on whether the proposal is scientifically sound and appropriate according to the state of development of the field. Accordingly, it may be acceptable that the response to the conflict of interest be not the person's exclusion from the review process, as required by § 46.107(e), but due disclosure of the conflict. Similarly, in countries where it is considered unseemly for

women to discuss intimate matters of sex with men, the requirement in § 46.107(b) that both sexes be represented on a review committee may not be observed where such matters are in issue; women's interests may be communicated indirectly if, as is likely, there is an all-male review committee.

The policy itself refers to compliance with the Declaration of Helsinki as an alternative that a Department or Agency head may determine to afford equivalent protections to those of the policy. However, the Declaration does not require that procedures be written in the detail described in § 46.103(b)(4) and (5), and a particular country's laws or regulations may be similarly undemanding. As a recipient of U.S. funds, the institution will be accountable for the means by which ethics review committees are composed and function, but the secretarial support that underpins domestic IRBs may not exist.

A transcending concern, not confined to resource-poor countries, is that the prospect of receiving U.S. funding of research may be so enticing to academic and health care institutions that risks of physical injury or discomfort, cultural offensiveness, and emotional insults to which prospective subjects may be exposed will be undervalued by investigators and members of ethical review committees. Members who have no conflict of interest in the classical sense of motives of personal enrichment or comparable self-interest may be inspired by a conviction that pursuit of the investigation will enhance the well-being of populations for which they care, the prestige of their institutions, and the careers of investigators in whom their institutions and countries have made significant investments. Similarly, their optimism that a study will be highly advantageous may distort their risk-to-benefit assessment.

The policy requires, in § 46.107(d), that each review committee "shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution." In stratified or racially or otherwise divided societies, independent-minded representative community members may be difficult for the institutions to identify. Community members they attract may be inclined to be deferential in the presence of members of institutionally affiliated elites, who, in accordance with the policy itself, may outnumber them four to one. Nonaffiliated peers of institutional members may serve in political, governmental, or similar social leadership roles and share other committee members' hopes for institutional advancement through U.S.-funded research.

Accordingly, it may be an act of faith for a Department or Agency head to determine that institutional procedures in some foreign countries "afford protections that are at least equivalent to those provided in this policy," as required by § 46.101(h). Unless particular proposals are also reviewed by IRBs in the United States, confidence may have to be placed in foreign institutions' conformity with substantive rules of ethical conduct for protection of human subjects of research.

Unless U.S. funding agencies are prepared to undertake on-site inspection of foreign ethics review committees that have not already received a form of U.S. accreditation, some degree of uncertainty of equivalent protection appears inescapable. An approach may be for funding agencies to classify degrees of risk that studies appear to present, separating risks to life or enduring health at one end of a spectrum from risks of cultural insensitivity at the other, and apply a higher level of scrutiny to how well host institutions review studies classified to present graver risks than to studies of intermediate- or low-level risk.

4. Substantive Rules of Ethical Research

A concern that has erupted particularly since 1997 in the United States[4] and elsewhere regarding U.S.-funded placebo-controlled studies has been their conduct in poor countries where sick subjects who are offered investigational products have no practical access to alternative therapeutic products that are available to treat their conditions in more favored countries. An ethical requirement is that sick persons offered an investigational product should have the option of access to alternative treatment available for the condition that appears to affect them. The Declaration of Helsinki provides in Article II(3) that:

> [i]n any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

The second sentence was added in the 1996 revision of the Declaration, for fear that the first sentence taken alone would be understood to proscribe all placebo controls.

The ethical question nevertheless remains, of whether "the best proven…method" means the best that medical science has to offer anywhere, or the best available to patients in their circumstances outside the study they are invited to join. It has been claimed to be exploitive of potential subjects' deprivation that they be offered randomization between treatment with an investigational product and with a placebo on the rationalization that, in their circumstances outside the study, "no proven diagnostic or therapeutic product exists," although a product does exist in more favored circumstances. Critics claim that investigators are ethically obliged to afford such subjects alternative access to "the best proven…method" that medical science has available. The fear is that unproven products will be tested among disadvantaged and deprived populations, because their members' randomization into the placebo arm of a study would not deprive them of any treatments they would otherwise have.

The claim that studies of investigational products in disadvantaged populations must provide subjects with alternative access to best treatment medical science can offer may be based on a more vigorous ethical doctrine than the Declaration of Helsinki itself provides. The Declaration may present an inadequate basis on which to distinguish right from wrong conduct, not only because its distinction between therapeutic and nontherapeutic research has been condemned as illogical and in need of revision,[5] but also because the Declaration itself is presented only as recommendations guiding physicians. Nevertheless, the ethics of studies proposed among deprived populations of less economically developed countries legitimately pose critical issues. They include whether investigators in U.S.-funded studies abroad may behave in ways that investigators in the United States may not, and whether the deprived populations enjoy "protections that are at least equivalent to those provided in this policy," as prescribed in § 46.101(h). The background fear is a breach of distributive justice, since products that disadvantaged populations bear the burden of testing are likely to be marketed in affluent countries and be unavailable to populations of poor countries that served as testing sites.

Developed countries themselves have subpopulations that are deprived of an adequate standard of diagnostic and therapeutic care and can avail themselves only of care that falls far below "the best proven…method," not least in the United States. Studies that propose to target such subpopulations for placebo-controlled studies on the basis that, for them, "no proven diagnostic or therapeutic method exists," might have considerable difficulty gaining IRBs' acceptance as ethical. This poses the question whether studies of this nature proposed to be conducted in foreign countries can be measured by different standards that achieve subjects' equivalent protection.

The better view appears to be that best proven methods are to be assessed by reference to local circumstances in a country as the baseline, rather than some objective, location-neutral standard of optimal care. As Robert J. Levine has explained,[6] resource-poor countries need studies that compare and contrast new investigational products with their usual standard of care, which may be nontreatment, rather than with an optimal standard they cannot achieve or maintain. Conducting studies to contrast an investigational treatment with the best standard in a resource-poor country would violate the principle of distributive justice, since research subjects in the host country would have few if any means to avail themselves of the treatment their risk-taking has shown to be preferable. The beneficiaries would be patients in more affluent settings of developed countries, which should therefore be the sites of studies testing unproven treatments against the optimum care available. Accordingly, the "best method" may be taken to focus on what is best in the circumstances of a foreign country. Local medical and related health care providers will be able to identify prevailing best care, and a local committee can best accomplish the required striking of the risk-to-benefit balance in deciding whether to host a proposed study of an investigational product.

For greater certainty, ethics review committees in host countries may be required to give more than passive approval to studies proposed for U.S. funding and be required actively to explain, perhaps through committee chairs, the benefits for their own communities they find to justify approval of individual proposals. That is, Department or Agency head approval of the foreign procedure might be made conditional on receipt of satisfactory identification of the advantages the local committee finds for the domestic health care system.

5. Risk-to-Benefit Assessment

The Declaration of Helsinki acknowledges in the fourth paragraph of its Introduction that:

> [i]n current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

In its Basic Principles, the Declaration provides in paragraph I.5 that:

> [e]very biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

Determinations of risk and of benefit, and of the excess of one over the other, can focus on various aspects of each. Medical research is usually directed to medical advance and tends to be assessed by clinical indicators, including a patient's better preventive care, diagnosis, therapy, post-operative or post-intervention recuperation and post-traumatic recovery. Similarly, risk tends to be judged clinically in medical terms, such as of death or injury from known side-effects of medical interventions, or, for instance, of unanticipated idiosyncratic reactions due to genetic, pharmacological, environmental, or other causes. Both risk and benefit may also be determined, however, by reference to public health or epidemiological measures, such as reduced prevalence of infection in a community or higher or lower mortality or morbidity or change in life expectancy. Criteria not directly related to medical outcomes may also weigh in the balance between risk and benefit, such as quality of life considerations, including individual capacity to discharge the functions of everyday life and to pursue particular interests or goals. Qualitative research methodologies have come to be employed for some of these assessments.

Which benefits members of a population or community consider most material to their interests to pursue and which risks most important to minimize or avoid may be most reliably determined by members themselves, or by those closely familiar with their values and perceptions of need. Whether a proposed study concerns interests that intended subjects consider at an intimate, personal level, at a family level, or at a communal wider level, and which benefits may be pursued at what costs, and which values must be preserved by sacrifice of others are to be determined by local assessment. Local authorities can determine, for instance, whether or how well a proposed study serves local health care priorities and whether its conduct would impose acceptable burdens on local resources of facilities, personnel, and, for instance, medications. Accordingly, a Department or Agency head may approve "the substitution of the foreign procedures in lieu of the procedural requirements" provided in the Federal Regulations where satisfied that assessments of benefits and risks can be made with equivalent protection of intended subjects at the relevant country or local level.

This is subject to compliance with transcending minimum or core protective values, on analogy with the legal perception that some principles are so fundamental that they are binding among all ("erga omines"). Central among these is the principle that each individual proposed to be at personal risk in a study should be able to give, or effectively deny, consent. The historic Nuremberg Code of 1947, which the 1964 Declaration of Helsinki was developed to amplify and explicate outside the Code's conditioning environment of outrageous crimes against humanity, states as its first principle that:

> The voluntary consent of the human subject is absolutely essential.

The Code goes on to elaborate the principle by explaining that:

> [t]his means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision.

The Code makes no mention of elements that are also considered critical to the ethical planning and conduct of research with human subjects, such as independent ethical review and, for instance, due preservation of confidentiality and disclosure of its limits. The Declaration of Helsinki considerably advances the detail of ethical conduct in research. Further, it addresses research with subjects incapable of making their own decisions or consent, reflecting the recognition that research extends beyond the exploitive sacrifice of vulnerable subjects that framed the Nuremberg Code, to include research, such as with mentally disabled people and with infants and children, that it is ethical to undertake and may be unethically discriminatory to deny.

A Department or Agency head may act under § 46.101(h) to approve review procedures for research conducted in foreign countries as providing equivalent protection of human subjects to that under the policy of the Federal Regulations when satisfied that, however local considerations of benefit and risk are determined and prioritized, basic requirements of subjects' protection will be observed.

Issues of intercultural and international dissonance will arise that will have to be satisfactorily resolved in the United States for funding of foreign studies. For instance, the appropriateness of placebo-controlled studies abroad that would not easily be acceptable in the United States has already been raised. Similarly in some foreign settings, where studies, for instance, into women's health are proposed, husbands may expect to decide on their wives' participation and perhaps to be able to bar their wives' entry, when their wives may want to join the studies in order to advance their health and self-determination. The prospect of local controversy over studies the United States is prepared to fund abroad, and perhaps encourage, exposes the limits of the equivalent protection language of § 46.101. The focus on protection of human subjects, rather than on promotion of health research that presumably motivates U.S. funding, reflects the origin of modern regulation of research with human subjects. This lies in the Nuremberg Tribunal's trials of "the Nazi doctors," Henry Beecher's 1966 exposure of research abuse in the United States, M.H. Pappworth's 1968 publication on several countries' mistreatment of "Human Guinea Pigs" and, for instance, revelation in the early 1970s of decades-long abuses in the Tuskegee Syphilis Study. Part 46 of the CFR is entitled "Protection of Human Subjects" because of the emphasis on protection, and in the context of potential abuse, protection is best achieved through potential subjects' nonparticipation.

In recent years, however, the perception has revived that medical research that may endanger individual subjects has the overall goal of advancing understanding and innovation in order to protect health and that sick patients' health cannot be advanced without the funding and appropriate conduct of medical research. That is, medical research itself serves the goal of protection of health, and its undue denial, prevention, or obstruction may prejudice health. This explains why promotion of research, for instance, into women's health, and containment of HIV infection, is encouraged by U.S. funding.

The protection of human subjects is therefore less a goal in itself than a necessary means or condition of promoting medical research designed to protect the long-term health of populations, some of whose members will be invited to take the risks of becoming its short-term subjects. This is the basis on which Federal Regulations have been amended in recent years, not to relax protections of individual subjects, but to facilitate research on care, for instance, of patients with early childhood diseases and traumatic head injuries. The requirement that research that takes place in foreign countries be conducted under equivalent protection to

that provided by IRBs is intended to promote ethical research, rather than to limit opportunities for research, provided that it be conducted consistently with "any foreign laws or regulations which may otherwise be applicable."[7]

The voluntary assumption of individual risk and the conscientious imposition of communal risk are the conditions of advancing communal health through medical research. As suggested above, an approach may be for Department and Agency heads to be required to classify risk levels in particular proposals for funding, to require local ethics review committees to articulate the grounds of local benefit on which they have found proposals acceptable, and to maintain stricter scrutiny of grounds for local acceptance of studies that are classified as presenting higher levels of risk.

6. Foreign Research Protections Compromised by U.S. Requirements

The conventional concern to ensure equivalent protection of human subjects of research conducted abroad has been apprehension that their well-being may not be as securely protected as are the interests of subjects of research governed by the Federal Regulations. The U.S. Regulations have been shaped in response to experiences, perceptions, and accountabilities concerning persons vulnerable to research-related risks to which governments abroad have not always been equally responsive. The Regulations also reflect U.S. sensitivity to the distributive injustice that medical studies sponsored abroad by U.S. Federal Departments and Agencies may achieve benefits for U.S. patients that populations abroad enjoy only disproportionately to the greater risks they accepted. The criticism is that "[a]s is so often the case, the results will probably find their greatest application in the developed world."[8]

However, recent political developments have created the possibility that foreign populations may find that pursuit of their interests under their local laws and regulations is compromised by provisions that originate in the United States. In 1974, the U.S. Agency for International Development (USAID) initiated a policy that prohibits U.S. funding for "information, education, training or communication programs that seek to promote abortion as a method of family planning."[9] Between 1984 and 1993, this prohibition was interpreted to cover all abortion except in cases of rape, incest, and danger to a woman's life. Late in 1999, omnibus appropriations legislation enacted to release funds toward payment of U.S. arrears to the United Nations had an attached prohibition of U.S. family planning funding of foreign nongovernmental organizations (NGOs) if, even with their own funds, they perform abortions, except in cases of forcible rape, incest, or danger to life. Funding is also prohibited if they engage in activities or efforts to alter the abortion laws or governmental policies of foreign countries, including their own, although they may give counseling about abortion and refer women to other organizations for services. In 2000, these prohibitions govern about $345 million in USAID family planning assistance for foreign NGOs.

Where foreign NGOs seek such funds for research projects that fall under 45 CFR § 46, the question arises whether their subjects have equivalent protection to that enjoyed by U.S. subjects. In the United States, the capacity of NGOs to perform and fund abortions is constitutionally protected and activity and efforts to alter laws are similarly protected, for instance, under rights of free speech, and to political participation in civil society and the democratic process. Further, in medical professional ethics, the Code of Medical Ethics that the American Medical Association adopted in 1980 provides that "[a] physician shall respect the law and also recognize a responsibility to seek changes in those requirements which are contrary to the best interests of the patient."[10] Physicians' ethical and legal responsibilities of advocacy on behalf of their patients[11] are an important element of patients' protection.

Foreign NGOs seeking to promote access to family planning services, particularly in poor countries, may find the prospect of eligibility for U.S. funding of research programs too attractive to forgo. They are clearly bound by prohibitions of their local law, but where this permits abortion they may accept the limits on expenditure of their own money for abortion services, for instance, on contraceptive failures, on which

U.S. funding is conditioned. They may similarly forgo their lawful and democratic rights to inform their own governments of the health burdens women bear due to untimely pregnancies, such as those that are too closely spaced, which access to lawful, safe abortion would relieve. They may also forgo statistical and other demonstrations of how frequently and at what cost the alternative to prohibited lawful abortion is—not childbirth, but unskilled and self-induced unlawful abortion. In short, foreign NGOs attracted to seek U.S. funds for family planning research may find that they have to discontinue and forgo activities that, in the United States, would be considered protective of research subjects who, in the course of research programs, experience health-endangering pregnancies, including those whose continuation endangers the health of their dependent children.

If a Department or Agency head determines that subjects of foreign NGO family planning research enjoy at least equivalent protection to that available for them under U.S. law, particularly when a research subject has a health-endangering pregnancy, the NGO may become ineligible for USAID funding. However, refusal of such a determination will also result in ineligibility, although the inferior protection is a result of U.S. policy, for instance, in barring NGO funding of abortion from its own funds when the procedure is lawful and therapeutically indicated in a subject's health interests. Department or Agency heads may, however, consider the prohibitive attachment to the 1999 appropriations legislation to be an enacted derogation from 45 CFR § 46.

Accordingly, such heads may determine foreign procedures to "afford protections that are at least equivalent to those provided in this policy" under § 46.101(h), except in so far as the 1999 enactment prevents such protections from being offered. The Federal Regulations, authorized under the Public Health Service Act, should be construed as subject to subsequent legislation restricting research funding capacity, even when its effect is to compromise protections that foreign subjects of research would otherwise enjoy in their own countries, provided that local committees knowingly accept funding on this condition.

7. Compliance with Both U.S. and Foreign Requirements

Under § 46.101(a), the Federal policy on Protection of Human Subjects "includes research conducted, supported, or otherwise subject to regulation by the Federal Government outside the United States." It does not necessarily follow from compliance with the procedure under § 46.101(h) for ensuring equivalent protection of subjects outside the United States to that available in the United States that research conducted and reviewed outside the United States will not be liable in addition to IRB review within the United States. Where U.S. institutions' personnel conduct research abroad, such as their faculty members, research staff, and students, the institutions' terms of employment and student regulations may require submission of research protocols to local IRBs. This is consistent with international requirements. For instance, the International Ethical Guidelines for Biomedical Research Involving Human Subjects, issued in 1993 by the Council for the International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization, provides in Guideline 15, on obligations of sponsoring and host countries, that:

> Externally sponsored research entails two ethical obligations:
>
> - An external sponsoring agency should submit the research protocol to ethical and scientific review according to the standards of the country of the sponsoring agency, and the ethical standards applied should be no less exacting than they would be in the case of research carried out in that country.
> - After scientific and ethical approval in the country of the sponsoring agency, the appropriate authorities of the host country, including a national or local ethical review committee or its equivalent, should satisfy themselves that the proposed research meets their own ethical requirements.[12]

The CIOMS Guidelines "are designed to be of use, particularly to developing countries, in defining national policies on the ethics of biomedical research, applying ethical standards in local circumstances, and establishing or redefining adequate mechanisms for ethical review.…"[13] Guideline 15 reflects the supposition of research sponsorship by a more economically developed country, such as the United States, and a developing host country. In 1991, the CIOMS also produced its International Guidelines for Ethical Review of Epidemiological Studies. These contain a comparable provision on externally sponsored research to that in its 1993 Guidelines, and include the explanation that:

> [i]t is in the interest of the host country to require that proposals initiated and financed externally be submitted for ethical approval in the initiating country, and for endorsement by a responsible authority of the same country, such as a health administration, a research council, or an academy of medicine or science.[14]

Advice that the host country should require study approval in the initiating country relates to the legal model of Conflict of Laws and the principle of Renvoi. By this principle, country A respects the law of country B and applies it to an issue involving the jurisdiction of country B, but refers not to country B's domestic law but to country B's doctrine on private international law, or Conflict of Laws. By this, country B may conclude that the governing law on the issue is the domestic law of country A. Accordingly, country A applies its own domestic law, not in disregard of country B's law but because that law requires country A to do so. Whether a judge in country A refers to the domestic law of country B or to its doctrine on Conflict of Laws may be governed by precedent, but where not, the judge will be influenced by parties' advocacy and argument.

The research application of this principle arises when a foreign country, such as a developing country, has no pharmaceutical or medical device regulatory authority or regulations of its own, but only a law providing that, for a drug or device to be imported and used in its territory, the drug or device must satisfy the laws and regulations of its country of origin. This will usually be a more economically and technologically developed country. Accordingly, when a product of U.S. manufacture is proposed for research or use in the host country, that country's own rules require only that U.S. domestic provisions be observed, including those on the protection of human research subjects.

This approach may be ethically unsatisfactory to U.S. authorities. The Commentary on Guideline 15 of the 1993 CIOMS guidelines notes that:

> [c]ommittees in the host country have the special responsibility to determine whether the goals of the research are responsive to the health needs and priorities of the host country. Moreover, because of their better understanding of the culture in which the research is proposed to be carried out, they have special responsibility for assuring the equitable selection of subjects and the acceptability of plans to obtain informed consent, to respect privacy, to maintain confidentiality, and to offer benefits that will not be considered excessive inducements to consent.[15]

When host country authorities simply provide that approval of a research proposal by an IRB in the United States, according to 45 CFR § 46, is adequate for local purposes, a Department or Agency head may determine that local potential subjects have not been afforded at least equivalent protection to that specified in § 46, because its criteria have not been applied to such subjects' special circumstances by committees and personnel with relevant knowledge. Accordingly, it may be recommended that equivalent protection cannot be determined unless an adequately composed ethics review committee in the host country has assessed and approved a proposal.

As against this, a Department or Agency head may claim to be satisfied that the particular facts of a case show that a study raises no special considerations of local health goals, needs or priorities, nor cultural concerns

regarding informed and free consent, privacy, or confidentiality. Local acceptance of IRB approval according to the substance of § 46 may therefore be proposed as appropriate, and to offer local subjects of the study not simply equivalent but identical protection to that required in U.S. domestic policy. This assessment is more easily made when the foreign site of a study is culturally, economically, and otherwise comparable to the United States. However, more immediately comparable countries, such as Australia, Canada, the United Kingdom, and those of Western Europe, have their own regulatory rules and agencies, and their institutions would be unlikely to be able to delegate approval of studies liable to be locally reviewed to U.S.-based IRBs, even though local review processes and principles are similar to those under 45 CFR § 46. For drug studies, the ICH Guideline for Good Clinical Practice goes far to unify standards of review in the European Union, Japan, the United States, and several comparable countries.

The real issues that Department or Agency heads face arise in more exotic and less economically developed countries where health needs and cultural traditions are unlike those of the U.S. mainstream. If there is a comparable community among the diverse populations of the United States through which an IRB can gain adequate input to apply § 46 with faithful reflection of the health priorities, resources, and cultural values and sensitivities relevant to the foreign site, and if a relevant host country institution is able to endorse the authenticity of IRB exposure to indigenous conditions, a Department or Agency head may consider it acceptable to forgo specific local review.

It may remain unclear, however, whether foreign acceptance of U.S.-based IRB approval is influenced primarily by the incentive of gaining U.S. research funds. It therefore appears necessary to require local review, according to satisfactory processes and substantive principles at least as detailed as provided in the Declaration of Helsinki or the CIOMS 1993 Guidelines. U.S. residents with special familiarity with the circumstances of foreign countries may advise U.S.-based IRBs accordingly, but cannot be accepted to replace review conducted in the country in which prospective research subjects live. Conditioning funding on local review appears ethically necessary.

8. Research Monitoring

The Achilles' heel of much research with human subjects is monitoring investigators' compliance with the scientific and ethical undertakings of a protocol. When significant resources are available, investigators' practices may be kept under credible scrutiny. Governmental agencies in the United States can make investigators aware that they are liable to be made to account for compliance with scientific, ethical, and fiscal terms of approval of their studies. Similarly, in significant drug, biological product, and comparable studies, sponsors may establish independent data monitoring boards that keep studies under surveillance in order to ensure the integrity of subject inclusion and exclusion practices, and, for instance, enforce or develop stopping rules, marking points in data acquisition and analysis at which studies would be prematurely ended, or their inclusion, exclusion, and informed consent criteria re-evaluated in light of evolving knowledge of safety and efficacy of outcomes. However, unless governments fund independent review inspectorates for studies they sponsor or, for instance, drug companies allocate an adequate proportion of the several hundreds of millions of dollars they budget for product testing to monitoring of research practices, monitoring may be doubtful.

The purpose and very meaning of "monitoring" may be unclear. Governments may monitor because they are accountable, often through political departmental heads, for the fiscal and wider integrity of projects they fund, and want to avoid funding of projects that cause injury and other harm. Drug manufacturers require monitoring of investigators in order to ensure the reliability of scientific data for submission for marketing approval and for quality control of products, as well as to identify and limit injuries to subjects. If a potentially marketable product is harmful, however, they want that harm to become manifest in scientifically rigorous studies, so that, for instance, risks of and contraindications to use are known. That is, a purpose of testing an unproven product

or therapy is to determine the extent to which it can be used effectively and safely and the extent to which it may cause harm. If testing on human subjects proves the harm of the product or therapy, compensation should be available to victims of that harm to restore them to the condition in which they would otherwise have been, in so far as monetary or other compensation can.

Monitoring may focus narrowly on the process of giving potential recruits information about the purpose and particularly the risks of a study for human subjects and ensuring that consent was freely given and neither coerced nor improperly induced. Coercion may arise, for instance, when a patient's consent is requested by a person on whose good will the patient feels dependent for care or comfort, and undue inducement when a financial or other reward exceeds the gratification that comes from altruism and converts an act of commitment to improved health care into selfish pursuit of personal advantage. Subjects' comprehension and freedom of consent can be monitored by observance of the processes of their recruitment, or, for instance, by asking them by what understanding and choice they came to participate in a study.

A wider view of monitoring may focus on how subjects were medically and otherwise managed, how data of their treatment and responses were recorded, and, for instance, of interim assessment of study outcomes, to ensure compliance with research protocols and identification and appropriate responses to adverse and other unexpected incidents. However, monitoring of adverse incidents shows a limit and potential dysfunction of protective monitoring by IRBs and their foreign equivalents.

By virtue of their composition, review committees include nonspecialists in the field of inquiry and non-scientists. Their understanding of whether a reported adverse incident is grave or minor, expected or unexpected, or study related or nonstudy related will often depend on information they receive from others. Those others may be fellow review committee members with relevant interpretive skills, but will not uncommonly be the investigators themselves. When review committee members depend for their comprehension of the significance of an isolated adverse event on how the investigators assess it, they are not monitoring the investigators. Lay members of review committees do not credibly protect human subjects when they depend on investigators' opinions of whether, for instance, in light of an adverse event, study recruitment or exclusion criteria should be amended or consent information or procedures should be changed. Members may ask investigators pertinent questions, such as whether the incident under enquiry reflects other incidents reported in the scientific literature or in anecdotal accounts, but usually depend on more specialized information than they alone possess to determine whether investigators' responses and proposals, particularly on maintenance or amendment of the protocol, are appropriate.

Even if review committee members could make reliable independent, individual assessments of an adverse incident, they may be unavailable, or, for instance, may have acquired a preclusive conflict of interest. They may have retired or otherwise left the institution that constituted the review committee, or they may be on leave. Despite obstacles to individual service on review committees, however, some feasible assurance of monitoring may be achievable. When review is entrusted to an institutional standing committee, the institution may accept responsibility to provide that its members will review adverse incidents as they arise and subject investigators to periodic review of compliance with their protocols and perhaps to liability without prenotification to random review of their practices and record keeping. Committee members may rotate, so that responsibilities for monitoring fall on members who were not necessarily involved in initial review of protocols, and they will not be engaged full time in committee work. Their task will be to ensure that people with appropriate skills and time undertake more detailed scrutiny of investigators' performance, such as scientific or other administrative staff who serve committees and make factual reports for committee members' evaluation. When institutions responsible for the conduct of research give assurances of monitoring of this nature, Department or Agency heads may find that subjects of research have protection comparable to that provided in the U.S. policy.

Although review committees and committee administrations are responsible for monitoring, they do not necessarily have to devise the means to do so. When submitting their protocols for review, investigators should

be asked what means of independent monitoring of their conduct they propose. Review committees are not bound to accept these proposals and may make alternative or additional requirements. These may be for more frequent reviews of safety and efficacy, or, for instance, more independent monitors. Investigators may be required to include budget items for monitoring in their financial plans, and U.S. funding agencies should expect project funding applications to include such items and related administrative charges to cover monitoring conducted by or on behalf of ethics review committees. Ensuring necessary monitoring by feasible means is a protective responsibility both of host countries and institutions and of U.S. sponsors. Reimbursement of costs of conducting ethics reviews is often an important issue, especially in impoverished host institutions and countries, that includes but transcends monitoring.

9. A New Code of International Practice?

When it is apprehended that review of research protocols in foreign countries is not conducted by appropriate procedures or fails adequately to apply governing principles, it is tempting to offer specific guidance on the minimum review procedures required as a condition of U.S. funding and key principles of protecting subjects from various types of harms and wrongs, including physical, psychological, cultural, confidential, and dignitary, that must be shown to be respected. In the United Kingdom, the Nuffield Council on Bioethics observed in October 1999 that:

> [o]ne of the main responses of sponsoring agents and donors from developed countries to these difficulties in achieving local ethical review has been to draw up additional guidelines and to try and [sic] ensure that studies with developing country partners are adequately reviewed. Despite such efforts, great difficulties remain with effective and efficient implementation of the Guidelines in some developing countries. This situation is unlikely to improve without raised awareness and an increase in open discussion. The development of increased capacity in scientific research partnerships may need to expand to support expertise and experience in ethical review.[16]

There is no scarcity of international guidelines on bioethics. In December 1999, a 20-page, small-print publication identified 62 intergovernmental and nongovernmental international agencies that had produced guidelines on a wide variety of bioethical topics and 29 miscellaneous international texts produced by ad hoc tribunals, congresses, and the like, beginning with the 1947 Nuremberg Code.[17] This Code, with the amended Declaration of Helsinki, the CIOMS 1991 and particularly the 1993 Guidelines and the ICH Guideline, are perhaps the best-known international documents on the ethics of biomedical research with human subjects. The Nuremberg Code ranks as international despite its exclusively U.S. origins because, like the classical Hippocratic Oath, there is widespread acceptance of its overarching inspiration, rather than of each of its detailed provisions. The Declaration of Helsinki and the CIOMS 1993 Guidelines have attracted a volume of criticism, however, and proposals for their reform are in active contention. Among national codes, the U.S. CFR on Protection of Human Subjects, 45 CFR § 46, is the basis upon which many other national codes have been developed, some refining its principles or trying to re-express them in less formidable, intimidating, and legalistic form.

All of the international and many of the leading national codes and guidelines are easily accessible in developing countries in print and electronic formats, so it is appropriate to wonder whether another expression of their key features is required, or helpful, and, indeed, whether a new version proposed as a condition of U.S. funding of research might be counterproductive. The expression “ethical imperialism” is already current in bioethical discourse, and it might be unhelpful to risk its embodiment in a document. Nevertheless, the Nuffield Council asked whether there is a need for a better guide than exists and how it might be developed. The last of the 68 paragraphs of its discussion paper states that:

> [t]here is clearly a very considerable distance between the broadly based principles outlined in international guidance and the practical issues being considered by local research ethics committees reviewing individual protocols. Is the most appropriate way forward to produce 'intermediate' guidelines to link these two levels of ethical assessment and if so, should they be generated by national or international bodies?[18]

The Council perhaps indicated its own answer in its paper's closing sentences:

> The recent debate has stimulated a number of bodies including the Nuffield Council on Bioethics, the World Health Organization, the U.S. National Bioethics Advisory Commission and the U.S. National Institutes of Health to consider some of the issues arising from sponsorship of developing country clinical research by developed countries. The importance of bringing these initiatives together to form coherent guidance has already been acknowledged by many of the bodies concerned.[19]

Beyond possible international collaboration to develop coherent guidance on applying the broadly based principles expressed in existing guidelines to the details and implications of individual protocols are initiatives, international, national, or both, to train personnel in developing countries to lead and guide ethical review procedures in their own institutions and countries. An initial task may be to train the trainers, identifying younger persons of appropriate (but diverse) educational backgrounds who could become their countries' resource personnel in interpreting international guidelines on matters of substance and in constituting adequately composed and staffed committees to conduct ethical review procedures.

Such trainees should be provided with opportunities, as their practical experience grows in their home settings, to collaborate in the refinement of guidelines prepared predominantly in developed countries, to accommodate the particular needs, values, and sensitivities of their own countries and regions, and to explain the impact of prevailing guidelines on promotion of research and protection of research subjects in their countries. They should be facilitated to work with their counterparts in the United States and other developed countries that fund foreign research to adjust regulations for the protection of research subjects to mutual satisfaction and to guide their colleagues at home in their observance. By their contributions, based on experience both of published research guidelines and the circumstances of their own countries, common understandings might be developed between funding agencies and recipient institutions of what research is appropriate and what protections of human subjects are feasible and convincing to funders and recipient institutions alike.

The approach of training personnel to equip developing countries to undertake ethical review of research proposals received impetus on March 13, 2000, when the Fogarty International Center in Bethesda, Maryland, in partnership with many of the National Institutes of Health Institutes, announced its proposal to fund an International Bioethics Education and Career Development award to allow graduates to attend "advanced study courses that primarily focus on the internationally relevant aspects of the ethical, legal and social principles guiding the responsible conduct of research in developing countries, particularly on scientific integrity and the protection of the interests of research participants." The focus on research in low- and middle-income nations would facilitate training of graduates primarily from those nations to become national leaders in the protection of research subjects and promotion of studies that meet national needs.

Reinforcement for recommending funding of the training of such graduates comes from the need to address the criticism that prevailing international research guidelines have emerged from narrow, privileged, and inadequately experienced origins. The Declaration of Helsinki is not alone in warranting the recent observation of its reform process, presented from the perspective of HIV vaccine trials, that:

> a look at the participants lists of virtually all major meetings which discussed proposed changes to the Declaration shows a marked absence of patient representatives…from developing countries.

> Often developing country delegates to such meetings were actually Western researchers working in such countries or they were developing country government representatives with no known expertise relating to clinical trials or research ethics.[20]

Although Western agencies and personnel may propose training individuals in developing countries to conduct research, this does not necessarily mean that these individuals will be equipped to determine for themselves under what conditions research should be internationally funded and conducted in their countries, with due regard for ethical values and the protection of research subjects. An improved process of guideline development, with educated, authentic international collaboration, may resolve several of the conflicts that currently beset the funding of foreign research. Training developing country personnel for such collaboration appears a prudent and timely investment, supporting the integrity of funding and receiving agencies alike.

Notes

1 Further amended in 1996.

2 Nottage, L., 2000, "The Vicissitudes of Transnational Commercial Arbitration and the *Lex Mercatoria*: A View from the Periphery," *Arbitration International* 16:53–78.

3 U.S. Constitution, Article IV(1).

4 Angell, M., 1997, "The Ethics of Clinical Research in the Third World," *New England Journal of Medicine* 337:847–849; Lurie, P., and Wolfe, S.M., 1997, "Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries," *New England Journal of Medicine* 337:853–856.

5 Levine, R.J., 1996, International Codes and Guidelines for Research Ethics: A Critical Appraisal. In *The Ethics of Research in Human Subjects: Facing the 21st Century*, ed. J.Y. Vanderpool, 235–259. Frederick, MD: University Publishing Group.

6 Levine, R.J., 1998, "The 'Best Proven Therapeutic Method' Standard in Clinical Trials in Technologically Developing Countries," *IRB* 20(1):5–9.

7 § 46.101(g).

8 Angell, M., 2000, "Investigators' Responsibilities for Human Subjects in Developing Countries," *New England Journal of Medicine* 342:967–969, 968.

9 Policy Determination No. 56 A.I.D. Policies Relative to Abortion-Related Activities 2 (1974); see now 48 CFR § 752.7016 (b) (1996).

10 American Medical Association, 1980, *Principles of Medical Ethics*; Principle III.

11 See *Wickline* v. *State*, 239 Cal. Rptr. 810 (Cal. Ct. App. 1986).

12 Council for International Organizations of Medical Sciences (CIOMS), 1993, *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, 43. Geneva: CIOMS.

13 Ibid., 7.

14 CIOMS, 1991, *International Guidelines for Ethical Review of Epidemiological Studies*, 23 para. 49. Geneva: CIOMS.

15 CIOMS, 1993, 44.

16 Nuffield Council on Bioethics, 1999, *The Ethics of Clinical Research in Developing Countries: A Discussion Paper*, 11 para 33. London: Nuffield Council.

17 Fluss, S.S., December 1999, "International Guidelines on Bioethics," *Supplement to the [European Forum for Good Clinical Practice] EFCGP News.*

18 Nuffield Council on Bioethics, 20 para 68.

19 Ibid.

20 Schüklenk, U., and Ashcroft, R., 2000, "International Research Ethics," *Bioethics* 14:158–172, 170.

ATTITUDES AND EXPERIENCES OF U.S. AND DEVELOPING COUNTRY INVESTIGATORS REGARDING U.S. HUMAN SUBJECTS REGULATIONS

Commissioned Paper
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Executive Summary

In recent years, controversies have erupted concerning the ethics of biomedical research sponsored by wealthy nations and conducted in resource-poor countries, generating bitter debates and dozens of editorial articles. However, little empirical research has been conducted on the ethics of research in developing countries, and thus little information has been available about the extent and nature of ethical problems encountered by researchers or the application of U.S. human subjects protections to research in these resource-poor settings. This project is the first large-scale study of researchers' experiences with ethics issues and human subjects regulations in the developing world. The results presented in this report should help to identify the key ethical issues and problems encountered by researchers working in resource-poor countries and suggest mechanisms to address these concerns. It is our hope that this report will be useful not only for current policy deliberations, but also to set the stage for further empirical investigation and thoughtful analysis of international research ethics.

This research project was undertaken at the Johns Hopkins University in 1998–2000 to investigate the attitudes and experiences of U.S. and developing country researchers regarding ethics issues and human subjects regulations in developing country research. This project was a collaborative effort between two investigators at Johns Hopkins School of Public Health: Dr. Nancy Kass of the Department of Health Policy and Management and Bioethics Institute and Dr. Adnan Hyder of the Department of International Health. Dr. Kass' study entailed surveying U.S. investigators who work in developing countries, while Dr. Hyder's consisted of parallel methods applied to developing country investigators.

The project involved collection of qualitative data in the form of focus groups and interviews and quantitative data from a mailed survey. Focus group participants were asked open-ended questions about informed consent; about Institutional Review Board (IRB)/ethics board review, both in the United States and in the host country; about ethics issues in their research; and about recommendations for changes in the U.S. regulations. The first focus groups conducted during this study provided qualitative data to help guide the design of the survey instrument, which was largely identical for both the U.S. and international surveys. The topics covered in the survey were the design of the index study; reasons for conducting this study outside the United States;

informed consent; U.S. and host country IRB/ethics board review; researcher attitudes regarding U.S. and other human subjects regulations; ethics issues in international research; and recommendations for changes in U.S. policy and guidelines.

For the U.S. survey, investigators were contacted at a variety of U.S.-based institutions, including academic, military, private nonprofit, private industry, and government. For the international survey, samples were drawn from membership lists of several international professional organizations relating to biomedical research. For both U.S. and international respondents, e-mail was the initial mode of contact for inviting researchers to respond to the survey, which was available on a password-protected website for these respondents. Follow-up mailings were sent through U.S. mail or by courier, and these respondents received a printed version of the survey. The data collected are extensive, including the results of a total of more than 500 completed surveys and 13 focus groups. The findings can be only summarized in this report. (See Appendix A for the U.S. focus group guide and Appendix B for the survey developed for U.S. researchers.)

The collective experiences of researchers in this study demonstrate that consideration of ethics is a part of the culture of international research that is seen as an essential component of conducting scientific investigations. Almost all studies described by researchers underwent review either in the United States, in the host country, or in both; the vast majority of researchers felt that, despite procedural difficulties, U.S. regulations sometimes or always ensure high ethical standards in research; informed consent is practiced by almost all researchers, who believe it to be an essential feature of the research; and researchers frequently stated that the informed consent process provided opportunities to discuss ethics issues with staff. At the same time, researchers noted significant concerns regarding oversight of international research. Current U.S. regulations and IRBs, they believed, emphasize procedural rather than substantive matters of ethics, such as focusing on consent forms rather than on participant understanding. Also, IRBs give little attention to what is owed participants during or after a study. Researchers also felt that U.S. ethics boards require a better understanding of the local contexts of developing countries and that international boards should have a better understanding of ethics. These findings are summarized below.

Informed Consent

There were several major findings in the area of informed consent. Researchers from both the United States and from developing countries demonstrated a commitment to the essential elements of consent, namely informing participants about the research and ensuring that their participation was voluntary. Researchers in both groups, however, asserted that the procedural requirements for informed consent—in particular, written consent forms—are no guarantee of participant understanding and, in some cases, impede the process of explaining a research study. The use of written consent forms for documentation of informed consent was seen as inappropriate by many respondents, especially when used in populations of low literacy. In addition, many respondents reported that in some settings participants felt threatened by the process of signing documents. Other or additional mechanisms were suggested and used for documenting consent, such as oral consent with a witness or a researcher signature. Researchers from both the United States and from developing countries described the use of a variety of methods for educating participants and stressed that the disclosure process must be tailored to fit the community. The vast majority of both U.S. and international researchers felt that more flexibility should be allowed in methods of documenting consent.

Respondents also believed that the complexity and legal language often required on consent forms by U.S. IRBs was a barrier to participant understanding. Respondents in both the United States and the international survey felt that the consent forms often served as legal protection for the researchers and their institutions rather than as protection for the research participants.

Researchers believed that improving participant understanding of research was the appropriate goal, in spite of the challenges involved. Respondents described situations in which potential study participants did not

share Western concepts of health and disease, and researchers, both from the United States and other countries, used creative methods to elucidate biomedical concepts and to convey the essential information about their research studies to potential participants. In many cases, an extensive period of community education and discussion took place before a research study began. Most researchers (65 percent of U.S. and 83 percent of international) were in favor of incorporating tests of participant understanding into protocols, although only 16 percent of U.S. and 27 percent of international researchers actually had done so in practice.

Investigators often described seeking permission or approval from community leaders in areas where a study will be conducted. This approval was seen as essential to the success of the research and as a precursor to any individual consent process. The majority of international respondents and a fifth of the U.S. respondents felt that such approval should be a requirement for conducting research in settings where this is appropriate. International researchers were more likely than U.S. researchers to believe that the consent process is too focused on the individual rather than on the family or the community (66 percent versus 23 percent), and many in both groups (47 percent of international and 37 percent of U.S. researchers) believed that the cultural norms of the study population were inconsistent with individual decisionmaking. Some researchers described how many residents of resource-poor communities look to their physicians to make medical decisions for them and are not accustomed to selecting their own treatments. Also, participants may not distinguish between research and clinical care, although the vast majority of U.S. and international researchers believed that their study participants were aware that they were participating in a research study. Researchers frequently described the difficulty of achieving voluntary participation in a setting lacking basic medical care and other services and where the research involves some direct benefit for participants. Most researchers (about 60 percent of each group) felt that participants joined their studies because of the benefits provided.

The vast majority of researchers, both U.S. and international, viewed the consent process as valuable in educating participants about their research projects. Participants expressed support for using informed consent procedures in all types of research, with more rigorous standards for participant understanding and documentation of consent being used in higher risk studies.

Risks, Benefits, and Study Design

Researchers struggled with issues surrounding the need to balance benefit for study participants with benefits for a larger community. This tension is present in all research, but it is made more acute by the conditions of poverty and by the lack of basic medical care found in many developing countries. Questions of study design and risk-benefit assessment were covered in both focus group and survey questions.

Only 12 percent of U.S. respondents and 5 percent of the international respondents reported that their studies entailed greater than minimal risk for study participants. In the U.S. survey, studies labeled greater than minimal risk were more likely to be questioned by IRBs regarding several issues, including risk, participant voluntariness, and the relevance of the research to the host country. Researchers with studies of greater than minimal risk were also more likely to report that some potential participants refused to enroll after learning about the study. It is reassuring that riskier studies are being scrutinized more closely by IRBs and by potential participants. Also, while the majority of all respondents believed that participants enrolled in their studies because of the benefits provided, researchers with riskier studies were more likely to report that participants overestimated the benefits they would receive. Better education about the nature of the research is needed to eliminate false hopes among study participants.

Many focus group respondents described different types of benefits afforded to participants, including free medical care, health screening or diagnostic tests, and cash reimbursements for travel expenses. Several focus group respondents expressed that, given the poverty of the setting and the lack of access to good medical care, it is understandable that potential participants are eager to join studies. Most researchers (about 60 percent of each group) said that medical care provided was not locally available outside the study.

For more than half of both the U.S. and international respondents, the low background levels of medical care in many settings created problems in determining what treatment to give to control groups. In focus groups, a number of respondents stated that locally available medical care should be considered the acceptable standard for control groups. In the survey, the majority of respondents (77 percent of international and 78 percent of U.S.) believed that the "standard of care" issue should be decided on a case-by-case basis. In general, researchers mentioned the need to balance concern for the well-being of study participants with the overall goal of gaining knowledge through the research that will benefit larger numbers of people.

In addition to difficult questions regarding control groups, researchers grappled with decisions about providing participants with medical care unrelated to the study question. In some cases, medical conditions were discovered during the course of the study, and treatment was provided; in other cases, unrelated care was not provided, while in still other cases, research could not be carried out because the medical care costs would have been prohibitive. Respondents described difficulty determining how much medical care unrelated to the study question was appropriate and feasible, and many mentioned that the U.S. IRBs seemed poorly informed and ill-equipped to help address these questions.

A key question in the design of a U.S.-funded project conducted in a developing country is the rationale for carrying out the study in a poor country rather than in the United States. Seventy-three percent of both U.S. and international researchers expressed a commitment to addressing global inequalities in health, and in some cases this commitment was associated with efforts to provide benefits to study communities after the research had concluded. U.S. respondents even more frequently mentioned as a reason the prevalence of disease in the host country (83 percent), and slightly less often the relevance of the intervention being tested (69 percent). Some practical concerns were also listed, such as lower cost or more rapid enrollment of participants. Interestingly, international researchers were more likely than U.S. researchers to believe that U.S.-funded research was conducted in their countries for pragmatic reasons, such as the need for marketing approval in that country (25 percent of international versus 12 percent of U.S. researchers) or U.S. strategic interests in the region (49 percent of international and 32 percent of U.S.). For both groups, however, these reasons were listed least often, compared to other reasons for working in developing countries.

In focus groups, some respondents described how they chose the countries for their research. Some pharmaceutical researchers made candid remarks about the ease of access to large numbers of patients; in the case of HIV research, researchers sought patients who had not had prior drug treatment. Several pharmaceutical researchers commented that completing their clinical trials rapidly was one of their main concerns, given the time pressure under which they work. Some of these respondents mentioned that the products being tested would not be available to the host countries after the research, but that the benefits provided to the study participants during and after the trial (which were otherwise not available) justified, in their minds, the conduct of the research in the resource-poor setting.

In addition to benefits provided during the research, researchers were asked what benefits accrued to host communities and countries after the research has ended. In the survey, roughly 40 percent of both U.S. and international researchers were conducting intervention studies. Of the U.S. researchers, 67 percent had plans to provide the intervention to some developing country residents at the conclusion of the study, while 92 percent of international researchers had such plans. Most often, for both U.S. and international respondents, the intervention was or would be provided to the study population; in some cases it was or would be provided to larger groups, such as the study community or the entire country. In the U.S. survey, the interventions being provided to the entire country were more likely to involve funding by the host country government. It would be valuable to study further those cases where the interventions were made widely available to see if useful models for negotiation and funding could be derived from these cases and if those interventions entailed lower cost, available infrastructure, or mechanisms for producing the intervention in the host country.

While the majority of international intervention studies had plans in place for distributing successful interventions, many researchers in the U.S. survey commented that this should not be a requirement for projects conducted in developing countries. International respondents were more insistent that such arrangements should be a prerequisite for conducting research; in the survey, three-quarters of the international respondents and half of the U.S. respondents agreed with this principle. In written comments at the end of the survey, many U.S. researchers remarked that an absolute requirement to provide an intervention would be an impediment to much research and would ultimately be more harmful to resource-poor countries. Furthermore, many stated that funding agencies would never be willing to fund research that entailed providing treatment at the end of the study. But the numerous plans in place to provide post-study interventions demonstrate that, in many cases, such arrangements are valued and are feasible. Many international focus group respondents expressed a strong belief that effective interventions should be implemented in the host countries and that U.S. or other foreign sponsors have an obligation to give something back to the countries that hosted their research projects.

Capacity building was discussed extensively by both international and U.S. researchers. U.S. researchers frequently said that their research depended upon effective collaborations with developing country scientists and that appropriate study design and communication with study communities could not be accomplished without these liaisons. Similarly, international respondents saw themselves as a crucial bridge between their own countries and Western researchers, because they are familiar with the political and cultural contexts of their own societies and are also well versed in the practice of biomedical research. Several international respondents expressed a sense of responsibility toward their home countries, to ensure that appropriate research is conducted and that ethical standards are followed. The majority of both U.S. and international researchers reported that developing country colleagues were involved in every step of the research process, from grant writing to recruitment of participants. Developing country scientists, however, were much less likely to participate in the more intellectual tasks, such as grant writing and data analysis, and were more likely to be involved in field operations. Both U.S. and international researchers mentioned a need for developing country scientists to be given opportunities to develop more substantive skills, particularly in the area of grant writing. The ability to procure funding for research projects through grant writing would enable developing country researchers to gain more control of the research agenda and to design and to conduct the studies in their own countries.

Both U.S. and international respondents also felt that ethics review should be a part of capacity building and that host countries with more experience in ethics review became more capable in this regard. Several respondents suggested specific training for ethics review for developing country IRBs.

A further element of capacity building is deciding which study-related resources will be left in the host country at the conclusion of the research. While practically all researchers left behind some type of resource, the nature of these resources ranged from medical equipment and supplies to buildings and water systems to better trained personnel. Many respondents stressed the fact that resources are only significant if trained personnel are on hand to utilize them.

Review and Oversight

The final topic in this report is oversight of research, including both U.S. and developing country IRB/ethics board review and the regulations and guidelines in place governing such review. The vast majority (91 percent) of studies reported by U.S. respondents underwent U.S. IRB review, and most, but not all, reported that a host country IRB also reviewed the study. In the international survey, significantly fewer (55 percent) of U.S.-funded studies underwent U.S. IRB review; of those studies that were not reviewed, two-thirds were funded by U.S. nonprofit organizations and one-third were funded by U.S. private companies. Although 97 percent of U.S. researchers said that U.S. regulations sometimes or always ensure high ethical standards in research, both U.S. and international researchers saw a great need for improved functioning of U.S. IRBs and a need for more

appropriate regulations with regard to developing country research. The issues raised by U.S. IRBs tended to be procedural in nature, such as the need for translations of consent forms and for letters of approval from developing country representatives. Less often, issues relating to fundamental ethics concerns were raised. U.S. focus group participants reiterated this theme, stating that many times U.S. IRBs were excessively bureaucratic and unhelpful in addressing true ethical dilemmas in their research. Comparison of host country IRB review with U.S. IRB review in the U.S. survey showed that similar issues were raised by both boards. In focus groups, however, U.S. researchers pointed out that developing country IRBs are crucial to ensuring that the research is conducted appropriately and that it is relevant to the country's needs and sensitive to local cultural and political conditions.

U.S. researchers expressed frustration with U.S. IRBs that did not seem to understand the realities of life in developing countries imposing inappropriate and unrealistic requirements. Sixty-six percent of the U.S. and 58 percent of the international researchers felt that U.S. IRBs were more concerned with politics than with protecting the interests of research subjects, and the vast majority of both groups of researchers felt that U.S. IRB regulations were insensitive to local cultural norms and traditions outside the United States. Researchers from both groups suggested in focus groups that for U.S. IRBs, education was needed in the realities of life in developing countries.

The vast majority of U.S. and international researchers felt that developing country investigators sometimes or always relied on U.S. human subjects regulations for guidance, while 77 percent of international and 64 percent of U.S. researchers felt that use of international guidelines was more appropriate than U.S. rules and regulations.

Ethics review in the host country was highly valued by most respondents: 85 percent of international and 77 percent of U.S. researchers felt that a developing country review should be required for all studies in those countries; both U.S. and international respondents in focus groups noted that more ethics training is needed for host country review boards. Most researchers reported that host country review had occurred at a collaborating institution, and a minority reported review at the national or provincial level. About one-third of the IRBs, researchers believed, were established because of the U.S. regulations requiring local ethics review. Sixty-three percent of international and 79 percent of U.S. researchers believed that host country ethics boards were more concerned with politics than with protecting research subjects. In focus group discussions, international researchers commented on the establishment and evolution of IRBs and ethics review capacity in their countries. Countries and regions that had more experience with research also had more experienced and effective review boards. Many respondents mentioned that host country review boards may be reviewing the science as well as or instead of the ethics of a proposal, while some commented that political considerations and financial gain were at stake in some host country reviews. Several international respondents commented that host country governments, as well as IRBs, need to be educated about ethics review and ethical issues in research.

A number of international respondents mentioned that there is currently no monitoring by IRBs or other agencies to ensure that research studies are actually being carried out according to the approved protocols. Examples were given where studies were conducted without appropriate follow-up procedures, and respondents remarked that there was no method of enforcing the guidelines set forth by the IRBs.

Another consideration raised by both U.S. and international researchers was the need for funding to support the work of host country IRBs. Since educated professionals are in great demand in many developing countries, these professionals may be taking time away from their many other responsibilities to serve on ethics boards, often with no compensation for time or travel expenses. In addition, funds often are needed for practical functions, such as computers, photocopiers, or other office equipment. A strong majority of all researchers agreed that U.S. funding agencies should support host country IRBs (85 percent of international and 70 percent of U.S. researchers concurred).

In the U.S. survey and in focus groups, extensive discussion was generated on the topic of Single Project Assurances (SPAs). SPAs have the aim of ensuring that an ethics board is constituted in the host country

according to U.S. guidelines and performs a review based on principles laid out in the U.S. regulations. Researchers who spoke on the topic of SPAs almost uniformly criticized the SPA process as time-consuming, overly bureaucratic, insulting to foreign governments, and ineffectual in ensuring an adequate ethics review or in protecting research subjects. Several focus group participants mentioned that the procedure was considered insulting and imperialistic by many developing country governments. In addition, because the SPA is tied to the funding for a project, new SPAs need to be obtained when funding changes, but not when protocols change. Also, researchers described interactions with staff from the National Institutes of Health's (NIH's) Office for Protection from Research Risks (OPRR) that revealed the agency's lack of experience and knowledge of developing country conditions. Respondents had no objection to the principle or goal of a substantive ethical review to be carried out in the host country, but felt that the SPAs did little or nothing to further this goal. Half of the U.S. respondents and 29 percent of the international researchers felt that the SPA procedure should be eliminated.

Recommendations

Based on our findings, we offer the following recommendations:

1. *Informed consent is central to the research process and is supported by developed and developing country researchers as a leading principle.*

Quantitative and qualitative data from both projects suggest that researchers agreed overwhelmingly that informed consent is important and necessary in the conduct of research. Researchers described it as both a means to educate participants about the study and to raise ethics issues with study staff.

2. *There should be greater flexibility in the means of informing participants about research and in the methods of documenting consent in international and collaborative research.*

While clearly valuing informed consent, many researchers were frustrated with how narrowly consent requirements have been interpreted by most U.S. IRBs. For these researchers, the goal of informing participants is not negotiable, but the means for doing so should be flexible. Methods generally should be sensitive to cultural norms and levels of literacy in the local community, and researchers in their applications to IRBs/ethics boards should justify their choice of methods.

3. *Tests of understanding should be incorporated into research studies.*

Respondents to our survey and focus group participants overwhelmingly thought that participant understanding was the appropriate goal for informed consent procedures. Ultimately, research can go forward only if participants understand what the research entails. While there was overwhelming support for trying to assess participants' understanding, most researchers admitted that they had never conducted such a test themselves. Regardless of the methods used for consent, the test of understanding will reveal the success or failure of efforts to communicate the study's procedures, risks, and benefits to the study population.

4. *All research studies concerning any topic, if they involve human subjects, should be reviewed by an appropriate ethics board, although review should be streamlined based on a study's level of risk.*

There may be cases where reviews are hastened to meet a deadline or a waiver granted after preliminary review (for secondary data analysis or extremely low-risk studies), but all studies, regardless of topic and method, need to be reviewed. The notion that studies pertaining to social sciences, especially anthropological sciences, and those involving qualitative research methods do not need to be reviewed must be negated. Some of the most sensitive issues of human interactions are raised in such studies, and risks arising from breaches of confidentiality, particularly in certain countries, can literally be life threatening.

Rather than determine whether review should occur based on a study's discipline or method, IRBs should streamline their review based on the level of *risk*. Riskier studies should have more rigorous and detailed reviews and should similarly require more justification from researchers, more thorough consent processes, and a higher threshold of participant understanding.

5. *Studies involving international collaborations need to be reviewed in both/all countries.*

All studies that involve collaborative research must be reviewed in both the United States and the host country. The United States has certain cultural and legal standards that require certain practices or approaches; host country boards are expected to be more cognizant of appropriate methods for informing participants, to be more aware of certain types of risks that would be overlooked by U.S. boards, to be more aware of what level of benefit is realistic to provide, and to be more attuned to the health priorities of their own countries.

6. *U.S. IRBs should gain greater expertise in the realities of life in a developing country.*

Many U.S. researchers expressed frustration with unrealistic requirements raised by their U.S. IRB that, to them, revealed their IRB's ignorance about field realities in a developing country. Having someone on the U.S. IRB with international experience is helpful or having, instead, an outside consultant to provide guidance can begin to address this problem. Moreover, even a short "in-service" training for U.S. IRB members and staff on how local conditions and/or beliefs might affect issues of research review, consent, expectations, or host IRB working conditions would be helpful.

7. *Host country ethics boards should gain additional experience in ethics.*

Many U.S. researchers voiced concerns that host country boards had little familiarity with ethics. Thus, when ethics boards convened, they focused on other issues where they felt more comfortable, such as the scientific design or the budget. While researchers should consider providing mechanisms for ethics training along with other types of training to their colleagues, funding agencies similarly should devise mechanisms for increasing ethics capacity in local countries.

8. *Collaborative research studies should be monitored at periodic intervals to ensure that procedures stated in the protocol are being carried out as planned.*

While IRBs and collaborating institutions can require certain ethical principles to be upheld in the design and planning of a research project, if the plans are not carried out as promised, the safety and interests of the study participants can be compromised. A mechanism must be put in place to ensure that appropriate study procedures actually are followed.

9. *Capacity building should be integral to any study.*

Research collaborations occur between rich and poor countries, not only because poor countries cannot afford to finance the studies, but often because there are not enough people trained locally to design, collect, and analyze data. It should be the U.S. researcher's goal to encourage capacity building during every research collaboration, such that ever-increasing proportions of study staff are local residents.

10. *The study population or community must benefit as a consequence of the study, and mechanisms to ensure this must be discussed and/or developed as part of the study proposal.*

All researchers, especially international researchers, overwhelmingly agreed that the study population must benefit as a consequence of research conducted within that community. They also encouraged the exploration of mechanisms to ensure that the benefits of research actually reach these people and promoted the inclusion of such discussions in the early stages of thinking about research.

Researchers believed, however, that consideration of future benefit should not be their responsibility alone. Innovative mechanisms must be devised for encouraging researchers to engage donors and aid agencies or service delivery organizations in discussions about realistic interventions before a study is initiated. Although researchers do not need to shoulder this responsibility alone, it still may not be appropriate for funders to support research where no one is taking responsibility for working on future access to effective health interventions.

A. Introduction

This report describes a research project at the Johns Hopkins University School of Public Health on human subjects regulations and ethical issues in developing country research that was commissioned by NBAC. The project involves the collection of information from researchers both in the United States and in developing countries who are involved with human subjects research in developing countries to ask about their experiences with U.S. regulations and guidelines and with ethical issues in their research. The project is an important component of the information being used by NBAC in making policy recommendations concerning international research. The sample of U.S. investigators and their developing country collaborators has direct experience with the application of human subjects protections to international research and is aware of the benefits and limitations of these regulations in practice.

To our knowledge, this is the first federally funded comprehensive study of researchers' attitudes and experiences in international research ethics. In 1994, Lane Porter and Lawrence Gostin of Georgetown University, Washington, D.C., wrote a report entitled "The Application of United States Protection of Human Subjects Regulations and Ethical Principles to United States Funded or Conducted HIV-Related Research in Foreign Countries" (Porter and Gostin 1994). The authors sought information through personal communications, interviews, and letters of inquiry from U.S. researchers, U.S. administrators, host country administrators, and host country researchers. The number of respondents was small—20 substantive narrative responses, with 12 quantitative responses. The report was not officially published, and it is unclear if its recommendations were formally used within the federal structure.

Porter and Gostin's study covered three issues: legal and ethical issues, practical issues, and special characteristics of HIV-related research. The section on legal and ethical issues was the most comprehensive and was organized further into eight areas: informed consent, confidentiality, establishment of local review boards, application of U.S. legal and ethical requirements, legal and ethical conflicts in collaboration, ethical reasons for foreign research, vulnerable populations, and research benefits and distributive justice.

A small-scale survey study was conducted by Alison Wichman and colleagues of the Office of Human Subjects Research at NIH, published in 1997 (Wichman, Smith, Mills, and Sandler). They surveyed 55 U.S. investigators working on collaborative research regarding the use of international SPAs. The response rate was 80 percent, and several of the findings of the study are pertinent to the current project.

There was strong concurrence (93 percent) among the researchers surveyed that U.S. investigators bear some responsibility for the protection of human subjects who participate in their research projects in other countries, even if they have no direct contact with these subjects. The researchers by and large placed a high value on IRB review in the country hosting the research project; 84 percent felt that on-site review was important in international collaborative studies. Agreement was not as strong (64 percent) that provision of educational materials about IRBs in collaborators' native languages would improve the system, and fewer than half the researchers (43 percent) considered that use of international guidelines such as the Council of International Organizations for Medical Sciences (CIOMS) would be more appropriate for international collaborative projects. Almost three-quarters (73 percent) of the respondents reported that researchers in other countries had refused the opportunity to collaborate because they did not want to negotiate an SPA.

Wichman and colleagues noted that the number of respondents to the survey was small and that the survey suggested some possible drawbacks of the current system, including inhibition of international collaborative research; difficulties in fostering good working relations among researchers; and an unfounded belief that the current international SPA process is fulfilling its important, intended goals.

In a review of the literature, no other empirical studies were found on the subject of researchers' experiences with human subjects regulations and ethical guidelines in international research ethics. Many of the recent publications in this arena are editorial pieces, and approximately 60 percent of the articles address the issue of HIV/AIDS, especially in Africa. Relatively little has been written about the interaction of Western clinical research ethics with non-Western cultural norms and how conflicts that might arise from cultural differences are being resolved.

This study consisted of two components: a study of U.S. investigators who work in developing countries and a parallel study of developing country researchers, some of whom have experience working on U.S.-funded projects. Quantitative and qualitative methods of data collection were used, through the conduct of a self-administered written survey and focus groups and in-depth interviews. In both methods, participants were queried on informed consent procedures; ethical reviews both in the United States and in developing countries; availability of interventions; ethical challenges faced by researchers; and U.S. and international ethical rules and guidelines.

U.S. investigators from four different sectors were included in this project: academic, military, government, and private industry. The investigation of developing country researchers' attitudes and opinions in this exploration is seen as an integral component of the study. The purpose of this effort is to gain an insight into their perspectives on research ethics, as they work on projects funded by U.S. sources or in collaboration with U.S.-based investigators. It is recognized that there are cultural, socio-economic, and governmental differences in these settings, which may affect the conduct of research. Such realities, which should be identified, may not be apparent even to U.S. researchers with experience in developing countries. The agenda, objectives, motives, and interests of developing country researchers may be different from those of their collaborating U.S. investigators in conducting a specific research project. These differences in perspective and actions made it essential to include a study of developing country researchers as well as those from the United States.

Results from the developing country component are presented in a separate section from those of the United States. Comparison of the two study groups is presented in a separate section, followed by recommendations for changes in U.S. policies regarding international research, based on the data in this study.

The main purpose of this data collection was to provide NBAC with a broad range of opinions and experiences relating to human subjects regulations in international research. Data has also been collected concerning the nature of ethical issues that researchers confront in developing country collaborations and their own recommendations about how human subjects regulations could best protect the interests of research participants in resource-poor settings. It is our hope that NBAC's recommendations for changes in U.S. policies and regulations will be more appropriate and effective based on the extensive data on researcher experiences presented in this report.

B. Methods

B.1 Methods Used for the Study of U.S. Investigators

There were two sources of data for the survey of U.S. investigators. Focus groups were conducted with U.S.-based researchers who conduct research in developing countries, and a written survey was distributed to similar researchers. Both focus groups and survey methods were reviewed and approved by the Office of Management and Budget (OMB) under the Paperwork Reduction Act and by the Johns Hopkins School of

Public Health Committee for Human Research, the IRB of this division of the university. The methodology for each form of data collection is described in this section.

B.1.1 Focus Groups

Focus groups were convened with researchers in four employment sectors: academia, the U.S. government, the U.S. military, and the pharmaceutical industry. All but one focus group were homogeneous with regard to the sector from which participating researchers were drawn. There were seven groups in total: one with academic researchers, one with military, two with government agency employees, two with private industry researchers, and one mixed group. Focus group participants were recruited through professional contacts and through referrals at different institutions. Researchers were eligible to participate in a focus group if they had experience conducting human subjects research in developing countries.

In each focus group, confidentiality procedures were described to participants, and their consent was obtained for participation and for recording the session. Participants were informed that data would be reported without using names of individuals or institutions and that broad, region names (e.g., continent) would be substituted for country names where appropriate, to protect confidentiality.

The Focus Group Guide

The focus group guide consisted of open-ended questions that were asked in every group. Then, consistent with focus group methodology, additional, follow-up questions were asked spontaneously based on participant responses and focus group discussion. The questions on the focus group guide were based on the stated interests of the funder (NBAC) on the literature concerning international research ethics, and, iteratively, the guide was modified after each focus group discussion if new ideas were raised by participants. Topics covered in the guide included informed consent procedures, U.S. and host country ethics review, developing country collaboration, attitudes about existing U.S. human subjects regulations, and types of ethics issues that arise in their work. Focus group participants also were asked to make recommendations concerning whether any changes should be made to current U.S. human subjects regulations. A court stenographer was present during every meeting to create a written transcript of the discussion. Participants received no compensation for their participation, other than refreshments.

Analysis

Focus group transcripts were read in their entirety by three members of the research team to identify relevant themes. Transcripts were then coded by two members of the team according to the major themes and sub-themes identified. Coded data were entered into one of two software packages: NUD*IST and Atlas/ti®. Data then were summarized according to each theme.

B.1.2 Written Survey

Survey Design

The survey instrument was designed based on the literature concerning international research ethics and using qualitative information generated in focus groups. The survey was reviewed by NBAC commissioners as well as by epidemiologists, international health researchers, and ethicists from academic, government, and/or private industry institutions, and it was revised accordingly. Limited pilot testing was conducted to determine the amount of time required to complete the survey. The final survey was professionally typeset and printed in a booklet and was transferred to a website by information systems staff of the Johns Hopkins University.

Sampling Frame

There were multiple sources of names for the survey's overall sampling frame. The first source used was the CRISP (Computer Retrieval of Information on Scientific Projects) database of NIH. The CRISP database contains the principal investigator's name and institution, the fiscal year of funding, and an abstract describing the

research of NIH-funded projects. This database was searched systematically, using developing country names as search terms one by one to compile a list of NIH-funded grantees whose projects were in developing countries. Each abstract identified was then read and coded for eligibility. Eligible research was defined as a "developing country research project involving human subjects." Laboratory studies were included only if they involved primary collection of human tissue samples in a developing country; otherwise they were excluded. To define "developing country," a developing country list was taken from a 1996 World Health Organization (WHO) report, "Investing in Health Research and Development" (WHO 1996). There were 252 potential respondents from this CRISP list, most of whom were university-based researchers.

University-based researchers also were recruited through university websites for descriptions of faculty research projects. Universities were selected based on their reputation for conducting international health research and/or their having received funds from the NIH's Fogarty International Center (FIC). Searching university websites yielded 269 researchers who had described some type of human subjects research in developing countries.

The remainder of the sample was recruited through personal contacts. A professional contact in the U.S. military, Dr. Edward Lane, Deputy Director of Navy Medical Research and Development, provided the names of commanding officers of U.S. and overseas research centers, who were contacted and informed of the survey. These commanding officers then forwarded names and e-mail addresses of researchers in their command who they felt would be relevant survey respondents. There were 23 respondents in this group.

Similarly, professional contacts at two federal agencies provided names and e-mail addresses of researchers willing to be contacted about the survey project. Eighty-five U.S. government intramural researchers were on this list. Federal government intramural researchers also appeared, although in relatively small numbers, in the NIH CRISP database described above.

Forty-six surveys were provided to personal contacts at three pharmaceutical companies for distribution to relevant researchers. In addition, the names of 52 researchers with private industry affiliations were obtained from the membership list of an internationally oriented professional association.

Additional respondents were referred by professional contacts at several different organizations and institutions, resulting in 139 additional names to the list of potential respondents from universities and 74 from private nonprofit research groups. One professional university-based contact provided a list of potential respondents, representing a variety of institutional affiliations. There were 34 names in this group.

Survey Distribution

For all potential respondents for whom we had an e-mail address, initial contact was made by e-mail. A disclosure letter was sent describing the project, the survey itself, and the confidentiality procedures. Included in the disclosure letter was the website address for the electronic version of our survey, along with a unique ID code for each respondent to use when logging in. Researchers who did not fill out the survey online were sent a paper disclosure letter and paper copy of the survey by U.S. mail, approximately four weeks after the initial e-mail had been sent. Following this mailing, two reminder e-mails were sent, as was a second paper copy by U.S. mail.

The first 362 respondents were also asked to provide the name and contact information of a project director or project coordinator on their staff who had coordinated one of their developing country projects. When paper copies of the survey were mailed to primary respondents, a second copy of the survey was included for the project director and was marked as such. A specific ID code was used for project director surveys in order to track the response from this group. After receiving a limited number of surveys from project directors, this strategy was discontinued, and, thereafter, primary respondents received one survey and were not asked for contact information regarding their staff.

Incentives to Survey Respondents

A U.S. $25 incentive was offered to respondents if they filled out and returned the survey either online or by paper copy. Respondents were eligible to receive the U.S. $25 if they answered all the "required" questions on the survey (approximately half of the questions), which were marked in color on the website and with bold numerals on the paper copy. A statement at the top of each page of the survey reminded respondents that they must fill out all required questions to receive the U.S. $25. At the end of the survey, respondents were asked to provide a mailing address on a separate sheet for receiving the U.S. $25 check. The payment was available to all respondents except those who work for the federal government and those who are forbidden by law to receive outside remuneration for services related to their employment.

Confidentiality Procedures

The survey itself does not ask respondents for their names, addresses, or institutions, and data are identifiable only by ID number. In addition, in order to protect respondent confidentiality, specific steps were taken when receiving both website and paper copies of the survey. In the case of paper copies, the name and mailing address at the end of the survey (provided to receive the U.S. $25 reimbursement) were separated from the paper copy prior to any data editing or data entry and were stored in a separate file for subject reimbursement. For website surveys, the names and addresses provided for reimbursement were printed separately from any part of the survey data and were not included in the data transferred to STATA® for statistical analysis. For purposes of survey follow-up, a master list of ID numbers, names, e-mail addresses, and mailing addresses was maintained in our address database, which was kept separate from our survey responses database. Once recruitment and survey follow-up were complete, ID numbers were removed from the address database so that survey data could never be linked with identifiers

Qualitative Data from Survey

At the end of the written survey, researchers asked two open-ended questions. The first question was whether they wished to elaborate on any of the closed-ended survey questions that they felt required more detailed responses; the other asked them to describe changes that they would make to the existing U.S. policy and regulations regarding human subjects research in developing countries.

Data from United Nations Human Development Indicators, Human Development Report

In order to assess the relevance of the host country's level of development for collaboration and capacity building and other ethical issues, the United Nations Development Programme (UNDP) Human Development Index (HDI) was incorporated into the survey database, after data collection had been completed (UNDP 1999). The HDI is a composite index consisting of life expectancy at birth, adult literacy rate, and adjusted per capita income. Each country reported by researchers as the site of their index study was assigned the appropriate HDI value (data obtained from the UNDP website). The new variable, HDI, was used in statistical analyses to determine if different levels of development were associated with other survey variables of interest.

Statistical Analysis

The database containing website responses was created using Microsoft Access 2000. Every week, new data were received from the website and converted into STATA®, Version 6. For quality control, data from the website were checked, and errors with skip patterns and/or incorrect codes were corrected during data cleaning. Participants who logged in to the website but answered three or fewer sections of the survey were excluded from the analysis. After these records were deleted, 190 records were included from the website.

Data from mailed surveys were entered manually using EPI-INFO, Version 6.04b. For quality control three steps were used:

i. ***Data editing:*** Surveys received through the U.S. mail were checked for errors before being entered in the data set. A "Data Editing Protocol" was used to ensure uniformity among data editors. The surveys were

checked for errors in skip patterns. If unanswered questions were found, the codes for missing values were assigned, and each survey response was circled in red to facilitate data entry.

ii. ***Data entry:*** Once the surveys were edited, they were entered into the data set. A "Data Entry Protocol" was created for data quality control purposes, to ensure consistency among data entry staff and to minimize errors. Additionally, legal values and skip patterns were programmed in the data entry file to reject invalid entries.

iii. ***Double data entry:*** As the final step for quality control, all data were entered twice, by two different data entry staff. Data were entered in two different files, then a validation test was performed using EPI-INFO. The validation test compared the files and reported differences. When differences were observed, the Data Manager checked the original record in question and corrected the data set appropriately. A total of 138 surveys were received as paper copies and entered in the EPI-INFO file. Once errors were fixed, the data was transferred to STATA® format, and appended to the database that contained the data from the web. The final data set contained 328 records.

Data Analysis

Statistical analysis was conducted using STATA®, Version 6. Descriptive, univariate statistics were generated for all survey variables. Bivariate analyses were conducted for all demographic variables by the other survey variables, as well as for multiple other comparisons of interest. To evaluate differences in proportions, the Chi-square, Fisher Exact test (if fewer than five in cells) were used, and p-values were generated to evaluate levels of statistical significance. Risk ratios and 95 percent confidence intervals were presented as the measure of strength and direction of the association. Stratified analysis was conducted to identify confounding effect or effect modification. Finally, multiple logistic regression models were used for multivariate analysis to predict certain outcomes of interest.

B.2 Methods Used for the Study of Developing Country Researchers

The study involved collection of both qualitative and quantitative data from developing country researchers with human subjects health research experience. The quantitative arm of the project was a (written) self-administered survey. The qualitative data collection was a series of in-depth interviews and focus groups conducted with developing country health researchers. Both methods of data collection were reviewed and approved by OMB under the Paperwork Reduction Act and by the Johns Hopkins School of Public Health Committee for Human Research, the IRB of this division of the university.

Quantitative (Survey)

Slightly more than 500 developing country health researchers working with human subjects were invited to participate in the survey, which was made available through a website that could be accessed by the researchers, who were given individual identification codes. E-mail attachment and hard copy versions of the survey were also made available to the researchers. The survey consisted of 9 sections with a total of 169 questions, covering IRB reviews; informed consent; relationships with collaborators; availability of interventions; ethical issues; U.S. and international rules and guidelines; description of the researchers' research studies (and experiences); and their recommendations.

Qualitative

Eight in-depth interviews and six focus group meetings were held with researchers from developing countries. They were questioned about their experiences with human subjects research regulations and with ethical issues in their research work collaborating with the United States and other countries. Their recommendations for change in U.S. regulations and policy concerning international research were also sought.

B.2.1 Quantitative Data Collection

Sample

In the process of identifying developing country researchers, the phrase "developing countries" requires explicit definition. Although it is a widely used concept in international health discourse, this term has both very general and specific meanings. In general, it refers to the group of countries marked by poverty, high burden of disease, and poor socio-economic development. It is often used synonymously with less industrialized third world and poor countries. Specifically, the term "developing country" may refer to an income-based social or demographic definition that allocates a country in that category. Each of these definitions is available in the literature and has its own perceived benefits.

For the purposes of this study, a developing country has been defined using the criteria adopted by the WHO's Ad Hoc Committee on Health Research Relating to Future Intervention Options (WHO 1996), a global effort to evaluate health research and development needs that represents an appropriate reference for purposes of the current survey. The definition used by this committee was based on the demographic development of the country, and this same definition has since been used in the Global Burden of Disease and Injury Study (Murray and Lopez 1996) as well. A list of these countries is included as Appendix C.

Tens of thousands (if not more) of developing country health researchers work with human subjects. It is neither possible to enumerate such a universe nor to assess it with a statistically representative sample. For the purposes of this study, we intended to secure a "measurable universe" of developing country researchers who could be expected to reasonably represent the true universe. A sample from such a list would then comprise the sample for the survey.

Because no single database lists all such developing country researchers, multiple information sources were used. A number of key organizations were identified based on their work with developing country researchers. Information was then obtained from these organizations to construct a master list of researchers. These organizations included the following:

1. The International Clinical Epidemiology Network (INCLEN)
2. The Council on Health Research for Development (COHRED)
3. Scientists for Health and Research for Development (SHARED)
4. Health Systems Trust (HST)

INCLEN was originally an organization for clinical epidemiologists largely from the developing world, but has since expanded to incorporate other sectors of public health. Members of INCLEN, especially those who are faculty, are mostly involved with human subject research on health issues. Many of the members work with international (including U.S.) collaboration and have established clinical epidemiology units that conduct continuing research in these countries.

COHRED continued the work of the global commission of the same name, which put forth the concept of "essential national health research." It focuses efforts at the national level for the development and implementation of health research agendas in the developing world. COHRED staff come from the health research community and are usually active in human subjects research. A majority of COHRED's database of approximately four thousand addresses are of researchers living in the Southern Hemisphere.

SHARED is a public-access repository of health research in the developing world. It contains information, by country and topic, on health research projects in many parts of the developing world. It covers the description of the project, personnel, collaborators, and funding sources.

HST is an independent nongovernmental organization (NGO) in South Africa. HST focuses on research, equity, and essential national health research and collaborates with international groups, including COHRED and SHARED. A total of 31 researchers' names were downloaded from the HST website, representing a relatively small portion of the Master List.

Each of these organizations provides a different perspective to the database, contributing to the diversity of researchers who have experience with laboratory, public health, behavioral, and clinical research. Together, these organizations also provide a wide coverage of different regions of the world, all of them focused on the developing world.

Other organizations contacted include the Global Forum for Health Research and the WHO Special Program for Research and Training in Tropical Diseases. Due to several constraints, their databases could not be used for this study.

INCLEN, COHRED, and SHARED, the three major organizations from whom we obtained our list of researchers (either directly or through their websites), were informed of the purpose of the project and of our intent to disseminate the survey to their members. We received approval from all three organizations to contact the researchers for the survey.

A master list was created from these databases after duplicate names, nonhealth researchers' names, and those without e-mail addresses were removed. If there were more than two researchers from the same department of the same institute or organization, they were randomly deleted as well. To our knowledge, this was the first time such a list of developing country researchers had been constructed.

For this study, all the developing countries were divided into three regions—Asia, Africa, and Latin America—according to their geographical location. One of the goals of the study was to ensure adequate representation from all regions of the developing world.

Survey Design

The survey instrument used for developing country researchers parallels the questionnaire developed for U.S. researchers, with appropriate modifications. (See Appendix D.) It contains similar themes for which information is requested from the researcher to enhance the comparability of the two surveys.

The survey is divided into 9 sections with a total of 167 closed-ended questions and 2 open-ended questions and covered the following topics:

Section A	Description of researcher's experience
Section B	Description of a research index study and U.S. IRB review
Section C	Developing country IRBs and other ethical review
Section D	Consent
Section E	Relationship with collaborators
Section F	Ethical issues in international research
Section G	Ethical guidelines and regulations in human subjects research
Section H	Recommendations
Section J	Researcher demographics

Survey Data Collection

In collaboration with the Johns Hopkins University's Information Systems Department, a website version of the survey was designed and tested. The U.S. and developing country surveys were first launched on the Internet on November 18, 1999. All of the selected researchers were informed via e-mail about the survey, and each researcher was given a specific ID code in order to log in. Completed surveys submitted via the Internet were automatically sent to the Johns Hopkins University's Information Systems Department and collected in a Microsoft Access 2000 database. Those researchers who preferred to complete the survey as an e-mail attachment or as a hard copy version were provided with those versions.

A random selection of 350 developing country researchers from the Master List was first contacted via e-mail to participate in the survey. Of these, 108 were returned undeliverable, and only 242 e-mail invitations presumably reached their destination. Due to the high volume of undeliverable e-mails and very poor response within the first two weeks, the decision to sample the entire Master List was taken. Several weeks later, a second

batch of new 320 developing country researchers (the remaining names on the Master List) were contacted via e-mail to participate in the survey, of which 84 e-mail invitations were returned undelivered.

A reminder e-mail message was sent to all the researchers whose e-mail was delivered three weeks following the first invitation to participate. In addition, the researchers were informed that e-mail attachments and hard copies of the survey were also available. Regular monitoring of the incoming responses indicated that further efforts would be required to reach a satisfactory response level. As a result, a decision was made to send hard copies of the surveys to each researcher who had not yet responded to the survey (in any form, but not including those whose e-mails were undelivered).

Survey data collection occurred for five months (November 18, 1999, to April 17, 2000). During that time, a total of 57 other additional developing country researchers were contacted to complete the survey. These researchers were referred by U.S. researchers who were participating in the U.S. survey. Five surveys were also completed by African researchers attending a Johns Hopkins international research ethics course in Malawi in March 2000. A total of 540 researchers were contacted to respond to the survey.

Respondents were reimbursed U.S. $25 as an expression of gratitude for their time and effort in completing the 26-page survey.

Confidentiality Procedures

The survey does not request respondents' names, addresses, or institutions. Data collected are identifiable only through assigned ID numbers. Names and mailing addresses at the end of the survey (required to mail the U.S. $25 reimbursement) were separated from the completed surveys before data cleaning and data entry began. Separate files were kept for reimbursement of the survey respondents. Likewise, personal information (names and addresses) were separated from the surveys completed from the website before analysis began. Once reimbursements were completed, ID numbers were removed from the address database to prevent survey data from being linked with individual survey respondents.

Statistical Analysis

Entries from the website surveys were stored in a Microsoft Access database, while hard copies of the surveys received were entered into an EPI-INFO 6.04b database. Both of these databases were transferred and merged using STATA® software.

Data editing (cleaning) was done using STATA®. Surveys in which three or fewer sections were completed were considered incomplete and were not used for data analysis. Codes were written in STATA® as "do" files for data editing and to fix skip patterns. All data were entered twice by two separate individuals for cross-checking, and corrections were made as appropriate by checking original survey entries.

After removing those surveys that were considered incomplete, a total of 203 surveys were used for the analysis. Overall, results from 37.6 percent of those invited to complete the survey were used as the final data set (203 surveys out of 540).

Data exploration and interpretation were done through frequency distribution for each variable. Cross tabs were run by 1) U.S.-funded studies, 2) educational status/profession of the researchers, 3) gender, 4) IRB membership, 5) employer, and 6) other variables of interest. To measure the strength of association between different variables, Chi Square test and p-values were calculated.

B.2.2 Qualitative Data Collection

Qualitative data were gathered regarding the opinions, experiences, and concerns of developing country investigators on the ethics of research involving human subjects. The primary purpose of this data is to provide empirical evidence to support, illustrate, and potentially explain certain quantitative findings and to illuminate areas of disagreement among respondents. This qualitative data will describe the range and depth of feelings and attitudes of developing country investigators and provide context and dimension to the numeric survey data.

Data Sources

Three separate data sources are integrated in this analysis: 6 focus group discussions; 8 in-depth interviews; and 78 responses to open-ended questions included in the survey questionnaires. Brief descriptions of these data sources follow.

The focus group discussions represent the primary source of data and were conducted from August 1999 through March 2000. A semi-structured field guide was developed by investigators and the research team to cover all major topics of interest, including informed consent, local and U.S. IRB and ethics review processes, specific concerns regarding ethics in research, and recommendations for improving review processes (see Appendix E). The field guide was reviewed by and assessed for coherence and comprehension among researchers from both the United States and developing countries. Project staff members trained in qualitative data collection techniques facilitated each session. Facilitators covered all questions included in the field guide and were also able to probe relevant topics or themes that emerged during the discussions that were of particular importance to the study. An observer was also present in each focus group to take notes on the flow of discussion and on participants' reactions as indicated by their body language and facial expressions.

In-depth interviews were conducted from August 1999 through March 2000 using a field guide similar to the one used in the focus group discussions (see Appendix F).The interviewer covered all of the questions in the field guide and also asked questions not included in the guide in order to probe particular relevant topics that emerged during the interview.

In both the focus groups and the in-depth interviews, consent was obtained using a written and signed consent form. Lunch and parking passes were provided for focus group participants, but no other compensation was offered. Typically, the focus group discussions lasted 90 minutes, and the interviews took about an hour.

Responses to two open-ended questions appearing at the end of the quantitative survey are also included in this analysis. These two questions ask the respondents to elaborate on any of the survey questions that they felt required more detailed responses and to describe the changes they would make to the existing U.S. policies on human subjects research. The responses were all hand written or typed directly onto the survey instruments by the respondents themselves.

Comments from the survey questionnaires have also been integrated into this analysis. These comments generally addressed issues raised in the survey. In one case, the typed comments are actually responses to the two survey questions previously described.

Sampling

Focus group and interview participants were identified through snowball sampling, a technique used in qualitative research where one or more informants are identified for the study and are asked to name others who would be appropriate study participants (Bernard 1994). This technique is used in research among unique groups of people who are likely to know one another. The only criterion for participant selection was that he or she have experience in research involving humans subjects.

Six focus group discussions and eight individual in-depth interviews were conducted. Two of the focus groups and five of the in-depth interviews were conducted in Asia. The remaining four focus groups were held in Baltimore at the Johns Hopkins University, and three in-depth interviews were conducted at the WHO headquarters in Geneva. All interviews and focus group discussions were tape recorded and later transcribed for analysis using the textual data analysis software program, Atlas/ti®. Biographical data were collected from each focus group participant to provide a demographic description of respondents, and this is included in the analysis.

The data described here are grouped into sections by major topic areas of discussion (Sections D.2 through D.5). Specific codes for analysis were created based on these topic areas. Relevant recommendations suggested by respondents are reported at the end of each section. A brief description of the demographic characteristics of focus group participants is included in Section D.1. All country names have been removed to protect the identity of the respondents. References to specific countries have been categorized into one of three world regions: Africa, Asia, and Latin America/Caribbean, and these appear in brackets. Text in brackets was also added in certain quotations in order to clarify meaning.

C. Results of the Study of U.S. Researchers

C.1 Description of Our Sample

C.1.1 Focus Group Participants

Seven focus groups were conducted in this study, with a total of 43 participants. Of these 43 participants, 28 percent were employed by government, 21 percent by universities, 9 percent by the U.S. military, 37 percent by private industry, and 2 percent by other types of institutions. A demographic data form was completed by 39 out of 43 respondents. Of these 39 respondents, 69 percent were men and 31 percent were women, and the average age was 46. Seventy-seven percent of respondents currently had a research project in a developing country, while 15 percent had a project within the last five years, and for 3 percent their last project was more than five years ago.

Researchers had an average of 8.2 years of experience working in developing countries and worked in an average of 2.7 countries. Thirty-one percent described their role as principal investigator or co-investigator, 44 percent were project directors, while 21 percent had other roles, such as administrator, medical monitor, sponsor, or human subjects contact. Focus group participants used different research methodologies and/or disciplines in their studies; they could categorize their studies in multiple ways on our data collection form. The majority (79 percent) conducted clinical trials, 38 percent used observational studies, and 31 percent used community-based interventions, while fewer used behavioral studies (13 percent). More than one funding source for studies often was checked. Funding sources included U.S. government funding (46 percent), U.S. military (13 percent), U.S. private company (47 percent), U.S. nonprofit (8 percent), non-U.S. government source (10 percent), and bilateral or international organizations, such as the Pan American Health Organization (PAHO) or the WHO (13 percent).

C.1.2 Written Survey Respondents

A total of 966 researchers were contacted about the written survey, and 51 were determined to be ineligible to complete it, because they did not conduct human subjects research in developing countries. Out of the remaining 915 researchers, 302 responded, resulting in an overall response rate of 33 percent. Ten submitted surveys with fewer than three sections completed out of ten and were excluded from the final data set. An additional 26 completed surveys were received from project directors who responded after being offered a survey by a principal investigator. The final data set consisted of 328 surveys. Table C.1.1 lists response rate by employment sector. As this table shows, the response rate is significantly lower for those in the private for-profit and private nonprofit employment sectors. If these groups are excluded, the response rate is 39 percent.

Table C.1.1: Response Rate by Employer

	Number	Response Rate
Government	136	51.2%
Military	25	54.2%
Private nonprofit	102	19.6%
Private for-profit	104	12.1%
University	598	34.2%

More than half (63 percent) of the surveys were received via the project website; the remaining 37 percent were received as paper copies.

Table C.1.2 lists the demographic characteristics of respondents. Thirty-five percent of respondents were female, and almost half were in the 40 to 49 age group. Respondents were also asked about their research experience. The median number of years researchers conducted research in developing countries was nine. Most researchers (67 percent) spent more than half their time conducting research, and 55 percent had worked on at least five developing country projects.

Twenty-three percent of respondents currently or previously were members of an IRB. Most respondents (60 percent) had resided in a developing country for six months or longer at one point. Most respondents were currently conducting research in a developing country (87 percent). Most of those who were not currently working in a developing country had been involved in such a project within the past five years (70 percent). Overall, only 4 percent of respondents had not been working in a developing country within the last five years.

Table C.1.2: Demographic Characteristics of Survey Respondents (n = 328)

Gender	Percent
Female	35
Male	65
Age	
<40	22
40-49	47
>=50	31
Employer	
University	62
Government agency	22
Private nonprofit research institution	8
Military	4
Pharmaceutical/biotech	3
Other	1
Degree	
MD, DDS, MBBS, MBChB	52
PhD, ScD, DrPH, PharmD	51
MPH, MS, MA, MHS	46
Other	26
How many studies (total) in developing countries have you been involved in?	
One	12
2-4	33
5-10	27
>10	28
In what regions of the developing world have you conducted research?	
Africa	60
Asia	57
South America	37
Central America/Mexico	28
Caribbean	20
Pacific Islands	6
Other	6

C. 2 Informed Consent and Disclosure

C.2.1 Disclosure and Documentation

Researchers in our study used a variety of methods for informed consent and disclosure. Table C.2.1 lists all methods in order of likelihood of being used. Seventy-six percent of the U.S. researchers in our sample used written informed consent (requiring a signature, thumbprint, or equivalent) in their studies. However, 100 percent of those in the military and of the respondents who work for pharmaceutical/biotechnology companies obtained written informed consent, compared with approximately 70 percent of those in universities or other nonprofit private organizations. Generally, researchers age 50 or older were less likely to use written consent than younger researchers (68 percent versus 81 percent, p = .02) but were more likely to use oral consent and community meetings and to seek permission from a village leader. Researchers funded by any U.S. source were twice as likely to use written methods as researchers funded by other sources.

Table C.2.1: Methods Used to Inform Participants and/or to Document Consent for the "Index" Research Project, in Order of Likelihood of Being Used

Method	% Who Used This Method
Written informed consent, requiring a signature, thumbprint, or equivalent	76
Explanation and question and answer session with participants (either individually or in groups)	74
Community meeting to describe the study	44
Approval from a village or community leader	42
Oral consent with a witness signature	40
Test of participant understanding of research before enrollment	16
In research with adults, approval or consent from another family member	14
Pictorial description of study or study procedures	7
Video to explain study	2

As can be seen in Table C.2.2, researchers were more likely to use written consent with higher literacy populations, but even among the lowest literacy population (defined as at least 80 percent of the population is illiterate), 60 percent of researchers still used written consent.

Among those who did not use written consent, 92 percent used another method or methods instead, including engaging in a question/answer session with participants (69 percent), holding a community meeting (51 percent), seeking approval

from a village leader (51 percent), obtaining oral consent with witness signature (38 percent), and seeking consent from another family member (13 percent). Even among those who obtained written consent, 89 percent used at least one other method to explain the study. Seventy-five percent engaged in a question/answer session, 41 percent had a community meeting, 40 percent also sought oral consent with witness signature, 39 percent sought approval from a village leader, and 14 percent sought consent from another family member. Female researchers were 1.9 times as likely as male researchers to explain the study and engage in a question/answer session with participants (p = .03).

Table C.2.2: Literacy Rate of Population by Use of Written Consent

% of Study Population That Is Literate	% of Researchers Using Written Consent
<20%	60
20-60%	67
>60-90%	82
>90%	86
n = 245; p = 0 .01	

Individual researchers volunteered through comments other methods that they used, including obtaining consent only after a discussion had occurred among family members; information sheets for participants; stories in the local press about the study; and a focus group discussion among potential participants. One researcher described hiring a public relations firm to develop posters and pamphlets to describe their study and to deflect misunderstandings about their study intervention. Many researchers also described in the survey that they had used oral disclosure *without* witness signature to explain their studies; therefore, our finding that oral disclosure was used by 40 percent of respondents is surely an underestimate, since our question asked only about oral disclosure *with* witness signature.

There was extensive discussion in focus groups, as well as in written comments on the survey, concerning written consent. Some researchers described written consent as having an inherent tension in serving to protect both the subject and the investigator and/or institution. Some researchers disclosed that their IRBs *required* written consent. Others described the difficulties of writing consent forms that include enough detail to satisfy U.S. regulations, but that are also written at an accessible reading level. Many researchers described negotiating the consent form language back and forth between U.S. IRBs and host country boards, especially with regard to the legal language and references to indemnity and health insurance typically required by U.S. boards:

> The stateside IRB and the NIH both expect consent forms that are narrowly delineated. And the developing country...IRB doesn't want anything to do with them. It's an anathema. The same way that the legalese, denial of responsibility for something that goes wrong is equally an anathema.…The United States, instead of acknowledging that, willfully signs on to consent forms that have ten pages of legal jargon that many of us can't understand in the United States, let alone anybody overseas. So we constantly pervert the process with the conscious assent of the NIH and our own IRBs.

Fifty-two percent reported on the survey that legal language required on consent forms was not meaningful to study participants, although 37 percent also believed that local staff shortened consent procedures. Researchers believed that staff were more likely to shorten consent procedures in lower literacy study populations than they were for populations with higher rates of literacy (45 percent versus 29 percent, p = .06). At the same time, one researcher described in a focus group the "intellectual and moral comfort" of having a signed consent form from a participant; another said it was helpful in challenges from the media. In the survey, 29 percent thought the consent process raised distrust among participants, although 82 percent agreed that the consent process creates a good opportunity to raise ethics issues among study staff.

In general, researchers voiced concern with a blanket requirement of written consent. One respondent wrote the following in the comments at the end of the survey:

> In [Latin American country], particularly those with limited reading ability are very hesitant about signing things. This is not a procedure typically followed by native researchers. Our insistence on informed consent was seen as culturally insensitive but was accepted out of understanding of our needs to satisfy our funding agency and government regulations (bureaucracy was certainly understood). More useful than this, I think, was the brochure we created, complete with an official project seal, that described the project, the institutions, and related services in the area that might be contacted. Also, afterwards, we gave each participant a certificate which seemed to be quite appreciated.

A focus group participant revealed, similarly:

> In some places, in some cultures, you don't sign an informed consent. It really freaked them out...once I wanted to enroll the patient for a tuberculosis treatment protocol. And I explained to him that it was very straightforward. There is no placebo. And I could see he was profoundly disturbed to sign the informed consent. And then he asked me, 'When am I going to die?' I said, 'Why are you saying that?' 'Well, you asked me to sign all these papers.' And to him, it was a sign that he was so ill that the written thing in the Muslim culture is something very strong: It's the will. It's the testimony at the end.

Another researcher said his or her subjects were worried that signing would mean they could never immigrate to the United States—that this would bring them to the attention of U.S. courts. Other researchers more generally voiced their belief that relying on written consent as the means to educate participants simply made no sense:

> So we get it translated into [local language] and back translated and it's delivered. And we field test it and we check it for its understandability, and we negotiate back and forth with [name of institution] here first to make sure it's acceptable to them. Then we send it out in the field and we get lots of thumb prints and signatures on that page. And everybody at [institution] is very happy...and the OPRR is happy with the way it's read to the patients verbatim….But the process is not clearly obtaining consent.

Another respondent recalled an ethicist saying that it was unethical to attempt to extract a signed consent form from someone who is marginally literate or illiterate, with a thumb print. The researcher went on to say, "We need to drive that message home here. I think our IRBs overseas understand this issue much more clearly than people do in the United States." Others similarly described situations in which their U.S. IRB had required written consent initially until the ethics board from the host country insisted that it was inappropriate locally.

Twenty-three percent of researchers believed the consent process is focused too much on the individual. There were lengthy discussions in all focus groups about the efforts researchers made to educate the study community prior to implementation of their projects. One researcher commented that U.S. IRB review focuses too narrowly on the process researchers engage in with individual participants and generally overlooks the extent to which they also engage in community-wide education and disclosure:

> When things go through the IRB here, it's a simplistic view of the whole consent procedure, because we just write up what the individual is going to hear, and in fact one does so much more. We do a lot more with the community education, discussion with community leaders. You sort of go all of the way through the system and then the final thing is, when the person is going to get their intervention, you have this one-on-one interaction, but here is all of this other stuff that surrounds it. You kind of say it in your application a little bit. But that process doesn't really get captured.

Another researcher described his or her process for informing a community and discussing with a community a potential research project:

> From a moral perspective, unrelated to regulation issues…we spend an enormous amount of time talking to communities well in advance of the study about what we're going to do, what's involved, participation, nonparticipation, willingness to get involved, ability to say no. That goes on both at the community level and the individual level at the time of the study. And we spend a lot of effort to hear what the community is saying and then to disseminate... information at the end of the study about what the results were.

Another agreed that "the community discussion groups are actually providing a better level of ethical review than some of the actual formally constituted IRBs."

One researcher discussed the importance of having a local liaison, who is from the local community, but also is educated and can communicate with researchers, to introduce the study to the community and to continue to serve as a liaison throughout the study:

> And they identified a local person who became educated but speaks the native languages and grew up in the villages themselves. And all research is done through him. They actually call him the master. They have a very high level of respect for this guy. You go with him to the village, and he formally greets the village chiefs. You see him perform a culturally defined give and take answers, asking them about their wives and their children, and has there been enough rain and how are the locusts, etc., etc. And [he] moves over to the subject of research and [it] is all done in a very culturally appropriate fashion.

In general, researchers said they wanted more flexibility. Informed consent was viewed as a valuable goal, "trying to genuinely get people to understand what you're doing so that they can make the right decision," but methods used to help participants understand and to document consent should be more flexible. Indeed, 85 percent of researchers agreed in the survey that U.S. regulations should allow more flexibility in ways of documenting informed consent, a belief that was raised numerous times in the qualitative findings. One focus group participant suggested a menu of choices from which investigators may select the most appropriate methods for disclosure and documentation of consent.

> From one setting to another, even within the same country, what makes sense in one place makes no sense at all in another. The bottom line is that most of these issues need to be dealt with on a case-by-case basis, and specific requirements as opposed to general guidelines are likely to create unintended new sets of problems for international research.

Another researcher wrote, similarly:

> I would just recommend that they have more flexibility and regard for local norms and practices, think more about the spirit of the law rather than the letter of the law. The atmosphere of paranoia that currently exists in the United States encouraging participants and regulators to assume that investigators are dishonest predators until proven otherwise is not necessarily something that needs to be exported.

Another recommended that the consent procedure be conceptualized as a communication process where materials and information are conveyed over time and in different formats. Overall, researchers should be required to demonstrate that they "have a process in place designed to protect the subject," not that they have a consent form. Other researchers suggested that consent forms and consent processes be piloted. They suggested that a

small amount of grant funds be released before the IRB approval was complete in order to determine what will work best locally. On the survey, 61 percent of researchers agreed that some research funds for piloting consent forms should be released before final IRB approval is obtained.

Generally, respondents thought the level of risk involved in study participation should determine the type of consent required. Several recommended a more informal, oral consent process for lower risk, observational, or epidemiological studies: "I would not relax the requirements for testing potentially risky interventions like vaccines and new drugs, but I would argue for considerable flexibility for epidemiological and observational studies that pose very low levels of risk." Related, essentially half (48 percent) of researchers agreed on the survey that "formal individual consent should not be necessary for observational studies." At the same time, respondents thought that whatever system is implemented, accountability must be ensured through monitoring and site visits:

> A key aspect of a safe study is having a site visit to make sure that the consent process is not being inappropriately abbreviated, observe the procedures for confidentiality and to get feedback from participants. However, so much money and time are wasted on the bureaucratic details that this is neglected.

C.2.2 Understanding

Eighty-seven percent of researchers believed that their study participants were aware they were in a research study, although 57 percent thought participants did not understand the concept of a placebo. Not surprisingly, 77 percent of researchers working in lower literacy populations believed their participants did not understand the concept of placebo, compared with 43 percent of researchers who worked with higher literacy populations ($p < .001$). Regression analysis revealed that researchers are five times as likely to believe populations of low literacy do not understand the concept of placebo ($p = .004$) and were four times as likely to shorten consent procedures with populations they believed did not understand the concept of placebo ($p = .008$).

Several researchers remarked on the difficulty of explaining placebos or control groups to participants, not simply because there might not be comparable words in local languages, but because many populations have no prior experience with such concepts:

> Culturally it's very difficult for them to understand how your doctor, who is supposed to want good for you, could propose you to take nothing. It defeats the principles of medicine to some extent. And you know you go a long way to try to explain that. And then the informed consent becomes very artificial when the very basis of the study design is not understood, and the purpose of it is not understood.

Western notions of science may be unfamiliar to participants. Frequently there are no words for "science," "research," or "virus" in the local language. Researchers described the difficult process of explaining complex biomedical information in ways that were relevant and meaningful to participants:

> The concept of immunology, an immune response, that there's something in your blood that is going to attack bacteria and viruses which you also don't have a concept for. I always wonder, when you do a consent form, and you first are explaining the idea that there are these things that are in your food and our air that you are ingesting, or you get from sex, and they are coming into your body and invading it, and then your body has these things that are attacking it. How 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?….We try to use, for example like immune cells, we talk about people who guard houses...it's a particular kind of watchman [in your body].

Another voiced a similar sentiment:

> Informed consent is a joke. It is not possible to claim a person who has never heard of a bacteria or virus is informed about what a vaccine or drug is doing or how their participation fits into any such study. The protection these people have is only from a) the ethics of the investigators; and b) the developing country review boards.

And another researcher wrote the following at the end of the survey:

> Another [challenge] we are facing is the advances in science needing to be translated into consent forms (i.e., telling an African village that their blood will be used to analyze the parasites' DNA for genetic mutations that confer resistance).

Another researcher pointed out, however, that excluding subjects for this reason also has problems:

> 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. 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.

Many participants thought the informed consent process should focus more on participants' understanding, since they believed this was the core of informed consent. On the survey, 65 percent thought formal mechanisms to test participants' understanding should be built into a study's design, although only 16 percent reported that they had included tests of understanding in their own studies. HIV/AIDS researchers were twice as likely to use tests of understanding as other researchers (49 percent versus 24 percent, $p = .001$). In multivariate analysis, researchers with at least five years' experience were three times as likely to use a test of understanding as those with less experience ($p = .01$). A focus group participant said:

> Maybe we should not be documenting consent, but documenting understanding of the consent process. What really might protect [institution] as an institution and funding agency is documentation that people participating in the study actually understand it.

C.2.3 Voluntariness and Decisionmaking

Seventy-two percent of researchers said that, after hearing about the study, some participants refused to participate. Female researchers were significantly more likely to report that some potential participants refused as were male researchers (81 percent versus 66 percent, $p = .009$), and participants were more likely to refuse participation in randomized ($p = .005$) or prospective studies ($p = .003$). Of some concern is that researchers working with lower literacy populations were less likely to report that participants refused. Specifically, 81 percent of researchers working in higher literacy populations said some potential participants refused, compared with 65 percent of researchers working in lower literacy populations ($p = .01$). Eighty-eight percent of researchers engaged in studies they called more than minimal risk had some potential participants refuse, compared with 69 percent of researchers engaged in studies they called minimal risk ($p = .07$). In regression analysis, female researchers were three times as likely to have participants refuse ($p = .006$), and researchers engaged in more than minimal risk studies were four times as likely to have participants refuse ($p = .04$). Those conducting randomized trials were 2.4 times as likely to have participants refuse ($p = .03$). However, literacy was no longer significant in regression models.

In terms of who made the decision about participation, 37 percent of researchers believed cultural norms where they work are inconsistent with the practice of individual decisionmaking. Those working with Muslim populations were more likely to report that cultural norms are inconsistent with the practice of individual decisionmaking than those working with other populations (46 percent versus 31 percent, p =. 01), as were those working with populations practicing a local indigenous religion (44 percent versus 33 percent, p =. 05). As stated above, 42 percent of researchers sought approval from a village or community leader for studies, although our data do not show how integral this was to individual participants' own decisions. Similarly, 14 percent of researchers conducting research with adults sought approval or consent from another family member. In regression models, researchers working with participants practicing a local indigenous religion were four times as likely to say that the religious or cultural norms of the community were inconsistent with individual decisionmaking, and those who had held a community meeting were 6 times as likely and those who had sought approval from another family member were 12 times as likely to believe that cultural norms were inconsistent with individual decisionmaking. Somewhat surprisingly, those who used pictorial descriptions and those who sought approval from a village leader were less likely to say cultural norms were inconsistent with individual decisionmaking.

In focus groups, there was much discussion about the degree to which individuals made decisions independently and/or autonomously and the degree to which others were involved in decisions or made decisions on behalf of participants:

> In [African country] and in other areas of sub-Saharan Africa where I've worked, [informed consent] is a communal process, and the last one who is involved is the family, the parent, and by the time you've gone through the chief and the elders and the village, the process is already well in motion….Their whole approach to decisionmaking is communally based...our IRBs and the NIH both have no clue of this as far as I can tell.

Another researcher described a similar situation, but also emphasized that the individual remains an important decisionmaker:

> If you go to countries like [West African country], you have the chief of the village, of the tribe….You can go to the individual after you have explained, and it takes a long time to educate these chiefs. Not to short cut them, that could be a mistake. To short cut the State if you work in [Asian country] or to short cut the chief of the tribe [in Africa], but to respect this hierarchy in this country and to educate them, to say that the individuals are important for the pharmaceutical company or for our institutions etc. And you explain to them this informed consent. Then they can explain this informed consent to their people without exerting pressure. And the best evidence of that is when the people refuse. That's a good sign. They are able to refuse, they are free to refuse.

Some researchers pointed out that leaders who are influential in decisionmaking do not always have the best interests of their subordinates in mind:

> Remember that those communities have internal hierarchies of sex and class, too, so that what is in the leader's best interests may not be in the individual men's or women's best interests.

Another researcher described conducting research in a political context in which rights were not guaranteed, thus potentially compromising the voluntariness of research:

> This concept of the consent of the individual, rights, and individual decisionmaking doesn't exist. And this is a country that has been under authoritative rule for a long, long time. And people do what they are told, and people are told what to do.

Clearly, where one conducts research is relevant to the question of whom to approach for permission. One researcher reported that in some settings, he or she had felt it imperative to go through village leaders; in other areas, he or she had "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." Another researcher had a similar experience, and was troubled by it:

> The [Asian country] government has basically told us that it is doubtful that we will receive 'official permission' to conduct our trial. However, it has become clear that they will not object if it is done 'clandestinely.' We feel this is a real ethical dilemma (at least from the U.S.A. perspective), though it is not so viewed by our host collaborators. We have not yet made a decision on how/where to go.

Finally, researchers believed economic realities of participants' lives sometimes compromised the voluntariness of their participation:

> If the patient has no other drug choices or has no drug choices, period, and you're coming in with an acceptable drug, and you have a 50 percent chance of getting the experimental drug...it's very difficult to say that they're making a true informed consent to participate in the study and they're not just trying to get the drug.

Indeed, 68 percent of researchers believed that participants joined their studies "because of the desire for compensation, medical care, or other benefits." However, only 10 percent of researchers reported their U.S. IRBs had raised in the study's review that voluntariness of participation could be compromised due to the incentives or medical care provided by the study; 7 percent said the host country board had raised this concern.

C.3 Study Design, Risks, and Benefits

Because the ethics of a study are integrally related to its design, we asked researchers to describe what topics they were studying in their research, what methods they were using, who comprised their sample, and why they were conducting research in a developing country. We asked them questions about how much risk and benefit they felt were inherent to their studies and the degree to which this was relevant to study subjects and review boards

C.3.1 Study Design: Topic, Method, Sample, and Reason for Being in a Developing Country

In the written survey, respondents were asked to answer multiple questions about an "index study," defined as the developing country study on which they had spent the most time in the last five years. As can be seen in Table C.3.1, these index studies most often were investigating questions related to infectious diseases other than HIV/AIDS; to HIV/AIDS; or to reproductive health. Half of the researchers categorized their studies as observational or descriptive, 28 percent said they were conducting randomized, controlled trials, and 13 percent were conducting a community-based intervention study. In a separate question, researchers were asked if they were conducting an intervention study, and 39 percent said that they were. The majority of researchers said the discipline of their study was epidemiology (67 percent), followed by behavioral science (18 percent), and microbiology (17 percent).

In order to explore the relationship between level of development of the host country and other variables of interest, HDI data from the UNDP 1999 Human Development Report were added to the survey database. These data are published by UNDP and are available on the UNDP website. The HDI indicator is a composite of life expectancy at birth, adult literacy rate, combined enrollment ratio, and adjusted per capita income. This development indicator was used in our statistical analyses to determine if there are relationships between level of development of the host country and other variables of interest. Overall, most index studies (72 percent) took place in countries with medium HDI scores[1] according to UNDP, while 23 percent occurred in countries

with low HDI scores, and 4 percent were in countries with high HDI scores. An additional 4 percent could not be classified because HDI values were not listed for those particular countries. For further analysis, the HDI levels of countries where the index studies occurred were categorized as low or high, using the 50th percentile of the HDI scores represented (0.632) as the cutoff point between low and high. The topics of the index studies were associated with the HDI level of the countries where the studies were carried out. (See Table C.3.2.)

We were interested in why researchers chose to conduct their research in a developing country and asked this question in some focus groups. Researchers frequently mentioned a commitment to addressing health priorities in developing countries, including addressing diseases prevalent in the developing world and testing interventions that would be affordable for those resource-poor countries that needed them. One researcher said:

> And I would say for most of us in the field the goal that we have is to prevent those [tropical disease] deaths. That's probably the ultimate humanitarian goal that we feel that motivates us going to work in the mornings. So we're trying to develop a vaccine.

Researchers also mentioned the need to find a study population that is appropriate to answer the particular research question at hand—in some cases, a population that has not had access to treatment previously:

> We also look at incidence rates of HIV. I think that's what really pulled us into [African country], is that there is such a great—a high incidence of HIV there, it seemed like the right place to do research. I think also there are considerations in terms of what types of patient populations you are looking for....I think also, in HIV we're looking for naïve patients, and most of the patients in [African country], they are not treated and they're all available to us.

Table C.3.1: Location, Topic, Method, and Discipline of Index Study (n = 327)

Study Location	Percent
Africa	32
Asia	25
South America	14
Pacific Islands	10
Central America/Mexico	10
Other	6
Caribbean	4
Study Topic (Respondents could check more than one topic)	
Infectious disease, non-HIV/AIDS	37
HIV/AIDS	27
Reproductive health	21
Cultural practices/behaviors	19
Chronic disease	15
Other	15
Nutrition	14
Genetics	13
Environmental health	12
Vaccine development/testing	9
Perinatal health/birth defects	9
Health systems/services	8
Injury	2
Study Methods (Respondents could check more than one method)	
Observational/descriptive study	51
Prospective study	39
Randomized controlled trial	28
Case-control study	20
Qualitative methods	16
Operational research/program evaluation	15
Community-based intervention	13
Other	9
Study Discipline (Respondents could check more than one discipline)	
Behavioral Science	18
Epidemiology	67
Microbiology	17
Clinical Care	14
Health Services Research	9
Other	28

Table C.3.2: Likelihood of Study Topic or Discipline Being Conducted in Host Country with Low Versus High HDI Level

Study Topic or Discipline	Lower HDI (< 0.632)	Upper HDI (> 0.632)	P-Value
Infectious disease, non-HIV/AIDS	62%	38%	0.001
HIV/AIDS	64%	36%	0.002
Chronic disease	21%	55%	< 0.001
Genetics	33%	67%	0.02
Environmental health	31%	69%	0.02
Health systems/services	71%	29%	0.03
Reproductive health	62%	38%	0.05
Perinatal health/birth defects	73%	27%	0.01
Behavioral science	66%	34%	0.005
Health services research	76%	24%	0.003
Qualitative methods	69%	31%	0.003

One focus group respondent mentioned that procedural difficulties in obtaining U.S. government clearance played a role in determining where she conducted her research:

> You only work in select countries where you know you [have an assurance]. And you just don't even work elsewhere. That's one of the big criteria I use nowadays when I'm trying to decide where to do research, and that's not the way it should be. Because, if anything, the people who need it most are the people you're not going to.

Other researchers mentioned other pragmatic reasons as well. This researcher, from private industry, described the need to balance the goals of his or her company's marketing division with a need to complete the research quickly, as well as a personal commitment to the ethical conduct of research:

> ...the commercial folks will have their input, because from their perspective, the best pre-marketing of any drug is doing clinical trials. So from their perspective, they would like us to use certain countries that they see has a good, you know, long-term outcome for the company. Our perspective is a little bit different. We try to take their advice and want to try to help, but we're looking at sites that can actually do the research ethically and can do the research efficiently, because we tend to be guided more by timelines. If we say that we're going to complete enrollment by X day, well, that might be nice to use country X, but knowing their Ministry of Health systems or knowing how slow they are, that might be a blockade for us to complete in a timely fashion.

Another pharmaceutical researcher was particularly candid about the reasons many private industry groups conduct studies in resource-poor countries:

> The vast majority of the trials I have done in the third world possibly are dose response trials. Developing the profile of the knowledge on the drug to get profit and benefit elsewhere. That's extremely clear. There is not a question about that. I'm sure the simple fact that the pharmaceutical industry is a profitable business with all the drugs that we use just tells me that. It's not a charitable business. It's a Wall Street hardcore business. And doing clinical trials in the third world sometimes may be motivated by a variety of reasons. In general, the vast majority

> is access to the patient in large numbers and a faster rate. And sometimes the third argument, nevertheless, is also at a cheaper price.…

In the survey, researchers were asked to select one or more options from a menu of reasons for conducting research in a developing country as opposed to in the United States. As shown in Table C.3.3, the top reasons why researchers conducted their studies in developing countries were that the prevalence of the disease in question was greater in the host country (83 percent), researchers had an interest in addressing global inequalities in health (73 percent), the host country researchers asked for U.S. collaboration (72 percent), and the intervention being tested was more relevant to the host country (70 percent).

Table C.3.3: Reasons for Conducting a Study in a Developing Country, in Order of Likelihood of Being Mentioned (Respondents could list more than one reason)

Reason	Total Number Who Answered This Question	% Yes
Prevalence of disease in question is much greater in the host country than in the United States	277	83
Interest in addressing global inequalities	263	73
Host country researchers asked for U.S. collaboration	260	72
Intervention being tested more relevant to host country than to United States	213	70
Easier to identify a cohort of patients relevant to research	218	62
Recruitment of patients more rapid in host country than in United States	219	47
Other reasons	166	47
Less expensive to do study in host developing country than in United States	214	36
Research question relevant to U.S. strategic interests in the region	234	32
Marketing approval for drug or device will be sought in host country	191	12

Due to limited numbers of survey respondents from the private sector, it was not possible to do statistical comparisons between the reasons of public versus private sector researchers. Comparisons among those who listed their employer as government, university, or military showed little difference in the percentage who answered "yes" to each of the reasons listed. Those conducting intervention studies were less likely to say that their studies were relevant for U.S. strategic interests in the study region (21 percent, compared to 39 percent for nonintervention studies, $p = .0005$) and were more likely to say that marketing approval for the drug/device will be sought in host country (17 percent versus 6 percent, $p = .017$). Those with intervention studies were not significantly different from those in nonintervention studies in their likelihood of checking "interest in addressing global inequalities in health."

The research topic, as one might expect, was associated with the reasons researchers gave for conducting their research in a developing country. Researchers listed "prevalence of disease is higher" more frequently when their study topic was infectious disease (95 percent versus 75 percent for noninfectious disease, $p < .001$), and less frequently when their topic was chronic disease (60 percent versus 88 percent, $p < .001$) or genetics (66 percent versus 76 percent, $p = .002$). Compared to those investigating other topics, researchers involved in infectious disease research were more likely to state "interest in addressing global health inequalities" as a reason (80 percent versus 70 percent, $p = .05$), as were those doing health systems research (96 percent versus 71 percent, $p = .013$). Those studying chronic diseases were more likely to say the study is less expensive to conduct in the developing country (63 percent versus 30 percent, $p < .001$). Those studying environmental health were more likely to say it is easier to identify a cohort (79 percent versus 59 percent, $p = .059$), while vaccine researchers were more likely to list marketing approval as a reason (40 percent versus 8 percent, $p < .001$).

We further compared the reasons why researchers worked in countries with a low development index, according to UNDP HDI indicators. Researchers working in countries with a low HDI level were more likely to explain why they work in a developing country in terms of the disease prevalence, relevance of interventions to the population, and interest in global health inequalities, whereas researchers in higher HDI countries were more likely to mention that marketing approval for an intervention would be sought. (See Table C.3.4.)

Table C.3.4: Reason to Do Study in Two Categories of Countries Based on Human Development Index (HDI-1 lower half, HDI-2 upper half)

Reason To Do Study in Host Country	% Yes		P- Value
	HDI-1	HDI-2	
Prevalence of disease is higher	92	74	<0.001
Intervention more relevant for developing country	83	52	<0.001
Marketing approval will be sought	7	17	0.027
Interest in addressing global inequalities	82	64	0.002

Forty percent of researchers admitted that the research priorities of their funding agency were "not congruent with the top priorities of the developing country." This did not differ by the HDI level of the country where they were conducting their research. Thirty percent of U.S. IRBs and 23 percent of host country review boards questioned the relevance of the study to the developing country. U.S. IRBs were particularly likely to raise the relevance of the study to the host country for genetic studies (43 percent versus 20 percent, p=.01).

C.3.2 Assessing Risks and Benefits

Risk

In the survey, respondents were asked to categorize the "index study" as minimal risk or greater than minimal risk. Relatively few studies (12 percent) were described as greater than minimal risk; however, 24 percent of the intervention studies were classified as greater than minimal risk, compared to 5 percent of the nonintervention studies ($p < .001$). Researchers who used either randomized controlled trials or community-based interventions were more likely to describe their studies as greater than minimal risk than researchers using any other method (29 percent versus 4 percent, $p < .0001$). Studies involving clinical care (29 percent versus 9 percent, $p < .001$) and randomized controlled trials (28 percent versus 6 percent, $p < .001$) were more likely than other studies to be categorized as greater than minimal risk, while observational/descriptive studies were less likely to be categorized this way (8 percent versus 16 percent, $p = .02$). Eighteen percent of HIV/AIDS research was classified as greater than minimal risk, compared with 9 percent of non-HIV research ($p = .03$). Greater than minimal risk studies were more likely to be conducted in settings with lower background standards of care; 65 percent of researchers conducting greater than minimal risk studies said the standard of care was lower in the host country, creating difficulties establishing procedures for the control group, compared with 48 percent of those conducting minimal risk studies ($p = .08$).

One focus group participant described the risks faced by potential study participants in a clinical study for a serious illness:

> And the first study I ever did, mortality was the primary variable, so I've done a number of studies...where death is the primary outcome which jacks it up quite a bit in terms of its visibility. And right now, we are contemplating a vaccine trial...where death in infants was the primary outcome variable. So that's one type of study. [There are studies] where an adverse outcome from the drug is a reasonable expectation and an adverse outcome from the disease itself is a reasonable expectation….

Even fewer of the studies that involved children were classified as greater than minimal risk. Out of the 142 studies that enrolled children, 8 percent were classified as greater than minimal risk, compared to 15 percent of studies that did not enroll children ($p = .05$). Studies that enrolled children also were more likely to be

conducted in lower HDI countries (57 percent were in lower HDI countries versus 43 percent in higher HDI countries, $p = .03$), as were studies that enrolled infants (62 percent lower HDI versus 38 percent higher HDI countries, $p = .007$). Studies with infants, however, were no more likely to be classified as risky than studies with other populations. One respondent in a focus group commented that standards for doing research with infants in another industrialized country were different from those in the United States. Whereas in the United States, regulations require that greater than minimal risk research with children only be done when there are potential benefits for those children in the trial, other countries may have different guidelines. Our survey data do not include sufficient information for analyzing risk/benefit ratios for each index study, thus we cannot assess risks and benefits specifically for studies involving children that were reported in the survey.

Forty-nine percent of researchers reported that the index study "gathered potentially sensitive or stigmatizing information about participants (e.g., HIV status, domestic violence)." Researchers conducting work in lower HDI countries were even more likely to say their studies gathered potentially sensitive information (57 percent versus 43 percent, $p = .01$). Those studying HIV/AIDS also were more likely to gather potentially sensitive information (91 percent versus 30 percent, $p < .001$), as were those studying cultural practice/behavior (71 percent versus 44 percent, $p < .001$), and reproductive health (67 percent versus 44 percent, $p = .001$). One researcher described how serious a risk a breach of confidentiality could be:

> Our [project] in [African city] is right next to the fever hospital, which is the big hospital of fevers of unknown origin. Of course, anybody that's HIV positive basically winds up there. And we do the test for HIV positivity. If it comes back, the only person it goes to is, it must be signed by [senior official of the research project]. And then it goes directly to the Minister of Health, and then that person disappears. And it is very difficult...[HIV cases] are actually very unusual in [African country] because there is very little because most of these people are taken out of society...there is only one thing that happens; they go to jail, and they are not heard of any more.

Another respondent commented at the end of the survey that his or her research involved collection of sensitive information that was sometimes questioned by study participants:

> In general, this survey focused on medical research, specifically research on interventions or drugs that might benefit the population. Most of my research is more behavioral or demographic in nature where sensitive questions are asked but there is not a specific intervention or drug that can be offered to individuals. We frequently get questions from respondents about why we need to know sensitive information, but without a specific treatment to offer them, I don't feel we can really respond.

As described earlier, a trend was observed for more researchers engaged in greater than minimal risk studies to have some participants refuse enrollment, compared with researchers engaged in minimal risk research (88 percent versus 69 percent, $p = .07$). However, researchers engaged in studies where they gathered potentially sensitive information were no more likely to have participants refuse than other researchers.

Benefit

There are three types of benefits that might be provided in the context of a study: benefits to the individual or community during the study itself, provision of the study intervention or other benefits after the study is over, and capacity building. The first of these, provision of benefits in the context of the study itself, will be addressed here; the other two topics will be addressed in Section C.4, Obligations to Subjects, Communities, and Countries.

Benefits provided directly to study participants may take several forms. The experimental intervention itself may be seen as a benefit, or the control intervention, if any, may be beneficial. Interventions provided to

experimental and/or control groups may include treatment or services that generally are not available to individuals in that setting. Decisions concerning what to provide are related to the design of the study itself and must satisfy both ethical and scientific standards. In addition, researchers in resource-poor areas often need to make decisions about what benefits to provide to study participants that are *unrelated* to the study questions. This latter type of benefit raises ethical questions about how much care to provide for unrelated health problems—that is, what obligation researchers have to offer general care and treatment for humanitarian reasons. These benefits differ in that they may not need to meet criteria for answering a scientific question, although, in some cases, they too can affect study outcomes. Both categories of benefits can be inducements for potential participants to join a research project.

Unfortunately, our survey did not include questions on what level or type of benefit researchers provided during the study, although other questions related to benefit were asked. Overall, 63 percent of researchers and 74 percent working in low HDI countries reported that it was true or sometimes true that "medical care provided to participants in this study generally is not available to local population outside the study." Fifty-two percent of researchers said that it was true or sometimes true that "the standard of medical care in the host country may be much lower than that of [the] funding country, creating difficulties in establishing appropriate procedures for the control group." For studies in lower HDI countries, 64 percent agreed, compared to 36 percent in higher HDI countries ($p < .001$). Those whose topic was HIV/AIDS were more likely than others to agree that local standards made it difficult to establish control group procedures (71 percent versus 42 percent, $p < .001$).

In focus groups, participants discussed the challenges in determining how much medical care to provide to participants. This arose in the context of determining what types of study interventions to provide to control groups and also in determining what medical care to provide that was unrelated to the research question.

Seventy-eight percent of researchers thought that standard of care issues should be decided on a case-by-case basis, and many focus group participants thought that locally available care was appropriate for control groups. Indeed, researchers in focus groups devoted much discussion to how they had grappled with establishing appropriate procedures for control groups in terms of both scientific and ethics implications. In some cases, researchers discussed how offering treatment to control groups makes it impossible to measure the outcome of interest—in this case, mortality rates:

> Let's say we develop a vaccine that can prevent death. Well, it has to be tested. We have to find out, 'Does it prevent death?'…So, we come into this knowing that without exception if we bring simply a physician with [an effective drug treatment] into a community...we essentially stop death due to [this disease]....So we cannot measure that end point if we intervene. Cannot measure it. The [effective intervention] is easy; it is cheap. In the course of HIV you're dealing with major financial restrictions. But for us to field the physician, [the effective intervention], costs pennies or just relatively little. So we need to go into a village...we need to give vaccine or some placebo vaccine or some other vaccine in a randomized way to several hundred or several thousand children. We have to just leave them and see what happens. Measure the mortality rate. But with a very small amount of effort, we could prevent mortality altogether. We could prevent those children from dying. So I have no answers to this question, but I would just put this out as a painful example of the kind of ethical dilemmas that we face.

In one case, a researcher described the study participants as being unwilling to participate in a controlled trial because they believed the intervention to be efficacious:

> We had some pilot data which suggested that putting an untrained volunteer to visit each house once or twice a week just to look for kids who were sick would reduce the incidence of severe malaria by 75 or more percent.…And to nail that down, we wanted to do a control

> study. And the people in the village were so impressed by what was happening in terms of the decrease in malaria, they said they would not permit a controlled study because they were convinced this was efficacious, and they didn't want us to do a controlled study in their village.

In survey comments, a respondent similarly addressed the tension between consideration of the needs of the study population versus the need to gather adequate data to answer the research question:

> Generalized rules may or may not apply under different circumstances. For example, when we research in nutrition, it is very difficult to justify a 'placebo' given that nutritional deficiencies are very common in developing countries where research is being done. However, there is a need to determine if a nutritional intervention will have a measurable health impact on the population or not, and whether nutrition programs should be based on adequate research-based evidence of a benefit.

There was extensive discussion in focus groups about how researchers should determine how much medical care should be provided to participants for conditions unrelated to the study topic. One researcher described how he or she had received no guidance from the IRB on this and instead discussed it with host country collaborators:

> We were doing lead surveys, and we looked for anemia and side effects of lead, and you find anemia and then you're looking at parasite burdens. And where do you stop?…And as far as the IRB is concerned, all you have to do, at least from our study, is refer them to what they would normally have which is someone at the local clinic.…We know the local clinic is not going to do anything.…Now we're launching this whole parasite screening thing which is not part of what we were doing initially….We talked with our collaborators and said what's basically the right thing to do here.…We decided we couldn't leave these kids there with likely huge parasite burdens.

In the context of HIV (or any other serious, chronic disease) the issue becomes only more complex, since any experimental or control treatments are needed for the long term. Thus, this researcher suggested that interventions that are short term and feasible should be provided during a study, but interventions that should realistically be continued indefinitely after the study is over should perhaps not be provided if they would be withdrawn when the study ends:

> A lot of times what they...I'm thinking specifically of the HIV issue. They [local IRB] don't want us to come in and start...offering something just for specific people in a research study that they are going to get for three to six months and then have it taken away from them. It's different than, say, treating somebody with an obvious case of severe malaria where you're benefiting them, and it may be a longer-term benefit. But to go in and give AZT for three months...during the duration of a study and then walk away with it...what are you really providing for them?...a lot of times...they don't want us to go in and interfere with what their local norm is for that. I think in terms of treatment of the specific treatable disease, if the medication is available, and it's really a resource issue, and we're willing to provide the resource...a lot of times...the local folks will come down...and say, 'You've got the mechanism to treat it, go ahead and treat it.' I mean they do that in the [African country] studies where they provide the anti-malarials free of charge if they identify somebody with it. It's one of the benefits to the study.

Another researcher described the difficulty in determining how much medical care should be provided for conditions unrelated to the research:

> If you make the diagnosis of something, what is your obligation to that individual? You may be doing him a service by making a diagnosis, but are you obligated then to incur several thousands of dollars worth of medical care and costs? Who is obligated to do what and where do you draw the lines? Sometimes, depending on the situation, we've paid for care that we're sure is totally unrelated to the event, but the perception is still there, and as the investigator that's discretion that we have to be able to use.

Another focus group member, on the other hand, described following children with asymptomatic disease without treating them:

> The two aspects of those studies that are the most relevant, one, that human studies follow children who are judged to be asymptomatically infected but they're followed without treatment, which is, indeed, the national policy of that country and the policy of WHO for Africa, but is quite at variance with the way most American IRBs would think of proceeding, [while being] totally in line with [what] the African investigators think of following the studies of disease. But it does and has created tensions in the IRB review process.

This same respondent also mentioned providing medical care for study participants for unrelated medical conditions:

> A second example which [another researcher] alluded to, is the big difference between a restrictive focus on a disease which is so typical in the United States and Europe. I go in to study abnormalities of the left toe, and if they are on the right toe, I ignore them. But if you go into a village and there are sick people, if you want to continue to work in that village, you have to provide some recourse, especially if that village is in an area where medical care is either totally unavailable or extremely hard to get.

Sometimes researchers performed health screening that was not related to the study question as a service to the community:

> Another aspect of the studies is sometimes the studies involve children. We go into schools and perform a school health survey and at the same time collect samples for them so it's a more extensive health screening than they would normally get. The results are provided to the school health doctors, and they act on them, treat the children for parasites. We screen them for parasites and other diseases, so there is an element of service that's provided, and at the same time we get the samples that we need.

That potential participants might be unduly influenced to join a study because of the study benefits was discussed frequently in focus groups. Virtually all the comments on this topic conveyed the message that study participants do in fact join studies because of the benefits provided and that these studies generally provide benefits that are not otherwise available. In the survey, 64 percent of researchers thought "participants join because of the desire for compensation, medical care or other benefits," while 33 percent thought that "participants have unrealistic hopes about personal benefit from participation." Researchers conducting studies related to HIV/AIDS were particularly likely to say their participants joined for compensation, medical care, or other benefits (77 percent versus 60 percent, $p = .005$), and those in lower HDI countries were more likely to have unrealistic expectations for personal benefit, according to researchers (60 percent versus 40 percent in higher HDI countries, $p = .023$). Participants in riskier studies were also more likely to have unrealistic hopes; 44 percent of researchers conducting greater than minimal risk studies said that study participants had unrealistic hopes about study benefits, compared to 28 percent for minimal risk studies ($p = .039$).

The types of benefits vary from study to study. One focus group participant commented on changes in hospital care during his study:

> I'm the chairman of the data management safety board and serve 1,500 children for a new treatment for [infectious disease]. What happens—it's happened to all of us, I'm sure—is you go in, you go into a community and based on the hospital record, the mortality rate of [infectious disease] is 33 percent. The moment you go in there and you are doing certain things, the mortality goes to 12 percent. The moment you leave, the mortality goes back up to 33 percent, so, of course, they'd be out of their minds not to participate in such a study because the quality of care is completely different.

Another researcher commented that studies involving drug treatments were frequently the only means for participants to receive any treatment:

> It must be very difficult from the patient perspective to give a truly independent informed consent when, in fact, what you're consenting to is to take something versus nothing. Where is the choice? And I think you can't fix that. You can't make treatment available for everybody so that your experimental agent is a truly deliberate choice where they have a real viable alternative outside of the study.

As will be discussed in the next section regarding obligations and justice, the question of whether or to what degree the benefit to individuals in the study justified conducting the study in a resource-poor country was raised by some researchers. This investigator, from a pharmaceutical company, believed that although his drug would never be available to the country in the future, it provided significant short-term benefit to the individuals who participated in the study, given that they otherwise had no access to therapies:

> I've come to the same level of acceptance, that is, if I look at what the alternative to going to a country where only a small number of individuals who will actually participate in the study will benefit. If the alternative is that no one goes to that country, that no one benefits, to me it's an easy choice. As long as the study is itself ethical and has appropriate safeguards and so forth, I don't…consider it to be exploitation of individuals to offer them something that some would say well, it's coercive because if you don't go there, they get nothing. Because to me the consequence or the logical conclusion is that therefore it's more ethical for you not to go there and let them die of their HIV.

C.4 Obligations to Subjects, Communities, and Countries

The previous sections addressed issues inherent to the ethical treatment of research participants before and during study enrollment. This chapter will explore the obligations of researchers and sponsors to subjects and communities after a research protocol has concluded, as well as the relationships of researchers with developing country colleagues. Three topics will be covered in this section: the degree to which interventions tested and proven efficacious through studies should be made available to participants, communities, and countries after the study is over—and under what conditions; collaborative arrangements between U.S. and developing country researchers; and capacity building—the development of the host country's capacity for conducting research or delivering health care based on resources and skills gained through collaboration with the United States.

C.4.1 Future Access to Interventions Tested in Studies

Thirty-eight percent of respondents overall and 47 percent working in lower HDI countries were conducting intervention studies. A small number (5 percent) of respondents did not answer any questions about intervention

studies; this group when examined was significantly more likely to have fewer than five years' experience working in developing countries, but was otherwise similar to those who did respond to questions about interventions in terms of gender, age, source of funding, and whether their study was completed or ongoing.

Among those conducting an intervention study, 53 percent said their intervention already was efficacious, 11 percent said it was not, and 31 percent did not yet know. Researchers who said their intervention was efficacious or did not yet know were asked if they planned to provide the intervention, if successful, to any groups within the host country at the conclusion of the study, or if they had already done so. The majority (67 percent) of those respondents who said that their intervention was, or might be, efficacious, said the intervention would be provided to "study participants or to any other host country residents at the conclusion of the study," while 20 percent did not know if it would be provided (see Table C.4.1). There was no significant difference in the likelihood of providing the intervention for those researchers whose index study had concluded compared to those whose study was ongoing. However, those researchers who did not yet know if their intervention was efficacious were less likely to say that it would be provided (52 percent versus 75 percent, $p = .03$). Of those who said they would provide the intervention, 9 percent said they would provide it for less than one year, 35 percent said two to five years, 28 percent said more than five years, while an additional 28 percent said they did not know how long it would be provided. Forty-three percent said it would be provided after the study was over to the study population, while 29 percent said it would be provided to the entire host country. Researchers studying HIV/AIDS and researchers studying reproductive health were more likely to say the intervention would be provided in the future than those studying other topics. Those who provided the intervention, compared to those who did not, were more likely to say that one of the reasons for conducting their study was "interest in addressing global inequalities in health" (85 percent versus 50 percent, $p = .021$).

Fifty-three percent of researchers agreed that "Research to test an intervention should not be carried out in a developing country unless the intervention, if found to be successful, will be made available to that country at the conclusion of the study." It is of note, however, that those actually conducting an intervention study were less likely to agree with this than those not conducting an intervention study (46 percent versus 58 percent, $p = .04$). In a different question, 27 percent of researchers believed that "international policy regarding research should require researchers to establish a mechanism for continuing delivery of medical care after completion of the study."

The topic of future provision of interventions arose frequently in qualitative data. One researcher said at the end of the survey:

> I agree with the notion…that formal steps be taken to insure certain actions after the study is completed (i.e., availability of drug or procedure studied to the study population/host population if benefit shown; reporting of findings to community; attempt to maintain or continue health services that were introduced to the community as part of the study, etc.).

Another agreed that benefits should flow to the host countries, but said that capacity building should occur in all cases, in case specific interventions are not provided:

> Simply put, the benefits of research conducted in developing countries should also be made available to developing countries at affordable rates as soon as those benefits become apparent. It would be very useful to make involvement of local researchers at any level available [and] part of each research project in order to improve training and education, and therefore at the very least these educational…experiences may be the only benefits derived by the local populations.

Table C.4.1: Provision of Intervention in the Future

	Percent of Studies
Percent reporting the intervention was or will be provided, if successful, to study participants or to any other host country residents at the conclusion of the study.	67
To whom was (or will) the intervention be provided? (Respondents could check more than one option)	**Percent of Studies**
Entire study population	43
Community from which the study population comes	42
Placebo or control group of study	29
Entire host country	29
Certain regions of host country	26
Other	14
What parties were (or will be) part of the arrangement to provide the intervention? (Respondents could check more than one option)	**Percent of Studies**
Host country research team	71
Host country government, including Ministry of Health	60
Host country institution (e.g., university, NGO, clinical center)	46
U.S. research team carrying out this study	44
U.S. institution carrying out this study	28
U.S. funding agency for this study	22
International agency (e.g., WHO, United Nations Children's Fund [UNICEF])	21
Private for-profit company	10
Other	9
Private foundation	7
How was (or will) the intervention be paid for? (Respondents could check more than one option)	**Percent of Studies**
Research grant for this study	35
International agency	29
Host country government	20
U.S. funding agency for this study	23
U.S. institution carrying out this study	20
Host country institution	17
Private for-profit company	12
Other	12
Private foundation	8

Others, while agreeing in principle that interventions should be provided in the future, believed that, in reality, this can be challenging. One respondent was concerned that a requirement for funding interventions indefinitely would put a halt to some types of research projects, due to the difficulty in obtaining funds for ongoing care:

> And the issue of what medical care to provide after the study is a thorny one—research can lead to suggested improvements in medical care but the funding of such improvements, and building of the management skills required to implement them, cannot be the focus of the research. This requirement means that for practical purposes, chronic illnesses cannot be researched since no research funding agency would agree to fund the treatment indefinitely.

Another researcher voiced a similar sentiment:

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

The concern about funding was heard from another researcher as well:

> These goals are usually but not always desirable if funding is available. No funding mechanism that I know of will guarantee such action. Therefore this requirement would ban almost all research in developing countries for whom it is the most beneficial even if many cannot benefit from the results. This is a case of best being the mortal enemy of good. I am very concerned that this kind of 'feel good' regulation will constrain research that is useful to poor people in developing countries.

Another respondent felt that researchers should not be the ones responsible for guaranteeing future access:

> I don't think that you can hold investigators responsible for the standard of medical care after the study is over—however, there should be thought in design whether the intervention, if effective, is feasible.

Another researcher also wondered about the limits of a researcher's responsibility:

> What is the horizon of responsibility of the investigator; is it specifically to those who are participating in a trial that the investigator is seeing on a regular basis and has personal contact with, or does it go to all of the people in the community, all of the people with that particular condition, and not only now, but in the future? So where does one's responsibility lie?...We were concerned about development of interventions that would be of value to the rest of the community, to the rest of the country, perhaps to the rest of the world. I find these kinds of situations very difficult to come to simple answers.

Another researcher voiced that future provision of interventions would be easier if drug prices could be lowered:

> I believe the issues of providing medical care and testing interventions in a developing country that may never be available there is a complex one. I think the answer does not lie in prohibiting research on interventions that will not be available but on changing the way drugs and other interventions are marketed. The current flap about AZT in Africa is a perfect case in point—the answer isn't that we shouldn't test AZT in Africa but that drug companies should not be allowed to protect their huge profit margins at the cost of blocking a South African drug company from producing AZT at a cost that Africa can afford. Changes in IRB aren't going to change the power of big business interests in the United States.

Another participant mentioned that successful interventions are frequently not implemented because of cost, even when the cost is relatively cheap by U.S. standards:

> There was actually a couple of years back a study from [African country] on use of bed nets that demonstrated substantial reduction in under five mortality from use of impregnated bed nets. The conclusion of the study was that this is a very nice study, but the [African country

> citizens] cannot afford to use bed nets. I found that distressing on almost every plain, but I think it raises the fundamental issue of where are the ethics of equity within countries and among countries; what are the cost issues, affordability issues?

Other researchers raised the more philosophical question of what defines "effective" in an intervention trial:

> The issue of what level of 'effectiveness' of an intervention should trigger replication of the intervention has not been addressed. 'Effectiveness' is not a yes/no question. If an intervention reduces transmission of say HIV by 10 percent, should it be implemented? What if another intervention might produce a 15 percent reduction, but the researchers are obliged to implement the 10 percent effective intervention?

As described briefly in Section C.3, researchers working on HIV/AIDS studies faced complicated challenges in providing care for their participants, because care for HIV needs to be ongoing, is expensive, and often needs to be modified over time to adequately control the disease. Thus, an HIV study that provides drugs invariably involves the question of what drugs will be available to participants after the study is over. One researcher had reached an agreement for providing medications to study participants:

> And the other thing is we are to negotiate, probably in [African country], one of the first requests I got is meds for life for the participant. And of course, it's not acceptable. Because it could be completely considered as an incentive to participate in whatever the research. You know, it's like buying a patient basically for the rest of his life....And that creates an impossibility on the budget side that we cannot afford to pay combination therapy for all the patients in the clinical trial forever. On the other hand, you've really got to find a solution because you can't put them on a therapy that would be ridiculous and stupid and really not helping anybody. So that is a struggle....We basically reach an agreement and some of the investigators refused and we didn't work with them. We said, the rule was set a priori that we would supply the medication for the patient and provide all medication and for an unlimited period of time as long as [the drugs] work....And we define the criteria for what is a response. That means an additional cost.

Another participant indicated that the local IRBs were opposed to providing HIV treatment that would be withdrawn when the study ended. In contrast, short-term treatments for diseases such as malaria provided during a research study may be more effective and beneficial. Other researchers, however, believed that controversies surrounding HIV/AIDS therapies were an example of "AIDS exceptionalism" and that many other interventions that would save many more lives, such as providing clean water to prevent diarrheal diseases in infants, were not being advocated.

One focus group participant described an example of research not being conducted because of concerns that the treatment being tested would not be available at a later date:

> We were going to look at an intervention using an [experimental drug] …and we had made arrangements to be able to provide antiretroviral drugs in those countries where they weren't routinely available, in this case [African country]. So the study design, those patients would get antivirals, everybody, for as long as they were felt to be of benefit even beyond the study, and that randomization would be to [experimental drug]. Well, the issue was, well, we're not sure that that is a treatment that would be available ever in that country, which is the type of statement that people make without much perspective, I think, on how things do change over time. In the HIV field we've heard this for CD4 counts, we've heard it for viral load monitoring. And then you see those things all come into place. So it's sort of an anticipation of the

> worst case scenario that at times ends up with research not being done in a developing country that I think could be of value to the country, doesn't put anyone at excessive risk, and, you know, has the ability to learn about the big question much more quickly.

The same researcher felt that availability of the intervention was important, but that it was essential to recognize that there might be a time lapse between successful trial results and widespread implementation of the intervention. His research team had made a commitment to provide treatment indefinitely to study participants after the conclusion of the study:

> I would feel uncomfortable if I thought there was no chance what we were doing would be of benefit to that country. It doesn't have to be a benefit to that country the day the study ends. The day the study ends, though, I do think that all the participants in the trial should have the benefit of whatever was found to be the best therapy....We had made provisions for them not to just get [experimental treatment], but to get the [existing treatment] they were going to be placed on...indefinitely. In the [African country] piece of the study, there was only going to be 300 patients. So we had arrangements of [pharmaceutical company] for [existing treatment], we had arrangements with [another pharmaceutical company] for [another existing treatment]. We had done everything we needed to do.

One researcher described submitting a manuscript for publication from an intervention study he had conducted in Africa. The editors of the journal to which he had submitted his paper challenged the ethics of the study, stating that the population of the country would never have access to this drug and that the benefit of the scientific knowledge would only accrue to the funding country, the United States. The investigator responded to this criticism:

> [Our response] was that the individual subjects who participate in this study did get benefit, because part of it was in order to evaluate the drug, everyone needed to be treated with the active drug to start with to clear up an infection and then they would have the protection from symptomatic [disease] for some period of time after treatment before they get a new infection. So everyone did benefit. And those who were randomized for the active [treatment] had continuing benefit for the 12 weeks for the randomized section of the study.

One respondent mentioned that in his or her study the "intervention" in question involved an enhancement of medical services, which may be difficult to maintain after the conclusion of the study:

> Our 'intervention' involves case finding activities, more extensive lab work than is normally provided, and the procurement of additional medication required to treat cases found. Medication is provided through the same government system it is normally provided through. However, it is my understanding that the involvement of researchers in normal public health activities has resulted in increased efficiency of medication procurement. These 'interventions' are not the focus of the study, but merely provide the cases for study. However, the improvement in health care provision experienced by the local population is unlikely to outlive the study....I'm concerned that the community will feel abandoned when the study ends and that this will negatively impact their trust of the local public health system which has been providing the enhanced services paid for by research funds. Also, study personnel have taken on reporting responsibilities for the communicable disease involved. When the study ends, reporting is likely to decrease dramatically unless the responsibility/awareness is thoughtfully transferred back to local providers.

In terms of dissemination of study findings, 62 percent of respondents believed that data from developing country studies should be made directly available to the study population. In comments, one researcher remarked that the form and manner of releasing data are significant:

> Release of data to the subject populations is a meaningless 'feel good' activity unless it is released to somebody who can use it for this or another similar population's benefit, and it is transmitted in such a form that it can be understood and is 'actionable' (identifies opportunities for action). Releasing data to subjects in such a way that it may result in detrimental outcomes to them or to others is not uncommon and is reprehensible. Thus, if data release is to be required, the way this is to be done must also be required so that it leads to a useful result.

C.4.2 Collaborative Arrangements

Researchers were asked about the involvement of host country researchers in different aspects of the research process, from grant writing and study design to manuscript preparation and authorship of papers.

Table C.4.2 reveals that developing country investigators are very heavily involved in U.S.-funded research projects conducted in their countries. At the same time, they are most likely to be involved in procedural tasks, such as recruiting participants or obtaining consent, and are less likely to be involved in substantive issues, such as grant writing and data analysis. One respondent noted, "I have observed that many American researchers inappropriately exclude foreign colleagues from authorship. This engenders resentment among foreign colleagues." However, survey data indicated that 97 percent of U.S. researchers did include developing country colleagues as authors on papers. Another respondent wrote that developing country researchers were often excluded from the more intellectual work:

> Emphasis should be given to more input from researchers of developing countries involved in the study. U.S. investigators have all the power, since they had the idea for the study, they wrote the grant....They therefore assume that they need to control all aspects of the study. It is sometimes like a paternal-son relationship. Also, it is sometimes visible that the local investigator is restricted to what he can do. The study sometimes will not teach them to become more independent, to learn how to write their own grant, even a small one.

Researchers with fewer than five years of experience conducting research in developing countries were less likely to involve developing country scientists in almost all tasks asked about on the survey. Researchers who were university employees were more likely than government or military employees to report that host country scientists participated in grant writing (62 percent versus 36 percent, $p < .001$). Those who were employed by public sector or nonprofit institutions, compared to those in private for-profit institutions, were more likely to include host country colleagues in study design (89 percent versus 55 percent, $p = .001$) and in data analysis (73 percent versus 18 percent, $p < .001$).

In addition, researchers whose projects received at least one source of funding from a developing country, compared to those who did not, were more

Table C.4.2: Research Tasks in Which Developing Country Scientists Were Involved

Developing country researchers were/are included in the following research tasks:	% Yes
Recruitment of participants	98
Training of research personnel	94
Listed as authors on papers	97
Changes in study design	94
Consent discussions with participants	94
Initial study design	87
Drafting manuscripts	83
Drafting consent form	82
Data analysis	69
Grant writing	53

likely to include host country scientists in grant writing (77 percent versus 48 percent, $p < .001$), in study design (97 percent versus 85 percent, $p = .01$), and in data analysis (85 percent versus 66 percent, $p = .006$). Countries with higher HDI were more likely to have researchers included in grant writing (60 percent versus 47 percent for lower HDI, $p = .03$.)

Researchers in focus groups frequently referred to the importance of having a good relationship with developing country collaborators. Researchers repeatedly stated that addressing ethical and cultural concerns in their research could only be accomplished successfully if a healthy relationship existed between the United States and host country scientists:

> The people you work with is the most important thing to getting anything done overseas. If you wanted to do something, and you go there and you say, 'I want to do this,' I mean, that's a hopeless situation. You have to—it's a long-term—it's certainly not a short-term thing. It takes a long time to develop relationships and understanding and trust and all those sorts of things. That's been invaluable in what we've done.

Another said, similarly:

> It has to be a collaboration. You have to go into the country, get some sense of the country, get some sense of who you feel comfortable working with in the country and what the norms are in it. And once you do that, then it is very easy, because you basically hand off a lot of things to the people in the country.

C.4.3 Capacity Building

Ninety-four percent of respondents reported that at least one "capacity building" resource remained in the host country after their index study was over. Table C.4.3 lists which resources investigators said remained in the host country.

Table C.4.3: Resources or Research Infrastructure That Will Remain After the Study Has Ended

Resource	Percent of Studies
Personnel trained in study	98
Medical, laboratory, or office equipment	90
Computer or data management systems	80
Medical laboratory, office, or pharmaceutical supplies	78
Organizational structure for health care or research	68
Buildings, laboratory facilities, or renovation	50
Power equipment, water systems, or motor vehicles	43
Other	12

Studies conducted in lower HDI countries were significantly more likely to leave behind medical, laboratory, office, or pharmaceutical supplies; buildings and other facilities; and power equipment, water systems, or motor vehicles.

Studies funded by the U.S. government were more likely to leave behind computers or data management systems. Studies with any source of U.S. funding were more likely to leave behind "power generating equipment, water systems, or motor vehicles," and those with any source of funding from the developing country were more likely to report that a health care or research infrastructure will be left behind.

One researcher mentioned that there are sometimes economic benefits to the entire community where the study is situated:

> We're just doing a study in [Asian country] in some God forsaken spot in the middle of no place. We're hiring everybody. We're building a place to do that. People are getting income during that period. That's coercion. It's positive. It's positive for them...you are inducing them to do this for reasons that are independent of the execution of the study, but if you go away, their life is going to be worse.

One researcher, finally, believed that part of capacity building should be helping to enhance host countries' capacity for ethics review:

> I think it's a good thing to promote ethical review of research in all countries, and if they don't have that capacity, to develop that....What I'm saying is make an offer for capacity building—we do it with everything else. That's part of it, is try to do capacity building technology transfer...a bilateral partnership so that both parties are educated about issues for both sides.

C.5 Review and Oversight

C.5.1 U.S. Review of Research

Ninety-one percent of researchers said their studies had undergone review by a U.S. IRB. The majority of studies (63 percent) had been reviewed by one IRB, and the remainder had been reviewed by two or more IRBs. For 42 percent of researchers, it took at least three months to receive approval from the IRB. Nine percent of researchers reported having *ever* abandoned a research project because it was impossible to get U.S. IRB approval, despite modifications.

Although more than 90 percent of researchers underwent IRB review in the U.S., only two out of the nine pharmaceutical researchers surveyed had their studies approved by a U.S. IRB. However, 100 percent of pharmaceutical researchers, as described below, underwent both Ministry of Health and ethics board review in the host country, and 100 percent, as described earlier, used written informed consent in their studies. One hundred percent of researchers from the U.S. government and the U.S. military had their studies reviewed by a U.S. IRB. Tables C.5.1 and C.5.2 show whether a study underwent U.S. IRB review according to the researcher's employer and the study's sponsor.

Table C.5.1: Percent of Studies Undergoing Review by U.S. IRB, Host Country Ministry of Health, or Host Country Ethics Board, by Researcher's Employer

Employer	Reviewed by U.S. IRB	Reviewed by Host Country Ministry of Health	Reviewed by Host Country Ethics Board
University	91%	72%	84%
U.S. government agency (nonmilitary)	100%	86%	97%
U.S. military	100%	100%	92%
Pharmaceutical/Biotech	22%	100%	100%

Table C.5.3 lists the issues raised in review of studies by U.S. IRBs. U.S. IRBs were most likely to raise the need for local language consent forms (66 percent) and letters from developing country officials (65 percent). Close to half (45 percent) also asked about the cultural appropriateness of study procedures, and 30 percent raised the relevance of the research to the developing country. Only 4 percent questioned whether the study was too risky. These numbers already exclude studies for which researchers said the issue (e.g., placebos) was not applicable. However, what our data cannot discern is whether IRBs did not raise a topic when applicable because researchers had addressed the issue adequately in their protocol submission or because the IRB overlooked it.

Table C.5.2: Percent of Studies Undergoing Review by U.S. IRB, Host Country Ministry of Health, or Host Country Ethics Board, by Source of Funding of Study

Source of Funding	Reviewed by U.S. IRB	Reviewed by Host Country Ministry of Health	Reviewed by Host Country Ethics Board
U.S. government (nonmilitary)	97%	74%	89%
U.S. military	100%	100%	95%
U.S. private company	91%	86%	95%
U.S. non-profit (foundation, NGO, etc)	91%	73%	71%
Bilateral or international organization (United States Agency for International Development [USAID], WHO, UNICEF, PAHO)	88%	91%	85%

Table C.5.3: Percent of Researchers Reporting Issues Raised by Their U.S. IRB(s) and by the Developing Country Ethics Boards in Order of Likelihood of Being Raised

Issue	Raised by U.S. IRB(s)	Raised by Developing Country Ethics Board(s)
	% Yes	% Yes
Need for local language consent form	66	50
Need for letters of approval from developing country representatives	65	31
Complexity of language on consent form	45	38
Cultural appropriateness of study procedure	48	29
Relevance of research question to country where research is conducted and/or rationale for doing study outside the United States	30	23
Availability of intervention (if successful) to host country after study is over	23	25
Appropriateness of procedures for control group	18	17
Confidentiality protections for participants were not adequate	14	8
Use of placebos	12	12
Participant voluntariness may be compromised because of benefits study provides	10	7
Political considerations	7	14
Intervention was considered too risky	4	4

Researchers engaged in certain types of studies or in certain contexts were more likely to have particular types of issues raised in U.S. IRB review. For example, the 12 percent of researchers engaged in studies they classified as more than minimal risk were more likely to report whether their U.S. IRB raised whether the intervention was too risky (18 percent versus 2 percent, $p < .001$), appropriateness of procedures for the control group (35 percent versus 15 percent, $p = .02$), the use of placebos (32 percent versus 7 percent, $p < .001$), whether voluntariness would be compromised because of the benefits provided (25 percent versus 8 percent, $p = .005$), the relevance of the research question to the developing country (59 percent versus 27 percent, $p < .001$), the availability of the intervention after the study was over (52 percent versus 17 percent, $p < .001$), the complexity of the language on the consent form (66 percent versus 42 percent, $p = .01$), and the need for a local language consent form (84 percent versus 63 percent, $p = .02$). Similarly, those conducting randomized trials were more likely to be asked about the use of placebos, the availability of the intervention after the study was over, and the complexity of the consent form. Studies focusing on HIV/AIDS or on vaccines also were more likely to be

asked about the availability of the intervention after the study was over, and vaccine researchers were also more likely to be asked about the cultural appropriateness of study procedures.

Researchers reporting that they worked in areas where "the standard of medical care may be much lower than in the funding country, creating difficulties in establishing appropriate procedures for the control group" were indeed more likely than others to be asked by their U.S. IRB about the appropriateness of procedures for the control group (30 percent versus 14 percent, $p = .02$). Researchers were more likely to be questioned about the cultural appropriateness of study procedures for studies where they believed that religious/cultural norms of the population were inconsistent with individual decisionmaking (57 percent versus 44 percent, $p = .02$).

Only 20 percent of index studies had Data Safety and Monitoring Boards (DSMBs). Studies classified by researchers as greater than minimal risk were significantly more likely to have DSMBs (50 percent versus 15 percent, $p < .001$), as were those funded by a U.S. pharmaceutical company (50 percent versus 17 percent, $p < .001$) or a European pharmaceutical company (72 percent versus 18 percent, $p < .001$). Randomized controlled trials, logically, were more likely to have a DSMB (55 percent versus 4 percent, $p < .001$), as were studies involving clinical care (35 percent versus 17 percent, $p = .008$). Almost half (45 percent) of those with DSMBs said the DSMB had raised ethics issues in their reviews, but there was no significant difference between greater than minimal and minimal risk studies in the likelihood of ethics issues being raised. Studies in lower HDI countries, however, were more likely to have ethics issues raised by DSMBs (76 percent versus 44 percent for upper HDI countries, $p = .03$).

Thirty-two percent of researchers said U.S. regulations were never flexible when they needed to be, and only 2 percent said they *always* were flexible when they needed to be (Table C.5.4). Almost all respondents (94 percent) said U.S. IRBs sometimes or always were insensitive to local cultural norms, and 66 percent said U.S. IRBs sometimes or always were more concerned with politics than with protecting the interests of subjects; and yet 97 percent said that current U.S. regulations sometimes or always ensure high ethical standards.

In written comments and in focus groups, researchers requested more flexibility in requirements from their U.S. IRBs and better education of IRBs to the conditions and realities of life in a developing country. Representative of so many researchers, one respondent said, "I think IRB chairmen should be required to do international site visits so they can see the realities of what they ask!" Another said:

> The IRB guidelines at my university are so narrowly defined that they didn't apply in any way to developing countries. I don't think there was a single member of the committee who had ever been in a developing country. They wanted me to include a phone number people could call with complaints when the closest phone to my project site was an hour's drive through the mountains and my subjects didn't have cars. The members of the Board had no clue how to make adaptations for people who can't read or write. It was a joke.

Another researcher similarly described being required to include the phone number and name of the chancellor of his or her university. Still another said:

> The U.S.-based IRB that I must use has essentially no experience with conditions and realities of life, medical care, and research in developing countries. Their actions often seem more focused on avoiding potential litigation than on protecting research subjects and very often make decisions that perpetuate bad public health situations overseas because of a poor understanding of realities.

One focus group respondent said, similarly:

> I would say most of the people who are [on] IRBs here have never put their feet in those countries. They really don't know anything about the real life in these countries....If the target is to

Table C.5.4: Researchers' Beliefs/Attitudes about U.S. and International Human Subjects Regulations and Guidelines

Options	%Always	%Sometimes	%Never
U.S. human subjects regulations are flexible where they need to be.	2	65	32
Developing country collaborators rely on U.S. ethics regulations for guidance.	13	78	9
U.S. IRBs are more concerned with politics than they are with protecting the interests of research subjects.	10	56	34
The current U.S. rules and regulations governing human subjects ensure high ethical standards in research.	27	68	3
U.S. IRB regulations are insensitive to local cultural norms and traditions outside the United States.	20	74	6
Developing country IRBs are more concerned with politics than they are with protecting the interests of research subjects.	3	76	21
Developing country IRBs have voiced concerns to me about the costs associated with the IRB carrying out its work.	6	20	74
National guidelines in developing countries are effective in protecting research subjects.	9	86	5

> improve the welfare of these people, we have probably to find some compromise and be more flexible between the concept of the individual rights and the feasibility not to miss the target in the field with different cultures.

Indeed, some researchers suggested that the lack of flexibility actually impedes public health:

> Institutional IRB regulations are quite strict and many times impossible to meet. This has caused many studies to not be conducted in developing countries....My feeling is that we have gone too far into rules and regulations and that many studies benefiting study groups are being abandoned because of the strict regulations. In the long term it is people like those included in a study population...that suffer, because the research is not being conducted.

Some researchers wanted more flexibility regarding particular requirements that originate in the United States but that they feel are inappropriate in developing countries. One example was provided by a researcher in a focus group of his U.S. institution requiring pregnant women to have the father of the unborn child sign a consent form for the woman's own HIV testing. The alternative, according to the U.S. IRB, was having the woman sign a statement that this researcher felt was no better:

> To raise this issue, you know, to have a woman sign 'this child's father is not reasonably available or the child is a product of rape,' or I forget the third one, is really pretty bizarre. Particularly if you're talking about HIV testing where in some countries that's a really big deal. You don't want your husband to know that you are getting HIV tested. There are real consequences for the woman for that. It's really inappropriate for us to be really forcing that issue.

C.5.2 Host Country Review

Seventy-seven percent of researchers reported that their studies had been reviewed by the host Ministry of Health and 87 percent by a host country ethics board. Of those reviewed by a host country ethics board, 84 percent were reviewed by the ethics board of the collaborating institution, 51 percent by a national board, and 16 percent by a state or provincial board. See tables C.5.1 and C.5.2 for a comparison of which boards reviewed respondents' studies, by the respondent's employer and research sponsor. Only 5 percent of studies overall were not reviewed in the host country by either the Ministry of Health or an ethics board. However, 12 percent

of studies funded by a U.S. or developing country nonprofit or NGO were not reviewed by either the host country Ministry of Health or a host country ethics board. All researchers whose studies were not reviewed by either the Ministry of Health or a host country ethics board were employed by U.S. universities. U.S. pharmaceutical company researchers were significantly more likely to have had their studies approved by a national ethics board than other researchers (78 percent versus 49 percent, $p = .03$) and were slightly more likely to report that host country review was required for them. Researchers believed 29 percent of the time that the developing country ethics board had been established because of U.S. human subjects regulations. Half of the studies took two months or less to be approved in-country, although 12 percent took more than six months to be approved by local boards. Six percent reported having ever had to abandon a research project because it was impossible to get developing country IRB approval, despite modifications.

Table C.5.3 shows which issues were raised by the host country ethics board. Issues most likely to be raised were whether there was a local language consent form (50 percent), the complexity of the form (38 percent), the need for a letter of approval from the host country representative (31 percent), and the cultural appropriateness of study procedures (29 percent). In general, each possible review topic was less likely to be raised by the host country board than by the U.S. IRB, according to researchers. The exception was the issue of availability of the intervention after the study was over, which was equally likely to be raised by host country boards and U.S. IRBs. Host country boards were most likely to question future availability for HIV/AIDS and vaccine studies. Political considerations also were most likely to arise with HIV/AIDS and vaccine studies. Researchers engaged in genetic studies were more likely to be asked by host boards about the relevance of the research question to the developing country (24 percent versus 10 percent, $p = .008$), and researchers working on perinatal health issues were more likely to be questioned by host country boards about their confidentiality procedures (25 percent versus 7 percent, $p = .02$) and about whether voluntariness could be compromised because of benefits provided (36 percent versus 7 percent, $p < .001$).

Whereas, as described earlier, studies classified by researchers as more than minimal risk had more issues raised in U.S. IRB review than did lower risk studies, the only issue raised more frequently in developing country review for more than minimal risk studies was the use of placebos (25 percent versus 9 percent, $p = .02$).

Respondents recognized the importance of local reviews, particularly with regard to their ability to raise concerns about cultural issues, and 77 percent thought a developing country ethical review should be required for all studies. Overall, 95 percent of researchers believed national guidelines in developing countries are sometimes or always effective in protecting research subjects. Researchers in focus groups also voiced their belief that local boards were in the best position to make ethical judgments regarding the welfare and needs of their communities:

> As much authority as possible should reside in local ethical review boards. Our [Asian country]-based ethical review board that has members from the Ministry of Health and general citizenry is vastly more qualified to pass judgment on a protocol to be executed in [Asian country] than a U.S.-based committee.

This same respondent added that local boards also may be more likely to consider the relevance of the study to their country's health priorities.

> These host international review boards are often interested in supporting research that is relevant to their perceived needs, and they're suspicious of studies which...may be to study some sort of drug which the local people of that country will not be able to purchase.

Researchers questioned the success of host country IRBs having community representation, however. In the survey, 50 percent of researchers thought there was inadequate community representation on local ethics

boards. We heard similar comments in focus groups, often emphasizing that in some countries, persons of differing backgrounds and/or class are unaccustomed to interacting with one another:

> OPRR expects that the IRB...at least have some representation of the community in which you're going to do studies. And traditionally in institutions' committees, whether they be IRBs or other types of committees in institutions in a place like [Asian country] are usually made up with people who run the thing or they're well-to-do/upper middle class community, and not necessarily representative of the lower class in the communities in which the studies are being done. And there's some resistance and some confusion about our insistence that there be representatives of commercial sex workers and STD patients sitting in the same room with each other, first of all and secondly, I'm sure the group dynamics in that situation, even with representation of the community at risk would make you wonder whether there's true representation, even if they're sitting at the same table, or whether they feel comfortable expressing their views.

Overall, researchers had varying experiences with host country IRBs, and several remarked how, in the years they have been conducting research, host country reviews had evolved from being a stamp of approval from one authority, such as the Ministry of Health, to a more rigorous and structured committee process. Still, just as researchers reported that they thought U.S. IRBs needed to learn more about the realities of life in developing countries, they believed host country IRBs needed to learn more about ethics. Ninety-one percent said developing country collaborators sometimes or always rely on U.S. ethics regulations for guidance. In a focus group, one participant said:

> I would like to see more initiative in development and implementation of ethics education and training in developing countries. The dialogue on this is dominated by the United States. It is not up to us to determine what is best for them.

One respondent suggested that a training grant could be established for academic institutions to work with local IRBs to provide education, training, and general IRB support. One researcher said, "Some of them do really quite a decent job, just as you would want them to be. And there are others that are completely rubber stamps, and nothing else.…Yes, there's an IRB, [but] I don't have any faith that there was any real review." One was quite concerned by this:

> [Local IRB members] may be people that are not all equipped intellectually, culturally, scientifically to deal with the issues you are asked to deal with. And therefore, you introduce a false sense of security and conformity with the rule, with the letter, when the spirit is actually vacant.

Another researcher said:

> In some cases, the developing country ethical review is actually a process of seeking permission to conduct research, and no ethical questions are raised at all. Developing country review boards are often more concerned about the financial aspects of the study than about ethics.

Another researcher reported that in the country where he or she was working, there still was no IRB, and the Ministry of Health believed that ethics review was not important. Thus, "our approval came in the form of a letter from the Director of the Division of Epidemiology and no IRB process was undertaken."

In the survey, 79 percent of researchers believed that developing country IRBs sometimes or always are more concerned with politics than they are with protecting the interests of research subjects. Another voiced the following concern:

> Some of the potential risks/ethics violations or cutting of corners can be perpetrated by collaborating investigators in other countries because the incentives to them (status, publications, foreign travel) to get the data collected are substantial enough as to be coercive. I don't know how policies and regulations could be written around this problem but I think it is not a trivial issue.

By contrast, another researcher had a different experience:

> Our current project in [African country]...they didn't have an IRB, but they made an IRB according to the NIH guidelines, and I was afraid that it was going to be a rubber stamp, but it turned out they had questions.... They actually raised issues and had questions that we had to address, and it was healthy….I think going through an IRB review establishes questions and then going through the process provides a cover for us and for that institution in case some kind of trouble occurs.

Twenty-six percent of researchers reported that developing country IRBs have voiced concerns to them about the costs associated with the IRB carrying out its work, and 70 percent believed funding agencies should provide funding to support the work of developing country IRBs. One researcher said:

> Foreign IRBs have no budget and will tell you, why should they use their time to meet U.S. OPRR regulations when no funds are provided for salary, secretarial, DHL, office, notification, etc?

Some researchers, however, were concerned about potential conflicts of interest when providing funding for the host country IRB. One researcher described his or her experience:

> Our research group has borne the responsibility for developing and maintaining an IRB in [Caribbean country]. This has been burdensome for us and at some level represents a conflict of interest. Our institutional IRB (as well as WHO and OPRR) have not been very realistic about the difficulties associated with ethical review in other countries.

C.5.3 SPAs and the OPRR

Sixty percent of researchers obtained an SPA for their studies, and 66 percent of those funded by the U.S. government had obtained an SPA. Those funded by any U.S. source were more likely to have an SPA than those not funded by a U.S. source (65 percent versus 19 percent, $p < .001$). For the majority of researchers, obtaining the SPA took three to six months, and for close to 20 percent it took more than six months. Six percent of researchers said they had ever abandoned a study because it was impossible to get an SPA. The majority of researchers (65 percent) did not find the SPA process valuable, and 49 percent thought the requirement should be eliminated. Not surprisingly, those for whom obtaining the SPA took at least three to six months were significantly more likely to believe that the SPA requirement should be eliminated than those who obtained their SPA more quickly (62 percent versus 41 percent, $p = .003$).

Twenty-one percent reported that they encountered resistance on the part of developing country officials in agreeing to an SPA; related, 24 percent reported encountering resistance on the part of developing country officials to U.S. requirements for IRB composition.

> The formation of an IRB board according to U.S. standards does nothing to assure appropriate review....The check of having the Board look like a U.S. Board seems to be designed to assuage consciences here rather than to get at the real issue of whether the protocol will be reviewed by members who are truly objective and include a 'member of the community' who can provide input into the study.

SPAs often became a heated topic during focus groups and were also mentioned more than any other topic in the open-ended comments researchers volunteered at the end of their surveys. One respondent wrote:

> The SPA process is burdensome to U.S. and developing country investigators. I have personally had to apply for three individual SPAs for the same project in order to satisfy the administrative structure of the project. This led to more than a six-month delay in providing our international collaborators with appropriate reimbursement.

Researchers often mentioned that the SPA requirement was duplicative at best and not designed to protect subjects at worst. They believed SPAs involved additional bureaucracy with little additional protection of subjects. One researcher wrote at the end of his or her survey:

> In my experience, if local review has been done, the assurances add no additional protection for human subjects (OPRR employees do not seem to have international experience). Ministries of Health are sometimes offended that the U.S. is dictating policy and the composition of ethics review boards in their countries. Furthermore, the delays in obtaining clearance often prevent researchers from addressing real public health issues in real time.

Another researcher had a similar reaction:

> In my experience they have not been very useful in terms of awareness regarding ethical issues. The guidelines and filling out of forms in this structured way is EXTREMELY difficult in developing countries. Mostly, it raises questions and in some way resentments. In many ways the requirements are just signed without being read, mostly because they are so cumbersome and complicated.

One researcher described how the act of signing a paper for collaborating agencies or government officials sometimes was met with resistance. Another researcher described that in areas of war or political conflict, the SPA requirement makes research impossible, since assurances require governmental signatures:

> I've had people just dying, whole villages getting wiped out by African trypanosomiasis. We can't work there [African country], because we can't get an assurance, because there's no government.

Multiple researchers felt that the strict imposition of procedural and administrative dictates was inappropriate: "The United States dictating how another sovereign nation should behave in the operation of medical research is a bit arrogant and colonialistic;" "It is humiliating to ask bodies in other countries to accept U.S. rules;" or "U.S. rules should not rule other countries. SPAs should be eliminated. Most countries get offended by having to be certified." Sometimes the rules inherent to the SPA process simply seemed irrational to researchers:

> I converted an NIH R29 grant into an R01 grant. Because the funding mechanism changed, I had to get a new SPA for essentially the same protocol, and the awarding of the grant was delayed for many months....On the other hand, I have a five-year contract that may ultimately support testing vaccines in Africa. I got an SPA for the first protocol executed under this project, an observational study. No additional assurance will be required by OPRR for this project, even for totally different protocols with much greater levels of risk.

In general, focus group discussions revealed that researchers believed SPAs had a bureaucratic, rather than ethics, focus, requiring original signatures of narrowly delineated officials. One respondent described a lengthy delay in starting his or her project because someone signed on the wrong line of a document. Fundamentally, one researcher shared, it indicated that the oversight of research has turned into a "sad" state of affairs where

researchers are spending the vast majority of their time attending to the paperwork requirements of oversight rather than the true ethics considerations:

> I think one of the sad things is that I think in general the investigators… really want to do what's right, and they really care about the ethics and the research that they're doing. And, yet, if you look at how much time on the average protocol in an international setting you spend on the ethics of it, versus how much you spend getting your assurance in place, getting the consent form down to an eighth grade level even though it's going to be translated into another language....So you spend so much time doing that. I would say probably less than 10 percent of the time is being spent on ethical issues, and the remainder of the time gets spent on paperwork, on exercises that don't protect human rights or human relations, human subjects. And I think that what's happening is that people are trying to now find ways to circumvent the IRB process, not because of the ethical issues but because of the paperwork, because of the assurances....And some projects are just not being done.

Others suggested that some researchers find current regulatory requirements so cumbersome that they now try calling their research by a different name, in order to avoid having to follow the regulations:

> It's like find a loophole in this so that it's not research....that's not helping your human subjects. In fact it's just facilitating people to do an end run around the whole process. So then you have no review. Oh, well, we're just going to provide treatment to some people as part of a program and call it [something else] instead of research. And then you have no review of that process. So, in fact...these OPRR regs and everything may...encourage people to go around the whole process.

One researcher said that the SPA application package from OPRR meant the end of his or her research collaboration: "I've sent it to some countries, and it's the last I've heard of them, places where you've been cultivating research for months and months." Another said:

> Our project almost ended. If we had not had a relationship before then, it would have ended. I was told it [OPRR regulations] was insulting. I was told it was being imperialistic: 'Didn't I think they were moral people?'

Several other researchers also objected to the rigidity with which U.S. guidelines or rules needed to be followed in other countries. One researcher described two recent examples where host country colleagues reacted: "'You know, maybe that's the way you do it in the West, but that's not the way we do it here.'" Another said:

> Rigid enforcement of U.S. regulations in another country or culture, however well meaning or politically correct, is a form of cultural imperialism and is often resented by [the] local population.

Many researchers were concerned that the staff at OPRR who reviewed SPA applications had inadequate experience in international settings. Some respondents recommended taking SPA reviewers to field study sites so they could see first-hand the conditions of the research. One researcher, however, suggested modifying, rather than eliminating, the process:

> Develop greater flexibility in the assurance process. This process should respect [the] scientific, intellectual, and ethical integrity of IRBs in developing countries. Allow foreign IRBs to have and maintain multiple project assurances [MPAs]. An IRB in a foreign country may start with an SPA but graduate to an MPA if it demonstrates that it can maintain standards acceptable to

> [the] United States. For some countries where there are many ongoing projects and the research infrastructure is well developed, this would make the process more efficient by reducing the need for a separate SPA for each project reviewed by the same committee.

Sixty-four percent believed international guidelines (e.g., CIOMS) should be used instead of U.S. rules and regulations, and 83 percent believed the composition of ethics review boards used in developing countries should not be dictated by U.S. regulations. One researcher said:

> I would like to see a U.S. policy that encourages developing countries to develop their own requirements. I believe that this would lead to a greater impact locally by implementation of requirements that they developed themselves.

There were general comments and recommendations concerning the future direction of international research ethics and oversight. One researcher asked from where moral authority arises:

> One can hear a perspective in a place like [Asian country] and maybe also in other developing country communities where the issue of consent or ethics or decisions about morality are really deferred to other people in a community. And so the idea of having an autonomous opinion about morality or ethics of a particular study for instance, really depends on who you are, whether you feel you have that moral authority or not, but whether you feel it's appropriate for you to make those decisions. So decisionmaking about issues like this I think are quite complex and may not fit the usual ideas we have of autonomy in our society.

And finally, two researchers talked about the fragility of trust and the potential for our regulatory framework to destroy that trust:

> We've suddenly tried to bureaucratize, that 'we trust you' issue....We're losing that and I'm not sure how to recapture it, but I think that's one of things we need to learn from our colleagues overseas is that they're trying to tell us something about trust, and then we do have to get our cultures in agreement...and that's the richness, I think, of collaborative research—we have to decide together what is an acceptable level of ethical behavior, and then how do we document that or how do we assure that.

Another wrote:

> The concept of 'ethics' should not be restricted to the narrow issue of protection against research risks. The NBAC must find a mechanism to view international research as a partnership, not as an exploiter/exploited relationship. The NBAC should actively try to explain the ethical framework as one of joint problem solving, and should do everything in its power to facilitate this noble enterprise. As it stands now, the ethical community is at serious risk of becoming marginalized and irrelevant to what is an exciting new era of trust, cooperation, and the alleviation of human suffering world-wide.

C.6 Discussion

C.6.1 Informed Consent

There were several important findings from both quantitative and qualitative data regarding informed consent. Researchers overwhelmingly use written informed consent, even when they believe it does not make sense to do so; researchers believe the consent process is an important means of educating participants about the study, although they want more flexibility in their methods to explain their research and document consent; and

researchers believe more attention should be given in the consent process to participant understanding, even though few researchers thus far have tested participant understanding themselves.

Given the educational and cultural contexts in which these researchers work, it was striking that as many as 76 percent of them reported obtaining written informed consent in their studies. Of note, the older the researchers were, the less likely they were to use written consent. Even when working in the lowest literacy populations (at least 80 percent of the study population illiterate), 60 percent of researchers still obtained written consent, although almost all researchers who used written consent also used at least one other method to explain their studies to participants. Indeed, researchers described in focus groups and in comments creative and multiple mechanisms for explaining research, ranging from focus groups and community meetings to brochures and media campaigns. Researchers overwhelmingly believed that the consent process provided an opportunity to discuss ethics issues with field staff, and host country staff were almost universally involved in explaining studies and seeking consent from participants.

The vast majority of researchers (85 percent) wanted more flexibility in methods of documenting informed consent. We have no way to know from our data whether the IRBs that reviewed the projects in question actually require written consent universally or whether they allow flexibility in certain situations, and investigators did not know this either. And yet, if the IRBs had more flexibility, one must wonder why they did not ask whether written consent was the most appropriate method to use. In some situations, researchers revealed that it was OPRR, in negotiating a SPA, that had required the written consent, or required that written consent forms grow in length from a couple of pages to more than five. Clearly, the U.S. Code of Federal Regulations does allow exceptions to written consent in certain situations. Presumably an experienced IRB would allow (or even require) researchers to use alternative methods when written consent either would be meaningless (e.g., when the population is illiterate) or when it would create more harms than benefits (e.g., when the purpose of signing the paper was significantly misunderstood or caused tremendous anxiety).

Written consent is the norm in domestic and international research, and it was the belief of most of our researchers that they had to use this method, even when it seemed ridiculous to them to do so. A recommendation that derives from this is that the new Office for Human Research Protections should reiterate more explicitly to both researchers and IRBs that, although written consent should remain the norm for most human subjects research, exceptions to written consent *are* allowed by current regulations and in some instances are morally preferable. It is a disservice to the intent of the regulations to obtain written consent in contexts where it is meaningless; in such situations, IRBs and researchers must consider broadly alternative methods to inform potential participants about the study and to document consent.

Many researchers suggested that IRBs expand their examination of a study's consent procedures from a seemingly exclusive focus on the individual researcher-participant interaction, to greater attention to the multiple methods researchers use to introduce the study to the community as a whole and/or to the family. As one researcher put it, after months of informing the community about the research, talking to leaders, and holding community meetings, to then be asked only how he was informing the individual participant indicated a lack of awareness of the process by which participants were informed.

Many researchers used oral consent with a witness signature to document consent. A related approach that we did not ask about is oral consent with the researcher's signature, whereby the researcher signs a form attesting that he or she explained the study to the participant and the participant voluntarily agreed to enroll. One researcher recommended that IRBs require researchers to use one or more methods from a "menu of choices" to reinforce within the research community that researchers must be thoughtful and considered about which methods of informing and documenting consent are most appropriate *for their target population* and should justify why they have selected a particular method.

Researchers further suggested that consent methods should be targeted to the study's design and level of risk. That is, some of them recommended that observational studies often should not require formal individual

consent and that higher risk studies should receive more scrutiny and have more rigorous requirements for consent and for understanding than lower risk studies. A clear recommendation is that researchers who have used diverse methods of informing or documenting consent should share their strategies and outcomes with colleagues and IRBs.

Certainly, many researchers referred to the tension between the presumed legal and ethics purposes of consent forms and procedures. On the one hand, informed consent was interpreted by researchers to be an ethics exercise, to ensure that their participants understand what they are being asked to do before deciding whether to participate. On the other hand, some of the requirements, like signatures or indemnity language, were seen as legal protection for themselves or their institutions. One focus group member suggested that if institutions need what researchers viewed as legal protection, this should be separated from consent procedures, so that procedures to protect subjects would be distinct from procedures to protect institutions.

Assessing participant understanding is significantly more challenging than drafting a consent form or engaging in alternative methods to inform participants. Researchers who were not required to perform such tests and who spent considerable time fulfilling other ethical requirements may have lacked time to address this issue. Also, it is difficult to know *what* elements of a study to ask participants about or how much understanding is sufficient, although the threshold certainly would vary with the study's risk. Only 16 percent of our respondents said they had used a test of understanding, despite the repeated assertion in focus groups that understanding was the relevant element of an ethical consent procedure and despite the fact that 65 percent of researchers agreed that "a mechanism to measure participants' understanding should be built into any research study."

That this area is challenging simply means that more empirical and conceptual work must be conducted to learn which methods to assess understanding seem most effective and what types of outcomes are most appropriate. An ethics challenge will always exist, however, in that certain concepts, despite broad and creative techniques to inform participants, and despite tests of understanding, are likely to still not be understood, or not understood the way Western researchers understand them. Concepts like DNA mapping, immunology, placebos, or randomization will be completely foreign to some individuals, and despite the most creative efforts, they will remain incomprehensible. Researchers and IRBs, then, must make the difficult balancing decision of whether the public health problem in question is important enough to warrant the conduct of research where participants have a less than complete understanding (assuming that they are protected from harm) or whether research will not be allowed in areas where participants cannot give consent with full understanding.

In terms of voluntariness, it is reassuring that researchers consistently reported that some numbers of participants refused participation. While this does not verify whether participants accurately understood the research, it does suggest that at least some knew that participation was not required. It is disconcerting, however, that refusals were less likely among populations of lower literacy, and of note that female researchers were more likely to have some participants refuse than male researchers. It is hard to interpret from our limited data the ethics implications of the involvement of village leaders or other family members in participants' decision to enroll and that these practices occurred more often in countries with lower HDI scores. That others are involved is not necessarily an indication that individual participants were denied independent choice, nor is it necessarily a sign that the choice made was an inappropriate or harmful one. Nonetheless, more empirical work should be conducted on the meaning of individual choice in different cultures, particularly in relation to gender, class, and political empowerment.

C.6.2 Study Design, Risks, and Benefits

A key survey question focused on why researchers were conducting their studies in developing countries rather than in the United States. Researchers could answer this question by selecting one or more reasons from a list provided. The most common reasons selected were that disease prevalence was higher, researchers had an

interest in addressing global inequalities in health, and host country collaborators asked for U.S. collaboration. Researchers also listed practical concerns, such as ease in identifying a relevant cohort, faster recruitment, and cheaper cost. Researchers who worked in lower HDI countries were even more likely to mention disease prevalence, relevance of intervention to the local community, and interest in global health inequalities.

In focus groups, some candid remarks were made by private industry researchers describing why their research was conducted in resource-poor areas. These justifications were practical, relating to faster recruitment of participants and, in HIV research, access to patients who had not had prior therapy. It is noteworthy that several of the private industry researchers in focus groups mentioned that completing a clinical trial quickly was one of their primary goals, based on the short timelines set for them by their employers. Several private industry researchers voiced their belief that, while the host countries were unlikely to be able to afford the new drugs that were being tested in their studies in the future, it was ethical to carry out the studies there because individual participants received some benefit during the study. In analyzing the survey data, it was not possible to make statistical comparisons between private and public sector researchers, due to very limited numbers of private sector respondents.

In the survey, relatively few (12 percent) of our respondents classified their research as greater than minimal risk, although 24 percent of researchers conducting intervention research classified their research this way, and researchers conducting randomized controlled trials or HIV/AIDS research were more likely to call their research greater than minimal risk. We have no means to objectively classify researchers' studies in terms of their level of risk, although it is possible that researchers, so close to their work, sometimes underestimate risk. At the same time, because IRBs and ethics boards rarely questioned researchers about risk in study review, it was clear that they were not concerned that researchers were underestimating risk.

Of note, researchers working with children were *less* likely to call their research greater than minimal risk. Although we asked researchers about the risk involved in their studies, we did not ask about potential clinical benefits that may result from study participation, and thus we cannot assess the risk/benefit ratio for studies reported in the survey that included children or infants. U.S. regulations require that greater than minimal risk research with children be conducted only when the children enrolled are likely to benefit directly, and the CIOMS guidelines specify certain conditions for conducting research with children, including determining that the purpose of the research is to obtain knowledge relevant to the health needs of children and that the research could not be conducted in adults and balancing any potential risks of the research with potential direct benefits for the children in the research study. In this survey, the norms for conducting research with children in developing countries have not been explored, while in focus groups, researchers mentioned that ethical guidelines for conducting research with children vary between industrialized countries. Further investigation of standards and practices regarding research with children in both industrialized and developing countries is warranted.

It is evident that the vast disparity in resources and background conditions between the U.S. and developing countries creates ethical challenges in the area of risks and benefits, in several ways. First, potential study participants may feel they have no choice but to join a research protocol, even a risky one, if it offers the chance of benefits unavailable outside the study. Moreover, in relatively deprived background situations, participants may be more vulnerable to misunderstanding the likelihood of personal benefit, out of their desperation and need for any type of health care. Most survey respondents (64 percent) felt that study participants joined their index project because of benefits obtained; and researchers in focus groups reiterated this theme. Seventy-six percent of researchers with greater than minimal risk studies stated that participants joined for benefits, and even 62 percent of those in minimal risk studies said the same. At least two focus group respondents felt that the direct benefits obtained by individual participants in a research project were sufficient justification for doing the research in a resource-poor setting, even if it did compromise voluntariness, and even if the treatments would not be available to the host country as a whole.

This raises questions about the degree to which voluntariness is compromised in such a setting and about the justification for doing research in populations that will not receive the larger benefit of access to successful treatments or research results. Certainly, since 30 percent of researchers generally and 44 percent of researchers conducting greater than minimal risk studies believed that their participants had unrealistic hopes about study benefits, further efforts to ensure participant understanding of study protocols must be implemented.

Second, this disparity in resources between rich and poor countries makes it difficult to establish procedures for control groups. Researchers repeatedly expressed concern about the appropriate treatments for control groups. Fifty percent of the survey respondents who had a control group stated that the standard of care was lower in the host country, creating difficulty in establishing appropriate treatment for the control groups. Furthermore, 78 percent of researchers believed that the issue of what standard of care to provide to study participants should be decided on a case-by-case basis. Several researchers commented that they believed it was ethical to offer study participants less than the best-known treatment in a controlled trial, if the best treatments were not locally available and if the study was addressing questions relevant to the needs of the study community. Determining the right standard to provide to control groups can be particularly challenging in HIV research. Most HIV drugs are very costly, making them prohibitive for most resource-poor countries and for the budgets of many research projects as they are currently constructed. In addition, the chronic nature of the disease demands that treatment be ongoing, and deciding when, if ever, study benefits should end becomes problematic. Also, even if drugs could be provided, they often require a health care infrastructure for testing and monitoring that is not available.

Third, this disparity in resources raises questions about what other treatments or care, *unrelated* to the study itself, researchers should provide to participants and/or to the larger community and for how long. This was a lengthy topic of discussion in several focus groups. In situations where study participants lack basic care, they often turn to the research team to address their health needs. Researchers described difficulty in determining how much care to provide, and, in some cases, they received little guidance from their U.S. IRBs in determining what was appropriate. Researchers sometimes found that a study could not be conducted in a particular population because the medical care costs would be overwhelming, and the researchers felt they could not conduct the study without providing this supplemental care. In some cases the medical needs of the population were not evident until after the study had been initiated. One researcher commented that IRB members may have assumed that medical care was locally available when it was not. From researchers' comments, it appeared that funding agencies and IRBs had no clear policy about the issue of medical care unrelated to the research question.

Finally, there is a tension between the desire to directly benefit the study population and the need or desire to gain scientific knowledge to eventually benefit larger numbers of people. While this tension exists in all research, it is heightened in resource-poor settings, since participants' likelihood of receiving comparable benefit outside the study is significantly less than it might be in other settings. This tension is further heightened in countries with lower human development indicators. Indeed, researchers described struggling with the question of whose benefit is paramount: study participants or a larger community, such as all those who suffer from particular disease. Many researchers stated that their primary motivation for working in developing countries was to contribute to long-term health benefits for these countries and to reduce global inequities in health; nonetheless, every researcher must face the practical dilemma of how to balance the acquisition of such knowledge with the health needs of the individual participants. Virtually all the researchers in focus groups expressed concern for the well-being of the study participants, but also described limitations of time, money, and infrastructure, as well as scientific goals, that sometimes circumscribed their efforts to provide benefits to individual participants.

Data from this project, both from surveys and focus groups, indicate that U.S. researchers are acutely aware of and are often quite troubled by these ethical issues. The challenge, of course, is how to respond to them.

That researchers are sensitive to the ethics dilemmas is an important first step. Raising awareness among IRBs, as described earlier, about the realities of life in a developing country and raising awareness of ethics issues among host country boards also should help. Ultimately, however, the ethics issues raised by a study that is providing care that is considerably better than care that is or will be provided in the surrounding community raises larger challenges than can be solved simply by educational interventions. Much greater attention should be devoted to these ethics issues at a policy level so that coherent policies can be developed concerning what researchers should provide to participants in terms of standards of care for control treatments and in terms of unrelated medical care.

C.6.3 Obligations to Participants, Communities, and Countries

While most researchers in our study agreed in principle that effective study interventions should be provided after a study ends, many voiced concern that the practical realities can make this problematic. Researchers raised issues involving who will pay to implement successful interventions, how adequate infrastructure can be established to deliver interventions, how equitable selection of recipient populations or groups can be accomplished, for how long future benefits should be provided, and more. In the written survey, researchers with intervention studies were asked a series of questions about their plans to provide the intervention, if successful, to any groups in the host country at the conclusion of the research. More than half of the respondents with successful interventions were planning to provide them to at least some groups at the end of the study. Thus, although providing interventions can be costly and difficult, arrangements already are being made to do so in many cases. Some of the interventions were being provided only to study participants, but 29 percent were provided to the entire host country. Host country governments, logically enough, were more likely to be involved in the plans to distribute the intervention to the entire country than in other plans; international agencies were more likely to be involved in providing the intervention in lower HDI countries.

It is notable that researchers who provided the intervention were more likely to say that they were conducting the study to address global inequalities in health. In two cases, researchers in focus groups reported having made specific plans to provide expensive drugs to study participants at the end of the study, although the drugs would not be made widely available in the host country. In general, researchers expressed the sentiment that providing interventions was a laudable goal, but that the economic realities of resource-poor countries made it impossible to accomplish on a broad scale. Fifty-three percent of researchers agreed that research should not be carried out in a developing country unless the intervention will be made available after the study, although many felt that imposing a precondition that interventions must be provided if research is to be carried out would prohibit much useful research that would have the potential to benefit poor communities in the developing world.

Some details of the arrangements to provide interventions were not obtained in the written survey, such as whether the intervention researchers were testing was a short-term or long-term one, its cost, and whether it required an accompanying infrastructure, all of which are related to the feasibility of future implementation and may have affected whether or not researchers provided their intervention. One respondent stated that high drug prices, particularly for HIV drugs, were a major obstacle in providing access to treatments in resource-poor areas and that this problem could never be resolved by ethics committees.

Other respondents noted that the utility of the intervention itself—for example, a new drug—hinged upon the infrastructure that was available in the host country. In many cases adequate infrastructure for health care does not exist, and providing an intervention would require large scale improvements in the health system. A few researchers mentioned the magnitude of the economic problems faced by resource-poor countries and stated that individual researchers were not in a position to address these inequities. At the same time, it was clear that U.S.-funded research did sometimes lead to lasting improvements in health care in the host countries. Many researchers said that they would welcome such improvements, but would be disturbed by policies

that put a halt to U.S. research projects that did not result in immediate widespread implementation of interventions, since in the end, they believe, this would be more harmful to resource-poor countries.

Fewer participants (27 percent) agreed that international policy should require researchers to establish a mechanism for continuing delivery of medical care after completion of the study. It is not clear whether researchers believed this question was referring to the ongoing provision of study-related interventions or to the provision of general medical care unrelated to the intervention. Medical care unrelated to the research question may be seen by researchers as a responsibility of the host country and international agencies rather than that of the U.S. research team. Many researchers felt that the global inequalities in health care and economic resources were too great to be addressed adequately by individual research projects in developing countries. However, many felt that it was desirable to continue medical care and other services that had been set up in host countries, if reasonable mechanisms, other than a requirement imposed on researchers themselves, could be developed to support this.

In sum, although most researchers expressed concern for a blanket requirement that all U.S.-funded research provide successful interventions to host countries' communities, many interventions, in fact, are being provided, and many researchers are taking steps to accomplish this goal. This is another area that deserves further inquiry regarding the mechanisms and policies that can address the goal of providing benefits to those communities in resource-poor countries that have participated in research projects, without halting or encumbering the research process.

Separate from research products, U.S.-sponsored research can, and should, include capacity building in developing countries for health care and research activities, including the enhancement of human capacity. Focus group participants frequently mentioned that collaboration with, and respect for, the host country researchers was essential to well-designed and appropriate international research. Several researchers described relationships they had with in-country colleagues for many years. Consistent with this, U.S. researchers with less experience were less likely to involve their colleagues in a number of the research tasks.

The survey results revealed a hierarchy of research tasks that involved collaboration, from more intellectual tasks, such as grant writing and data analysis, to field operations, such as recruitment of study participants and training of research personnel. Developing country colleagues were more often included in the field operations than in the intellectual work, although a significant number were included in both. The lowest level of participation by developing country scientists was in grant writing; those projects that included some developing country funding, logically enough, were more likely to involve host country scientists in the grant writing process. One respondent remarked in survey comments that U.S. researchers often had a paternalistic attitude towards their developing country colleagues and that host country scientists were not allowed to develop skills, such as grant writing, that would enable them to work independently. Grant writing is one area in particular in which more extensive capacity building seems warranted; developing country scientists who could obtain funding could gain more control of the research and could direct the research towards goals relevant to their country's needs.

Capacity building also involves resources for health care or research infrastructure, which may be left in the host country at the conclusion of the study. The vast majority (94 percent) of survey respondents said that some resources remained, ranging from medical equipment, organizational structure, and computers to better-trained personnel. Studies conducted in lower HDI countries were more likely to leave behind resources such as buildings or power equipment than studies in higher HDI countries, and studies with some developing country funding were more likely to leave organizational structure. Focus group participants commented that equipment and supplies are only useful if the technical expertise is left behind to utilize them. In 68 percent of the index studies, organizational structure was left behind; however, funding may not exist to carry on research or health care activities.

One survey respondent described enhanced public health surveillance and procurement of medication in his or her study that would not be maintained at the conclusion of the research; another described better hospital treatments for a life-threatening disease, which reduced the mortality rate during the study. These researchers mentioned their concern that at the conclusion of the research, conditions would revert to their previous state. Thus, in some cases, the benefits of research may be short lived if sustained efforts are not made after study completion to continue collaborative relationships and to continue to build the human and material capacity of host country communities.

C.6.4 Oversight and Research Review

Overall, 91 percent of studies were reviewed by a U.S. IRB, 87 percent were reviewed by a host country ethics board, and 77 percent were reviewed by the host country Ministry of Health. Indeed, only 5 percent of studies were not reviewed by any board. That almost all studies received outside ethics review suggests that, in the relatively short period since U.S. regulations and international guidelines governing human subjects research have been in place, the idea that studies should receive prior review from an outside committee has become a standard practice.

Our small sample of researchers from the pharmaceutical industry were significantly less likely to have their studies reviewed by a U.S. IRB, but in every case their studies were reviewed in the developing country. In focus groups, pharmaceutical researchers from two companies commented that their company policy required local (host country) review at each study site, but did not require U.S. IRB review. The requirement for local IRB review fulfills Food and Drug Administration (FDA) requirements, which companies must follow when submitting clinical data to the FDA for drug approval. It should be noted FDA regulations are the only ones applicable to private industry, since private companies are exempt from the Common Rule[2], which requires U.S. IRB review for projects carried out outside the United States.

While outside and prior ethics review has become standard practice, it is less clear what the content of that review is. From researchers' reports of which issues were raised in review of their studies, it is clear that procedural issues are far more likely to be raised by U.S. and to a lesser degree host country boards than are substantive issues. U.S. IRBs were most likely to ask researchers about the need for a local language consent form (again, despite the questionable appropriateness of written consent), for letters of approval from developing country representatives, and about the complexity of language on consent forms. The substantive issue addressed most frequently was whether the research question was relevant to the host country (or why the study was being conducted in the host country), although this issue was raised with fewer than one-third of researchers.

Lagging further behind was the future availability of the intervention to the host country (addressed by 23 percent of IRBs) and issues of design, such as the appropriateness of procedures for the control group and whether the intervention might be too risky, addressed by only 4 percent of IRBs. Of course, that an IRB did not raise an issue might have meant that the researcher had addressed the issue adequately before submitting the protocol; alternatively, our findings suggest that IRBs truly are better equipped or more schooled in discerning procedural issues, such as whether or not a local language consent form has been submitted, which certainly are easier for IRB staff or reviewers to ascertain through such means as a check list. These are items that can be gleaned from U.S. regulations and then easily noted to be present or absent in each study. Such items do not require as much training or experience in real research ethics; thus, a more sophisticated analysis of the *adequacy* of the materials presented by a researcher from human subjects perspective need not occur.

Certainly, some number of procedural requirements are inevitable and appropriate in even the most sophisticated of reviews. Moreover, one could argue that procedural issues apply to all studies, and particular substantive issues will apply only to particular studies, so of course the likelihood of procedural issues being raised should be higher than each individual substantive issue. On the other hand, we asked respondents to report

whether the IRB had raised an issue *only* if the issue (e.g., adequacy of the intervention provided to the control group) was relevant to their own study. Fortunately and appropriately, IRBs were significantly more likely to raise substantive issues with the 12 percent of studies investigators classified as greater than minimal risk. For such studies, issues from the appropriateness of interventions for the control group to whether the study was too risky were more likely to be addressed by U.S. IRBs.

U.S. IRBs also were more likely to ask about issues that researchers themselves thought were relevant to the study. For example, researchers who reported in the survey that they believed that the standard of care in the host country was lower than that of the funding country—and that this made it difficult to establish procedures for the control group—indeed were more likely to be asked about the adequacy of control group interventions by the IRB. Of course, from our retrospective survey, one does not know whether the U.S. IRB brought this issue to the researcher's attention, whether the researcher brought it to the attention of the IRB, or whether both the researcher and IRB independently believed the issue was relevant.

Host country boards, like U.S. IRBs, asked about the need for a local language consent form more than any other issue. Host country boards, however, were less likely to ask about *all* issues than the U.S. IRB, with the exceptions of the availability of the intervention after the study was over and the appropriateness of using placebos, which were asked equally often. It is possible that host country boards raised fewer issues because they generally reviewed studies only after U.S. IRBs had approved them and researchers had cleared up issues of concern; however, it is possible that because the host country review was submitted by the respondent's developing country colleague, the U.S. researcher was not fully aware of all of the issues raised. Or, it might be that developing country boards are truly less likely to raise a variety of issues in their reviews. Certainly researchers believed developing country ethics boards needed additional training in ethics and that host country boards often raised scientific or budgetary issues rather than ethical issues. Certainly, ethics capacity building can be part of the general capacity building in which researchers participate as part of research collaborations.

The FIC of the NIH recently released for the first time a request for proposals to provide long-term ethics training to developing country scientists, presumably to address this need. It is less clear how U.S. IRBs or the new OPRS will learn more about the realities of international health work, as was also suggested. Short of requiring extensive travel, one possibility is to require someone with substantial experience in developing countries to review studies, as is required for research with prisoners or with Native American populations. Further, even a small amount of required continuing education for IRB members and staff could provide statistics about typical distances from phones or health clinics, the likelihood of having a car, typical literacy rates, or even the frequency with which in-country ethics boards meet and the operating budgets of local ethics boards.

It is important to emphasize that U.S. researchers believed strongly in the importance of host country review, and 77 percent believed it should be required for all studies. Researchers reported that it is during the host country review that culturally relevant concerns are likely to be raised. Indeed, in our survey, cultural appropriateness of study procedures was the second most likely issue to be raised by host country ethics boards. Several researchers further commented that when a thorny ethics dilemma arises (e.g., what standard of care should be used or what study end point is appropriate), it is the host country that should decide.

An issue that raised considerable emotional response in focus groups involved SPAs, which currently are required for all federally funded researchers and/or those otherwise required to follow the Common Rule when they work in developing countries. Most would agree that the intent of the SPA requirement is good: SPAs are designed to ensure that a host country board reviewed the study and that the composition of the board was both varied and legitimate. The SPA requirement is a way to make sure that a single person, such as a co-investigator, or even a government official, did not simply write a letter approving the study. The requirement, further, was designed to ensure that the host country review was an ethics review, rather than one based on

financial or political considerations. While these goals are laudable and appropriate, the system in execution, according to our respondents, generally has been a failure.

First, there was consensus that the process for obtaining an SPA is excessively bureaucratic. Whereas all other ethics and design decisions and negotiations occur locally between the United States and the host country researchers and institutions, to obtain an SPA, the U.S. federal government must become involved. This not only delays the process significantly, but more importantly from an ethics perspective, it brings individuals into the mix who, according to our respondents, in general have less familiarity with both particular research settings and international health research than the other parties already providing external review.

Several researchers wondered, in focus groups, why their U.S. IRB cannot decide the adequacy of the host country board if there are generic concerns about composition. Many researchers used the word "ridiculous" when describing current SPA requirements and cited issues such as the need for original signatures from narrowly specified officials in the host country or the need for a completely new SPA every time a new or follow-up study is conducted between the same institutions or in conjunction with the same ethics board that already had been sanctioned by OPRR and granted an SPA. Of little surprise, then, 65 percent of researchers believed the SPA process was not valuable, and half thought it should be eliminated.

Not only did researchers believe that the SPA added little to the ethical conduct of their research, they further were concerned that it offended their colleagues, a practical and a moral concern. From a practical perspective, gaining trust and interpersonal familiarity can take months or years and is essential to the smooth execution of a cross-national collaborative project. Outside requirements that threaten this relationship, because they are offensive or "imperialistic," to quote our respondents, clearly impede the research process. Arguably more important, however, from a moral perspective, a goal of U.S. and international guidelines is to respect persons and communities. While it is appropriate, according to our researchers, for U.S. guidelines to require host country review and to require that certain elements (such as evaluations of risk and benefit or appropriateness of consent procedures) constitute that review, to delineate too precisely the composition of boards or the types of people who have authority over their procedures can be disrespectful of how other countries conduct their work. Requiring other countries to follow certain *procedures* seemed to be more offensive to our respondents' colleagues, they reported, than requiring that certain *substantive* areas be covered in a review. If our government is concerned about the adequacy of ethics capacity in some developing countries, specifying who can sign off on the board's composition is not the answer.

Many researchers in both focus groups and the survey recommended allowing developing country boards international guidelines (such as CIOMS) rather than having to follow U.S. regulations. The majority of respondents (64 percent) thought international guidelines should be used; only 7 percent disagreed.

Researchers' global comments regarding IRB review and SPAs overlapped, as one would expect, with their comments regarding informed consent. Informed consent was a significant part of research review, so when researchers asked for greater flexibility in how to inform participants or how to document consent, they often more broadly expressed the desire for greater flexibility in the review process. Researchers again requested flexibility both in how IRBs interpret federal guidelines and in the guidelines themselves.

In general, researchers voiced strong interest in and support for the spirit of ethics guidelines—that is, to protect the interests of research subjects and their communities. However there was widespread concern that the regulations themselves and their interpretation by IRBs often failed to adequately protect populations in developing countries and, in fact, impeded the process of conducting research that meets substantive ethical standards.

D. Results of the Study of Developing Country Researchers

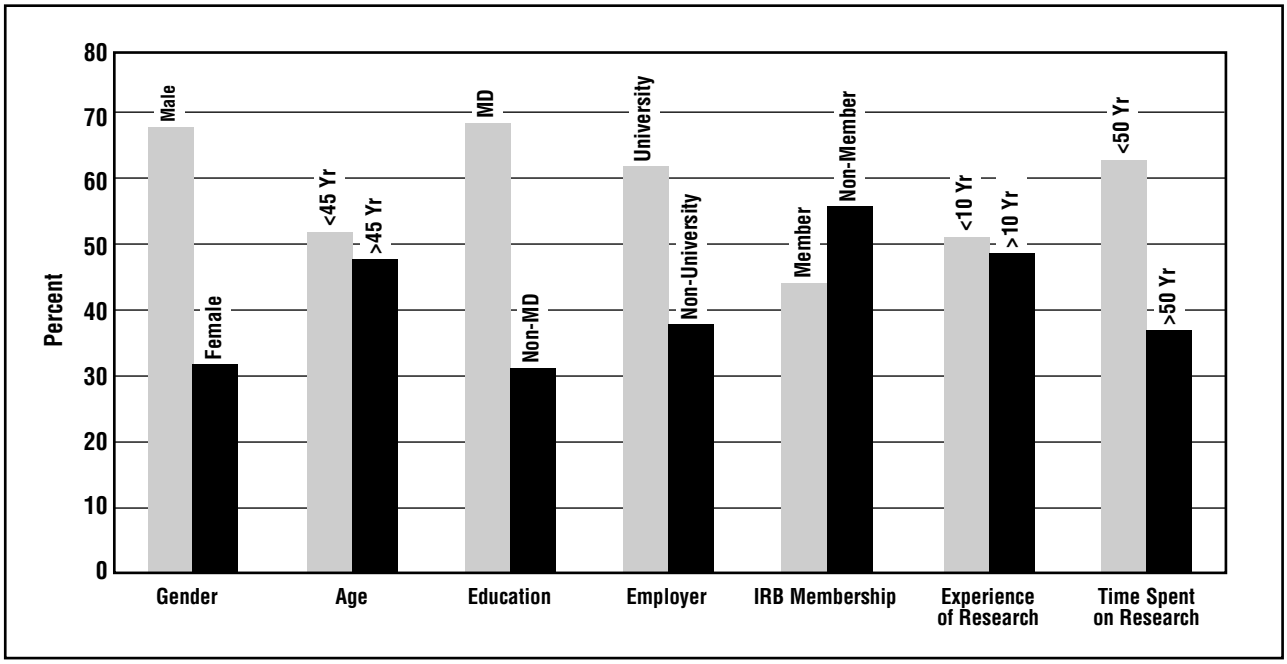
D.1 Description of Developing Country Researchers and Their Work

D.1.1 Quantitative Research Component

Demographic information pertaining to participants in the developing country survey is shown in Figure D.1.1. More males (68 percent) comprised our sample as compared to females, and a little more than half (53 percent) of the respondents were less than 45 years of age. The majority of our survey respondents were physicians (M.D.s) or equivalent (69.3 percent) and were employed by universities (62 percent). Forty-four percent of the researchers were members of an IRB/ethics board at either the national/state or local level. Three-quarters (74 percent) of IRB members were male. In addition, more than half (63 percent) of the IRB members are older researchers (>45 years of age).

In order to determine their level of experience, the researchers were asked about the numbers of years they have been involved in conducting research in developing countries, the average time they spend on research, and the number of studies they have conducted. About half of them (53 percent) had fewer than ten years of research experience in developing countries, while the other half had more than ten years of experience. Eighty-one percent of the researchers had conducted more than five research studies, while fewer researchers spent more than half of their time conducting research.

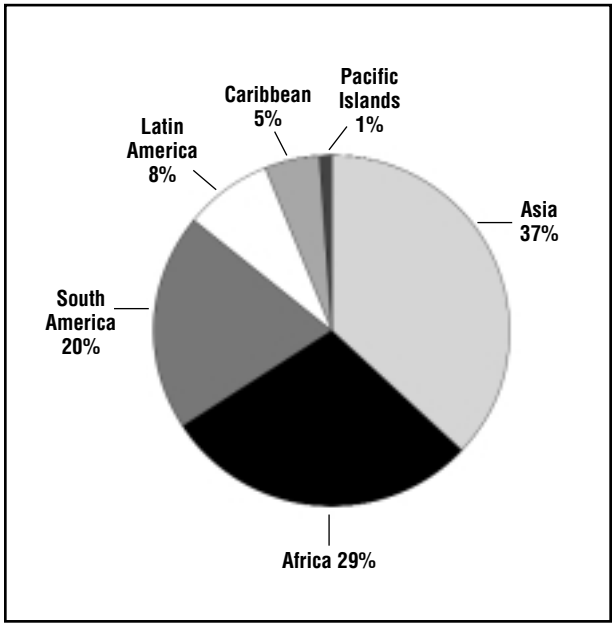
Figure D.1.1. Socio-Demographic Information on Researchers



In our survey sample, most of the researchers (37 percent) were conducting studies in Asia, followed by Africa (29 percent) (see Figure D.1.2).

To explore the types of studies being conducted, their topics, and the methodological approaches that are being used to investigate those topics, we asked the researchers to provide information about their work. Those researchers who had been involved in a research project and had received funds from the United States and/or who had collaborated with U.S. investigators were asked to identify that project as the "index study." Researchers who were neither involved in U.S.-funded studies nor had collaboration with U.S. researchers were

Figure D.1.2. Regions of the Developing World Where Health Researchers Conducted Research (*Researchers could check more than one region*) (n = 200)



asked to identify a research project they had been working on for the past five years that would be labeled the "index study."

Researchers were asked to provide information regarding their respective index studies. The results of these questions are shown in Table D.1.1. Almost one-third (31 percent) of the studies involved infectious diseases excluding HIV/AIDS, and nearly 45 percent of the studies were conducted on infectious diseases including HIV/AIDS. Twenty-seven percent of the studies addressed issues in health systems/services research, and a quarter of the studies (24 percent) in chronic disease research. Only 5 percent were related to vaccine development and testing.

In response to the question regarding the discipline of the study, nearly half (52 percent) of the studies were related to epidemiology, while one-third (30 percent) were in health systems research and 24 percent in clinical care. Anthropology and behavioral studies were also included in nearly one-third of the responses.

Among the various methodological approaches being used to carry out different studies, 53 percent of the respondents were conducting observational and descriptive studies. Twenty-eight percent were prospective studies, while 27 percent were labeled as

Table D.1.1: Information on the Developing Country Researchers' Index Studies (Respondents could check more than one option)

Topic of the Study	Number of Responses	Percent
Infectious disease, non-HIV/AIDS	61	31
Health systems/services	52	27
Chronic disease	46	24
Cultural practices/behavior	40	21
Reproductive health	35	18
HIV/AIDS	28	14
Nutrition	25	13
Environmental health	23	12
Injury	11	6
Other	9	5
Vaccine development/testing	9	5
Perinatal health/birth defects	9	5
Genetics	8	4
Discipline of the Study	**Number of Responses**	**Percent**
Epidemiology	103	52
Health Services Research	60	30
Clinical Care	47	24
Behavioral Science	34	17
Microbiology	28	14
Anthropology	23	12
Psychology/Mental Health	14	7
Other	10	5
Ethics	6	3
Method of the Study	**Number of Responses**	**Percent**
Observational/descriptive study	105	53
Prospective study	56	28
Randomized controlled trial	54	27
Qualitative methods	53	27
Operational research/program evaluation	41	21
Community-based intervention	40	20
Case-control	36	18
Other	8	4
Cross-sectional study	7	4

"randomized controlled trials" that are liable to be clinical in nature. Twenty-seven percent of the reported studies used qualitative methods.

The survey gathered information about the source of funds being provided to carry out the index studies (Table D.1.2). Developing country governments funded 35 percent of the studies, followed by international organizations, which provided funds for 25 percent of the studies. Developing country sources funded a large number of the studies, whereas the private sector (any source) funded fewer studies overall.

Table D.1.2. Sources of Funding for the Study (Multiple answers question)

Source	Number of Responses	Percent
Developing country government	69	35
International organization (WHO, PAHO, etc)	49	25
U.S. nonprofit (foundation, NGO)	42	21
U.S. government (nonmilitary)	36	18
Bilateral organization (USAID, etc)	35	18
European government (nonmilitary)	25	13
Developing country nonprofit (foundation, NGO)	18	9
U.S. private company	14	7
European nonprofit	12	6
Developing country private company	12	6
Other	10	5
U.S. military	7	4
European private company	7	4

U.S.-funded studies comprised an important group for the purpose of our study. Studies having one or more than one sources of U.S. funding were defined as U.S.-funded studies. It excluded bilateral organizations. Forty-four percent of the studies were funded by one or more than one U.S. sources (Table D.1.3). U.S. nonprofit organizations were the largest funding source amongst the U.S.-funded studies.

The relationship of the source of funding (whether U.S. or non-U.S.) with the topic of the study was further explored and is displayed in Figure D.1.3. More (74 percent) studies on HIV/AIDS were funded by U.S. sources than by non-U.S. sources (p = .001). Of all the health systems studies, 69 percent were funded by non-U.S. agencies and 31 percent by U.S. sources (p = .024). More (54 percent) of the studies on infectious diseases (excluding HIV/AIDS) were funded by U.S. agencies (p = .05). Forty-one percent of the studies on reproductive health were funded by non-U.S. sources, and 59 percent had U.S. funding (p = .046).

Table D.1.3: U.S. Versus Non-U.S.-Funded Research

Funding	Percent of Studies
Non-U.S.	56
U.S.	44

Researchers were also asked to provide information about the study population. The responses are shown in Table D.1.4.

The largest number of studies was conducted on nonpregnant women (78 percent), followed by men, who were involved in 66 percent of the studies. Fewer studies enrolled infants. The majority of the studies involved participants who were Christians (71 percent), followed by Muslims and local indigenous religions. Nearly half of the respondents said that their study population had 6 to 12 years of formal schooling, and 4 percent of the studies involved populations who were university educated.

D.1.2 Qualitative Research Component

Focus group respondents for the developing country study were nearly equally male and female, 19 (53 percent) and 17 (47 percent) respectively. The majority of respondents had primary citizenship in developing countries (89 percent), followed by 8 percent with U.S. citizenship, and 1 percent had citizenship in other developed countries. Half of the respondents were aged 32 to 43 years, with all respondents under the age of 65. Respondents conducted different types of research with many reporting observational studies and community-based intervention studies (see Table D.1.5).

Figure D.1.3. U.S. Versus Non-U.S.-Funded Research (n = 199)

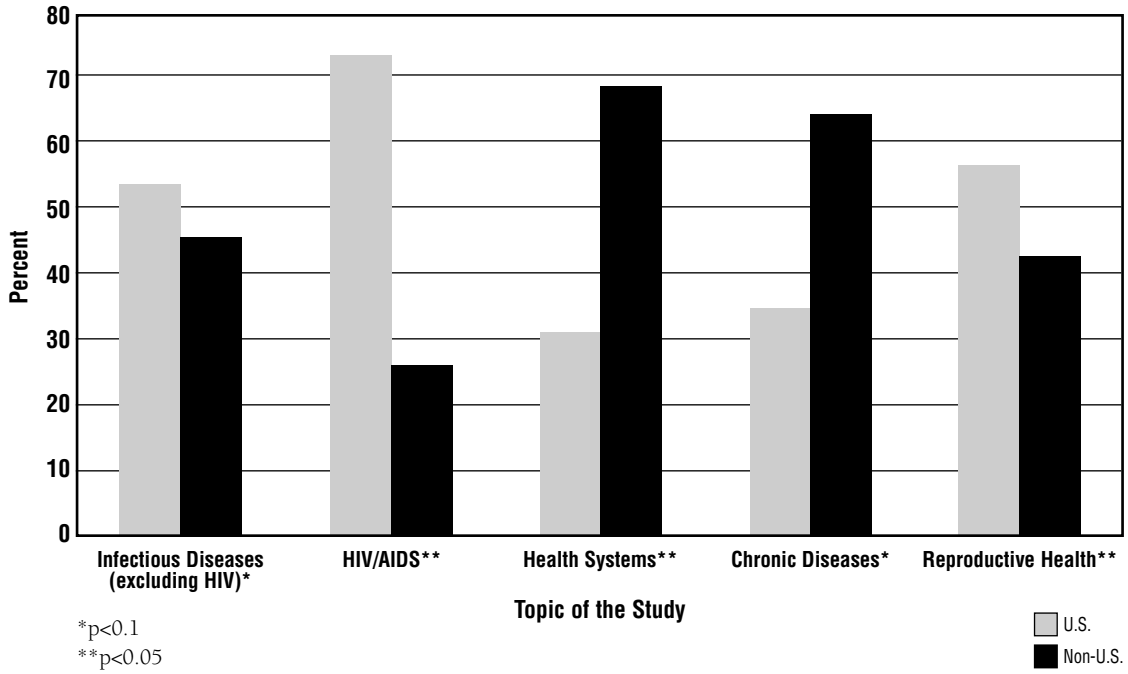


Table D.1.4: Information on Index Study Participants

Groups	Number (%) Yes
Nonpregnant women	152 (78)
Men	128 (66)
Pregnant women	92 (47)
Children 1 to 5 years	83 (43)
Infants (younger than 1)	48 (25)
Religion	**Number (%) Yes**
Christian	139 (71)
Muslim	77 (39)
Local indigenous religion	52 (26)
Buddhist	36 (18)
Hindu	28 (14)
Don't know	15 (8)
Animist	10 (5)
Jewish	9 (5)
Other	7 (4)
None	17 (7)
Education	**Number (%) Yes**
6 to 12 years of formal schooling	94 (51)
1 to 6 years of formal schooling	64 (35)
No formal education	11 (6)
University educated	7 (4)
Other/don't know	9 (5)

Table D.1.5: Types of Research

Study Design	Frequency (%)
Clinical trials	14 (38)
Observational studies	24 (65)
Community-based studies	21 (57)
Behavioral studies	17 (46)
Anthropological studies	8 (22)

A total of 68 percent of respondents were currently involved in research. Of the 12 respondents not currently involved in research, 7 had done some research in the past five years and 5 had last been involved in research over five years ago. The majority of respondents had between eight and ten years of research experience involving human subjects. Slightly more than half of the respondents reported functioning in the role of principal investigator on research projects, while 29 percent served as co-investigator. Three global regions were most frequently mentioned as the sites of research activities (see Table D.1.6).

Various sources for research funding were reported (see Table D.1.7).

Table D.1.6: Research Sites

Research Location	Frequency (%)
Asia	21 (54)
Africa	12 (32)
Latin America/Caribbean	5 (14)

Table D.1.7 Funding Sources for Research

Funding Source	Frequency (%)
U.S. government	9 (26)
U.S. military	2 (6)
U.S. private company	2 (6)
U.S. nonprofit, foundation, NGO	11 (32)
Non-U.S. government	8 (23)
Non-U.S. private company	1 (3)
Non-U.S. nonprofit	7 (20)
Bilateral organization	14 (40)
Other funding	7 (21)

For 78 percent of the respondents, their primary employer was located in a developing country, while the remaining 22 percent had primary employers located in the United States. Half of the respondents identified their primary employer to be a university. Other primary employers included government agencies and research institutions (see Table D.1.8).

Table D.1.8: Primary Employers

Primary employer	Frequency (%)
University	50%
Government agency	20%
Private nonprofit research institute	11%
Private for-profit research institute	6%
Independent consultant	3%

D.2 Informed Consent

D.2.1 Results from the Survey

The requirement for obtaining voluntary, informed consent from human subjects study participants is a fundamental aspect of research ethics. This section covers the area of informing and obtaining informed consent from study participants in the developing countries. The results are based on the survey questionnaire completed by developing country researchers.

Disclosure

Survey participants were asked about the different methods they used to inform participants on their research studies. Three out of four (77 percent) of the developing country researchers used explanations, as well as question and answer sessions with participants, either individually or in groups, as a way to inform and/or to obtain consent for study participation (Table D.2.1). Only one out of five researchers used pictorial descriptions of the study or study procedures to inform the participants. Academic researchers tend to use pictorial descriptions more (27 percent) than nonacademic researchers (11 percent, $p = .017$). Only a small percentage (4 percent) of the survey respondents stated that they used videos to explain the study.

Half (50 percent) used community meetings to describe their studies, although a majority (63 percent) agreed that where appropriate, community leaders' approval should be required by U.S. IRBs, in addition to individual informed consent (see Table D.2.4 on Recommendations).

Table D.2.1: Methods Used to Inform Participants and/or to Document Consent for the "Index" Research Project, in Order of Likelihood of Being Used

Option	% Yes
Explanation and question and answer session with participants (either individually or in groups)	77
Written informed consent, requiring a signature, thumbprint, or equivalent	62
Community meeting to describe the study	50
Approval from a village or community leader	49
Other methods	36
Oral consent with a witness signature	33
Test of participant understanding of research before enrollment	27
Pictorial description of study or study procedures	20
In research with adults, approval or consent from another family member	19
Video to explain study	4

In their studies, 27 percent of researchers had tested participants' understanding of the research study before enrollment (Table D.2.1). When asked for their recommendations, a very high percentage (84 percent) of them recommended that a mechanism to measure participants' understanding should be built into any research study.

More than half (58 percent) of the researchers disagreed that the formality of going through the informed consent process raises distrust in study participants. Nonacademic researchers were more likely to disagree (70 percent) with this statement than academic researchers (48 percent, p = .019).

More than half (58 percent) of the survey respondents agreed that some potential participants declined to enroll after learning about the study (Table D.2.2). One-third (32 percent) of all survey respondents disagreed that some potential participants declined enrollment after learning about the study.

Table D.2.2: Responses to Statements Regarding Consent in Index Studies

Option	% Strongly Agreed and Agreed	% Neutral	% Strongly Disagreed and Disagreed
The informed consent process is focused too much on the individual rather than on the family and/or community.	66	10	24
Participants often do not understand the concept of placebo.	50	24	26
Study participants are usually aware that they are in a research study.	84	10	6
The consent process is an important means of educating participants about the study.	94	3	3
The consent process provides an opportunity to discuss ethics issues with field staff.	89	6	5
After learning about the study, some potential participants declined enrollment.	58	10	32
The formality of going through the informed consent process raises distrust in study participants.	27	15	58
Local staff shortened or simplified the consent procedures compared to the original protocol.	35	16	49
Legalistic language was required on consent forms that was not meaningful to study participants.	29	9	62

Informed Consent Procedures

Written Consent. The survey respondents were asked about the methods of informing participants and/or documenting consent (Table D.2.1). Sixty-two percent of the researchers in our sample used written informed consent, requiring a signature, thumbprint or equivalent. However, a higher percentage of physicians in the sample used written informed consent (68 percent), whereas only 47 percent of nonphysicians used it (p = .014). IRB members were noted to use written consent more often (69 percent) than non-IRB members (55 percent), in their research studies (p = .062). When the population of study participants is less than 20 percent literate, written informed consent was obtained from only a third (33 percent). When the population's literacy rate is over 20 percent, written informed consent was obtained from two-thirds (65 percent, p = .023).

Shortening or Simplifying Consent Procedures. Half (49 percent) of the researchers disagreed that local staff shortened or simplified the consent procedures compared to the original protocol, while 35 percent agreed (Table D.2.2). Sixteen percent of the researchers were neutral on the question. Academic researchers were more likely to agree (45 percent) than other types of researchers (24 percent) that local staff shortened or simplified the consent procedures (p = .025). When the population of study participants is less than 20 percent literate, over 60 percent of the researchers agree or strongly agree that local staff shortened the consent procedures, versus 32 percent, when the population's literacy rate is over 20 percent (p = .001).

A very high percentage (89 percent) of the researchers agreed that the consent process provides an opportunity to discuss ethical issues with the field staff (Table D.2.2).

Oral Consent. One-third (33 percent) of the researchers used oral consent with a witness signature (Table D.2.1). Older researchers (> 45 years of age) (39 percent) tend to use oral consent with witness signatures more than younger researchers (25 percent, p = .054).

Approval from the Village or Community Leader. Half (49 percent) of the researchers sought approval from a village or community leader as a method for informing participants and/or documenting consent for their specific research studies (Table D.2.1). Nonphysician researchers sought approval from the village or community leader more often (60 percent) than physician researchers (44 percent, p = .051). Those researchers who did not obtain written informed consent were also more likely to obtain approval from village or community leaders (69 percent) than those who did obtain written informed consent (50 percent, p = .015).

Consent from Another Family Member. In research with adults, one out of five (19 percent) of the researchers obtained consent from another family member (Table D.2.1). It is interesting to note that only half as many IRB member researchers (13 percent) used this method, compared to non-IRB member researchers (26 percent, p = .063). Those researchers who did not obtain written consent from the study participants were more likely to obtain consent from another family member (28 percent) than those who did obtain written informed consent (11 percent, p = .008).

Overall, two-thirds (66 percent) of the researchers perceived the informed consent process as being focused too much on the individual rather than on the family and/or community (Table D.2.2). Among the researchers, most academic researchers (73 percent) said it is too focused on the individual, while fewer (55 percent) of nonacademic researchers agreed on the same issue (p = .019).

Forty-seven percent of the survey respondents said it is true or sometimes true that religious beliefs and/or cultural norms of study populations were inconsistent with the practice of individual decisionmaking (Table D.2.3). When the researchers identified their study populations as being of the Muslim faith, a higher percentage (59 percent) stated that it was true or sometimes true that the religious beliefs and/or cultural norms were inconsistent with the practice of individual decisionmaking. In contrast, 36 percent of the researchers who identified their study populations as being of other faiths reported that it was true or sometimes true that the religious beliefs and/or cultural norms were inconsistent with the practice of individual decisionmaking (p = .004).

Table D.2.3: Responses to Ethical Issues in International Research

Option	% True and Sometimes True
Medical care provided to participants generally is not available outside the study.	61
Study gathered potentially sensitive information about participants.	58
Study participants have unrealistic hopes about personal benefits from study participation.	55
The standard of medical care in the host country may be much lower than that of funding country, creating difficulties in establishing appropriate procedures for the control group.	66
Participants join because of the desire for compensation, medical care, or other benefits.	63
Research priorities of funding agency are not congruent with priorities of developing country.	58
Treatment or intervention being tested is unlikely to be available to most citizens of developing country in the foreseeable future.	48
Inadequate community representation on the local IRBs/ ethics boards.	61
Religious beliefs and/or cultural norms of study population are inconsistent with the practice of individual decisionmaking.	47
Ethics issues are rarely discussed with field staff on this research project.	39

Study Participants' Understanding of Informed Consent

Almost all respondents (94 percent) agreed that the consent process is an important means of educating participants about the study (Table D.2.2). A high percentage (84 percent) of them also said that the study participants are usually aware that they are in a research study (Table D.2.2). Eighty-nine percent of researchers not employed by universities and 79 percent of researchers employed by universities said that study participants are usually aware that they are in a research study ($p = .036$).

Concept of Placebo. Half of the survey respondents (50 percent) agreed that study participants often did not understand the concept of placebo. Twenty-six percent disagreed while 24 percent of them were neutral. Older researchers (> 45 years of age) were twice as likely (67 percent) to say that participants often do not understand the placebo concept than younger researchers (<45 years of age) (34 percent, $p = .006$)

Sixty-two percent of the respondents disagreed that legalistic language required on the consent forms was not meaningful to study participants (Table D.2.2). As many as half (51 percent) of the academic researchers and three-quarters (75 percent) of the nonacademic researchers disagreed that the legalistic language required on the consent forms was not meaningful to study participants ($p = .021$).

Researchers' Perception of Study Participants. Slightly more than half (55 percent) of the researchers stated that it was true or sometimes true that the research study participants had unrealistic hopes about personal benefits from participating in the study. Sixty-three percent of them said it is true or sometimes true that participants joined because of the desire for compensation, medical care, or other benefits.

Recommendations

Survey respondents were asked for their recommendations in the area of informing and obtaining consent from study participants. Responses from all the researchers versus only those whose studies are/were funded by the United States are compared in Table D.2.4.

The key recommendations based on the survey sample in the areas of disclosure and informed consent are as follows:

1. The majority (72 percent) of survey respondents preferred that human subjects regulations allow more flexibility in ways of documenting informed consent (e.g., nonwritten methods), while 20 percent disagreed. For those researchers who have been funded by the United States, 77 percent of them agreed that human subjects regulations should allow more flexibility.
2. For observational studies, 40 percent overall and one-third (32 percent) of U.S.-funded developing country researchers agreed that formal individual consent should not be necessary.
3. Sixty-three percent of respondents agreed that where appropriate, U.S. IRBs should require the approval of community leaders, in addition to individual informed consent.
4. Most of them (84 percent) agreed that a mechanism to measure participants' understanding should be built into any research study.

Table D.2.4: Recommendations

Recommendations	Developing Country Researchers* n	% Strongly Agree and Agree	% Neutral	% Strongly Disagree and Disagree	Developing Country Researchers (U.S. Funded)** n	% Strongly Agree and Agree	% Neutral	% Strongly Disagree and Disagree
Human subjects regulations should allow more flexibility in ways of documenting informed consent (e.g., nonwritten methods).	187	72	8	20	82	77	4	19
Formal individual consent should not be necessary for observational studies.	189	40	15	45	81	32	17	51
Where appropriate, community leaders' approval should be required by U.S. IRBs, in addition to individual informed consent.	189	63	16	21	81	64	12	24
A mechanism to measure participants' understanding should be built into any research study.	188	84	11	5	82	84	10	6

*Survey respondents from developing countries

**Survey respondents from developing countries whose index studies are/were funded by the United States.

D.2.2 Results from Qualitative Research

Disclosure, Voluntary Participation, and Informed Consent

The topic of informed consent consistently generated a great deal of discussion throughout these interviews. Informed consent is a fundamental element of U.S. guidelines and regulations for research and must be implemented by U.S. researchers worldwide. Although the cultural and structural contexts of research vary greatly across countries and within countries, some common themes emerged in the data. Generally, respondents considered there to be three separate issues in the informed consent process:

- Community and potential participant education.
- Documentation.
- Level of participant understanding.

Many respondents felt that education of the study community and potential study participants about research and making the concepts of the research project understandable to them was critical in gaining informed consent. U.S. regulations for the documentation of consent were discussed at length.

Informing the Community. Community and individual education was viewed as fundamental, as this respondent remarked:

> …for individual consent, I feel it is right for every individual to know what type of research is going on. And I feel that for any group that is going to decide, there should be [an] adequate time interval, when they would be educating the people as to what they will be carrying out, and what they are likely to benefit and what they may not benefit for it, before they come in to carry out the procedures of research.

Several respondents described lengthy consent processes that involved meeting with village leaders and community members to explain the proposed study, which was not required by any U.S. guidelines or regulations. However, one respondent described a specific phase of the study that was the pre-study community education component required by the study sponsor, NIH. Researchers were required to go into the study community seven days in advance of implementing the study and meet with community leaders and talk with potential study participants about the research and the proposed study.

Several respondents explained a process that was used to communicate difficult medical concepts to members of the study community. One respondent said:

> I gathered around 22 representatives of community and talked to them, they all listened attentively. When I came back I knew I was unable to reach them. So I decided there is something wrong with the way I approached them. I requested them to gather again, meanwhile, I prepared myself and educated myself and tried to explain in their own language by giving examples of things which are of their own interest…how water is necessary for growing crops and similarly water is necessary otherwise the child gets dehydrated…before plowing you prepare the land and then put seed in it so that the yield is healthy and plenty, in case of your children do you prepare your women for childbirth to have a healthy baby…this is how I made myself and my team acceptable in the village.

In gaining informed consent, one salient issue was that it should be done in a culturally appropriate manner. Although the written and signed consents seemed to be more difficult to execute in many study communities, the overall concept of consent seemed to be consistent with local cultural practices, as this respondent explained:

> …it's [informed consent] a cultural practice and part and parcel of our cultural norm, that you introduce yourself and tell them why you have come.

Respondents emphasized the importance of following local social norms and cultural customs during the recruitment of study volunteers, even if it is a time-consuming process. This was of high priority and concern for some respondents. In one university, students are graded on how well they dress and interact with the study population. Another respondent remarked:

> …if you do not conduct yourself [in] what is a socially accepted way, they will kick you out. I mean it is as simple as that. So, if you go there you have to follow the accepted norms in that society and explain what you want to do.

Informing the community is held as the critically important component in gaining informed consent. As one respondent remarked, the standard that is always used is individual informed consent. But because so few participants are really familiar with research, getting informed consent was viewed as depending on how well the individual and the community were educated about the study. Individual consent is the end result of a lot of conscious and unconscious "community consultation." As this respondent commented:

> People get information through the media and through what other people in the community are talking about, although the aim is for individual consent.

Standards of Disclosure

Disclosure of medical information was not discussed at great length. One respondent mentioned this issue in terms of the discomfort of the disclosure of medical diagnosis for which there was no local treatment available.

Disclosure of HIV test results was mentioned as being provided with pre- and post-test counseling. Another respondent disclosed cancer diagnoses gradually over a period of time, as was culturally more appropriate.

More often, disclosure was described in terms of communicating the risks and benefits of research participation to potential study volunteers. Full disclosure to study volunteers was perceived to influence the success of not only the current study, but also future research projects. As one respondent stated:

> In [African country] we see it as a very essential complement of any successful research because be it at, the community level or in the hospital, rumors spread very fast. Misinformation goes around very rapidly, so to have any successful research, we think it is important to be transparent and to get the patient to understand exactly what they need to go through. So for us it's a must.

Several respondents mentioned that poorly supervised recruitment efforts or staff who receive monetary incentives for achieving recruitment quotas could result in a failure to communicate all aspects of the study. This situation created negative consequences for present and future research efforts. In one case, study participants wanted to leave the study early because they were not made fully aware that blood would be drawn on a monthly basis. As this respondent stated:

> …so right at the beginning I would try to explain that [negative consequences]…because other people who are participating [recruiters] were more interested in recruiting that person and would tell them the positive side of participating and not mention the negatives.

Another respondent described incompetence in adherence to regulations among data collectors and admitted:

> In certain situations the forms are just handed over to data collectors and they are not supervised. The problem arises when the next round of data collection starts and false hopes are raised.

This was true of hospital settings as well, where written consent forms are given to the patient, but are typically just signed without being read or without any explanation given by the provider. Although specific risks and benefits may be included in the consent form, the consent process in those cases is reduced to "just getting a signature."

Voluntary Participation

Several respondents made very clear statements that participants understand that study participation is voluntary. This respondent expressed concern that respondents are told explicitly about the voluntary nature of study participation:

> One of the important things…is, including in the consent forms is that it's a moral obligation thing. Like we have to say, and this is my own feeling, that if you do not answer the question and if you refuse to on the interview…don't feel bad about it. Sometimes they do that…it's I don't have time or I don't have energy. So this is something which is not in the regular consent forms.

Another respondent agreed:

> It is on us to make, to let them know that [study participation is voluntary] because if you don't make it clear, then they're tied to this stuff, which is not good.

Several respondents also mentioned cultural and structural barriers to voluntary participation. Two respondents commented on specific cultural factors:

> …if you're coming from the government system or from the university, and you turn up and you're doing research, traditionally people are very receptive anyway for visitors. So they extend [to] you that traditional hospitality and they will answer questions without…hesitation.
>
> You know in our country, people feel that they are morally bound not to refuse a guest. We assure them that if they refuse, their reputation will not fall in our eyes.

A situation was described of how voluntary participation was not allowed in a study among military conscripts. The data collection was conducted in one large room where military conscripts were present with their superiors who initially did not allow conscripts to leave without participating in the study. This respondent related the experience:

> …we somehow negotiate[d] with the superiors to let them walk out if they don't want to participate in the study.

One respondent raised a concern regarding local policy and informed consent. In this particular case, a U.S. organization was conducting large national demographic surveys in two African countries. This work is typically organized and implemented through the national statistical offices most often found as a nondepartmental entity or within departments dealing with economics, finance, or planning. Most developing countries have such offices, and they are responsible for gathering certain information that is used for statistical purposes. Providing this information is considered mandatory by the government. The problem arose in two countries where the national statistical offices felt that the information included in this national survey was within their legal mandate for gathering data to be used for statistical purposes. A consent form was implemented in gathering the survey data; however, all references to the data collection as being voluntary were deleted from the consent form. When blood was drawn as part of the survey for gathering information on biomarkers, the entire consent form was permitted including the statements that participation was voluntary.

Documentation

Written Consent. Respondents felt it important for study participants to provide consent, but found it difficult to fulfill U.S. consent documentation requirements. The concept of the written consent form was new in most study communities and has only reached familiarity in settings where people regularly participate in research. One of the most salient problems with informed consent was the amount and detail of information required to be included in written consent forms. These statements reflect the concern of most respondents:

> I found that the consent document as required in this country. I mean it lists so many subheadings, that for a lot of situations in which we are doing research, people generally find it irrelevant. They will either grant you consent or not.
>
> You are kind of complicating the whole situation by …go[ing] into depth about asking permission and all of that.

Respondents reported using written consent forms of up to eight to ten pages in length. Generally respondents felt the required content made consent forms too complicated and detailed. Some study participants were described as being intimidated and frightened by official-looking written documents. However, one respondent suggested that the NIH regulations had "very clear guidelines" that "they were able to translate…into a rural culture." Another respondent disagreed with this and explained that condensing the consent form to even one page does not address all barriers:

> But that doesn't make any difference if you're dealing with an illiterate person. That's the case for more than 60 percent of the population of [Caribbean country]. Even though we have one-page informed consent, that doesn't make any difference.

Illiteracy was the concern of several respondents:

> In many parts of endemic areas, [a] relatively high percentage of local people are illiterate. Thus asking for written consent is unfair.

Several respondents felt that the consent form regulations focused on the legal protection of investigators or universities and were being applied in locations that do not have a legal framework similar to the United States to sustain or guide the process. As one respondent said regarding these procedures, "It is driven by the American system." Another respondent commented that there were no answers for study participants when they asked about the confusing language of "giving up legal rights" found in the consent form. The complexity of written consent forms can unfairly exclude people from participating in research:

> …it's making it difficult for people and I even question the ethics of it. By making the form so complicated, are we preventing people who should have a right to participate from participating because they cannot read or interpret that lengthy, you know [consent form]….We are excluding people because of that, and they should have a right to participate too. So we need to look at that.

Several respondents, who felt that these forms should not be used in lieu of a thorough ethical review, commented on the emphasis on legal protection in the consent form requirements. These respondents felt that consent forms should not excuse ethics violations or take on what is the responsibility of the review boards. One participant commented:

> I think institutional review boards must review the ethics of studies and not necessarily the unethics [unethical aspects] of the study with a piece of paper [consent form] saying we told the patients...it must be reviewed to see if it's ethical.…

Verbal Consent. Many respondents felt that in certain situations, using an oral consent process was more appropriate than using a written consent form. In order to provide the necessary and sufficient information so that people could understand and make a decision, many respondents felt that this could only be done verbally:

> Informed consent for me is not giving a paper and then sign. We have to explain because when we explain what does it really mean, like you have explained to me right? What is the objective of the research, what you have come [for], what is the benefit there or no benefit there, what is his right or her right or whether he can say, yes or no, so given all the explanation and description what you're really going to do so that he or she can form an opinion of whether he or she wants to participate.…

The typical verbal consent process described in the data involved the study staff reading a written consent form or a disclosure statement to the study volunteer followed by discussion and an opportunity for the study volunteer to clarify information and ask questions. The person may or may not sign the form, in some cases a thumbprint is used, and often there is no record of the consent. Several respondents reported having the staff person as a witness who signs the consent form stating that the study volunteer understood the conditions of the study and agreed to participate. Some respondents describe this oral consent process as an opportunity to not only "explain"' and "clarify" the conditions and implications of the study but also, as one respondent said:

> It's a great venue to teach, to really educate people, especially with HIV disease…it gives you an opportunity to really sit one on one almost like counseling.…

Other respondents described the time-consuming process of talking and discussing the study with potential volunteers over a long period of time before they decide whether or not to participate.

Verbal consent was a very appropriate technique for many respondents in the settings, where literacy levels are low and verbal exchanges and discussion are the cultural norm. Respondents commented that written consent forms possibly were more appropriate in some settings, such as urban areas, and for intervention studies versus observational studies or for epidemiological studies that do not cover sensitive topics. As one respondent noted:

> In a noninterventional study it is more important to sit with people or individuals and explain to them verbally rather than signing a document.

Heated debates were reported among respondents who had to deal with the inappropriateness of the written consent forms in some of their study communities. In conducting a national survey, one respondent reported this issue was resolved by using the written consent form as the goal, while allowing study staff to adapt this to their settings, using verbal consent as necessary. Respondents referred to "formal" and "informal" consent, but no clear definition of these terms emerged in the data.

Signed Consent. Many respondents felt that the signed consent form, regardless of how well the issues of the study are explained, verbally or in writing, created suspicion and discomfort among potential study volunteers and actually served to deter research participation. There are several reasons for this, including a history of political unrest and conflict, as this respondent explained:

> …this is mainly because of the history that our country has gone through with sometimes repressive regimes…if you sign any document…somebody could use it against you at a certain point.

In some countries signing a document is synonymous with potential harm, while in other countries, it is associated with property, and signing a consent form may be misconstrued as signing away a home or land. Other respondents stated that when a document is signed it signifies that there is distrust between the two parties or that the document refers to something legal to which the person is now bound. Several respondents reported that study participants were willing to answer any questions for the study but were reluctant and unwilling to sign the consent form. There may be other, more specific cultural meanings attached to the act of signing one's name that were not mentioned here.

Level of Risk and Consent Requirements. One respondent commented on her ten years of research experience and the differing requirements of consent by local ethics review committees that she has observed. Different types of studies were required to have different types of consent. Clinical trials required written and signed consent forms; community-based interventions and trials required verbal consent which could be documented, but signatures were not required; and, until recently, observational studies did not require documentation of informed consent.

Social Science Research. Two respondents were particularly concerned about social science research being conducted to gather data on sensitive personal topics without the use of consent forms. According to one respondent, there has been "gross indifference to ethics and self-regulation" in the social sciences. One of these respondents recognized a need to develop ethical guidelines for social science research "to protect participants and uphold their dignity."

Research Versus Program. Others questioned the development-oriented programs that are not research per se but that have conducted surveys or evaluations without using consent forms:

> I don't know how like somebody should know like the World Bank or the WHO, UNICEF, when these organizations conduct studies….I know there's a lot of studies conducted by or sponsored by these organizations and I've never seen consent forms.

Communal and Surrogate Consent

While the U.S. ethical guidelines emphasize individual autonomy, in many developing countries, emphasis is on the collective well-being of the community, and reaching community consensus is paramount. One respondent commented on this fundamental cultural difference:

> There are a lot of cultural differences…my experience of research in the United States is very limited. However, there people are more concerned about what they will get out of it and once you explain it to them that there will be no immediate benefit, they are a bit disappointed initially. The basic difference I think is that in [the] United States, an individual can make a decision on his own.

Seeking approval or permission for the study from community leaders or through the established hierarchy of leadership was critically important in some study communities. Although this was often not a requirement of investigators per U.S. guidelines, it was a critical step in gaining access to the community. Several respondents described the process of meeting with village leaders to explain and discuss the details of the proposed study. The leaders discussed and asked questions, and when they reached a consensus, they would either grant or deny permission for the research to be implemented in their community.

Once the village leaders gave their permission, the investigators could comfortably approach individuals for their participation. Individuals could refuse to participate despite their community leaders' approval of the project. Regarding this process one respondent said:

> …if you've had all of the authorizations from the Ministry of Health, and locally you read everything to them (community leaders) and they understand what you're going to do in the community, then they sign the consent. But if you're going to individual consent, you are going to scare people. But as long as local leaders are giving consent, then every program is complete, because they explain everything to the subjects.

Government approval was mentioned by one respondent as being particularly effective in gaining community and religious leaders' permission for the study:

> But what we do, successfully what we have been doing is when we launch a study, we take the permission from the general health or general family planning, and he sends a letter to all of the district levels [down]…to the lowest hierarchy of the [local] health facility.

Other respondents disagreed with the process of communal consent. While they recognized the importance of community leaders' involvement and awareness of the study, they did not feel community leaders should provide consent. As this respondent remarked:

> It may be appropriate or sufficient to ensure community leaders are informed of the research rather than requiring their approval. In communities where leadership could either be aligned to prevailing politics or/and biased towards men, such a requirement may not fulfill the ethical aims as intended.

Another respondent felt that the protection of individual rights and particularly rights of minorities and women is made difficult in settings where surrogate or communal consents are culturally promoted. One respondent suggested the way around protecting the autonomy of individuals, but still seeking permission from community leaders, is to ask for signed consent from individual participants or from a third party where literacy is low:

> The way around that could be to, you know, to…have a consent. Read up [the consent form] to individuals [and] have a third person as [a witness] who can then sign the form for the individual. But I…wouldn't think it would be enough to just use the community leader's permission to go ahead and do the study.

Another respondent disagreed with this and felt that true informed consent will take years of community education and exposure to research:

> I would agree with you, but we are talking about meantime. Meantime. Like for example, in [African country] meantime, if you have to do a research, I think it would be okay to go ahead and just get consent from the leaders. But for personal autonomy in the long run you have to educate the people in terms of their rights… You can't actually expect someone on an individual level to actually give, what is called informed consent…I mean, otherwise, [you are] just getting a signature, really.

Surrogate Consent. Individual consent is not culturally appropriate in some settings where individual decisionmaking is not the norm. Surrogate consent was a particularly poignant issue for women. In many cultures women are in a position of little to no decisionmaking power within their household. This has been an important concern in some countries and has been raised on local ethics review boards. A respondent described this specific incident:

> I think in our society husband's permission is very important so that should somehow be made part of the regulations. Well, we had this experience that we took permission from the woman, conducted the interview and at that time the woman did not think it was important to get the husband's permission. But later she had lots of trouble with her husband and her mother-in-law. After that we explicitly asked for husband's permission.

Legal advice was sought in one case to determine whether or not a husband or a son could provide permission for their wife or mother to have surgery. In another example, a respondent explained how a video of a puppet show on breastfeeding to be shown to mothers in the community had to be performed for community leaders before the study was implemented to provide proof that it included nothing that was culturally inappropriate. Only after permission was granted was the video shown to the mothers.

The inappropriateness of individual consent was also mentioned in the context of conducting research among the elderly. One respondent provided the example of a study on Alzheimer's disease in which participants were recruited door-to-door. In this particular host country, the elderly are cared for by their relatives and rarely live alone. The family, in a sense, serves to protect their elderly relatives. Surrogate consent was the only acceptable method for gaining informed consent in this context:

> In [Asian country] you find very few elderly living alone. At the time we were doing the study probably something like two to five percent. Five percent is even too high. It is like two to three percent were living alone. So, therefore, when you not knock on the house and there is an older person, the consent is given by family and relatives, not by that older person. And they decide whether to let you or to allow that older person to answer questions. So, you have to explain to them what you are doing.

While all participants felt it was important to protect human subjects rights, they also recognized that these particular cultural issues should be addressed in designing appropriate consent processes.

One respondent related the idea of communal consent to a group of peer investigators with whom he would conduct HIV research. Investigators were intimidated by HIV disease, which carried an enormous stigma in the host country, as in many other parts of the world. After presenting the study and allowing investigators to

discuss and ask questions, the discomfort and fear of researching and talking about HIV was reduced. The respondent also felt that because a local and not a Western investigator conducted the presentation, the information was more easily accepted.

Level of Understanding

Most respondents felt it unrealistic to think that study participants will be able to comprehend all of the details of the study. It is very clear among respondents that the idea of the consent form is useless unless the person understands it. These two respondents commented as follows:

> …informed consent means nothing if the participant has not understood it. Otherwise it is just a piece of paper. It is just rubbish.

> Is it meaningful? As a tool to improve research…but not all of the patients understand in our city, a big university hospital.

Respondents generally felt that broad concepts should be communicated without confusing participants with too much technical or medical information that unnecessarily raises their anxiety. Again, the educational process was emphasized as one respondent said:

> I think informed consent is the most difficult part of research. It is also the most sensitive. It depends on how well you educate the patient and how much awareness there [is]….

Another respondent described a long process of recruitment of couples for a study. She visited each family's house individually, returning several times to answer questions and provide explanation before the couples made a decision. She commented that this took a great deal of time but that "it was important that they understand" what study participation entailed. The education component was important.

Several respondents did think that it was possible for study participants to have an acceptable level of understanding to be involved in the study. A respondent stated:

> It doesn't take a whole lot of research that someone should get a Ph.D. to understand some of these things. You just need to explain in the vernacular, what research is so they understand what they are getting into.

One respondent felt that there should be an assessment of the level of understanding of the participant before introducing the consent form. This respondent commented as follows:

> I think…it [informed consent] is extremely important, informed consent has a place in research because the people that in my case….I would take a skin snip or blood or remove nodules from people and they need to understand the relationship between those nodules and blindness. I need to go through the life cycle of whatever you're doing with the patients to that point so that they understand…So we find out that they know what we want and they know what to get from it [study participation]. Once that is established, then informed consent [documentation] is absolutely important.

Another respondent described the process of trying to explain complex biomedical information using language and concepts comprehensible to participants. This respondent said:

> Working with HIV was really very difficult to put all of that information down there. So we had to break it down really like…although it wasn't…very accurate, you know…to talk about retroviruses and even clinicians themselves don't know what you're talking about, so we had to break it down.

Many respondents discussed the difficulty of explaining placebo and control arms and the logic behind applying them in study designs. Study participants generally wanted to receive the intervention and did not understand the concept of "placebo."

Barriers to Autonomy. While the decision to participate in research is preferably an informed and autonomous one, social and contextual factors greatly influence decisionmaking. In many societies, patients defer to their doctor in health care decisions. Several respondents described this situation:

> …I think in our culture people expect when they go to a doctor or a medical person, the medic knows best…and the whole notion of questioning or arguing with their doctor is just [for] a very, very small elite that is highly educated and so on that actually starts to do that. But I will say a lot of the people they go to the doctor they say, okay, you are the doctor. You decide for me what is best.

> …in my experience, most of the times the patients tell me to decide for themselves which is very common in my society….Some people tell you what to do. You're not as an individual empowered to decide on your own or to steer yourself. So it's the mentality, which is different. I think most of the times or at least half of the times the patient feels like it should be better for him or her; otherwise the physician wouldn't suggest [it].

> In [Asian country], many of the patients, most [studies are] done by doctors, many of the patients, when they are talking to the doctor,...[they think] this person is definitely trying to do something good for us. He's like a God.

In some countries, the lack of awareness among health officials presented a barrier to providing education and informed consent. This respondent described the attitudes of local health authorities:

> …if you are providing health service, it's good for the person. They don't have to say, yes, I agree that I want to participate in this…it's [informed consent] seen as an inconvenience and that the people you are dealing with don't know what you're talking about anyway, so let it go. That climate of opinion isn't there yet, and that's part of the work we need to do is to make them aware.

One respondent remarked that research staff often encouraged people to stay in the study because they consider this their job responsibility:

> Sometimes those who that were working on the project, I mean not ourselves as the main researcher, but the others that came, it was their duty to keep them in the research and to convince them to stay in the research. That is their task.

Conducting research in poor communities is challenging for investigators in explaining the benefits of the study to people who have more immediate needs, such as access to potable water. These respondents feel constrained by informed consent guidelines:

> It is restrictive. Researchers have reacted to it. In [Asian country] at times you are spending so much time telling why you are here etc., it's not that we are coercive. Half the time the challenge is to convince the people that this research is needed, as they do not see any benefit.

> To tell the truth the researcher[s] are least concerned about consent and more concerned about acceptability. You have to go with your heart tied, that I need this information for the greater good. Our agenda is different from the agenda of the woman being interviewed. She will see less utility of interview over feeding her kids or animals.

Recommendations

Documentation. The most frequently mentioned recommendations involved flexibility in applying guidelines for informed consent documentation. Where written consent forms are not applicable, verbal consent should be acceptable. Although several respondents felt it was advisable to have written consent forms for therapeutic interventions considered to be invasive procedures, such as drug trials, in areas of high levels of illiteracy, a verbal consent procedure should be acceptable.

Respondents recommended the application of various innovative techniques for community education and informed consent such as videos, small group discussions, and the use of visual aids. One participant recommended, particularly in studies regarding family planning or reproductive health issues, providing information to potential participants and allowing them to take a few days to discuss it with significant others before returning to give their individual consent.

The issue of the content of the consent form should be revisited, with an emphasis on broad concepts and general explanations of the risks and benefits involved in study participation and the conditions and responsibilities of study participants and the investigators. At least one respondent recommended that host country investigators develop consent forms. Local religious beliefs, level of education, cultural norms, and legal needs should also be considered. The appropriate local language should be used in writing consent forms, with a focus on translating concepts, not individual words that have no meaning in certain cultural settings, such as "blood pressure" and "cholesterol." Several respondents recommended that written consent forms should be no more than one or two pages long.

In terms of requiring signed consent, many respondents opposed this as a requirement in cases other than for surgery or invasive procedures. The only recommendation offered was to have a third party witness the participant's consent and sign the form for the study participant. Several respondents recommended a short assessment of the level of understanding of each individual of their role and basic concepts of the study at the completion of study participation.

Autonomy and Consent. Communal or familial consent versus individual consent requires substantial exploration. Cultural, political, and social factors are important in examining this issue. Several respondents cautioned against advocating for the necessity of community leaders' approval of the study due to their political or personal interests that could potentially not be in the best interest of the community. However, the majority of respondents advocated a review of the cultural sensitivity of guidelines regarding communal and surrogate consent.

Respondents also suggested multilevel education activities for individual, community, and government officials to raise awareness of research and related ethical issues and principles. Implementing a pre-study community education phase where members of the study community have an opportunity to receive and discuss information about the proposed research with study investigators was also recommended.

Personal autonomy in decisionmaking was sometimes viewed as a long-term goal in research, but others suggested that the IRB should find ways "to increase the ability of persons to make competent and autonomous decisions." At the government level, education and training for health officials and researchers alike was recommended. A general discussion of the philosophy and purpose of informed consent was recommended for developing country officials and investigators before writing specific guidelines at the local level regarding this process.

D.3 Risks and Benefits

D.3.1 Results from Survey

One of the challenging ethical issues in international research is whether a research design that could not be implemented in the sponsoring industrialized country can be ethically justified in the host country where the research is carried out. In the survey, developing country researchers were asked about reasons for the study being carried out in the host (developing) country as opposed to in the United States. All of the survey respondents' answers were compared with answers of those respondents whose studies are/were funded only by U.S. sources, as shown in Table D.3.1.

Overall, 66 percent of the developing country researchers who completed the survey agreed that prevalence of disease in question is much greater in the host country than in the United States. Sixty-four percent of those developing country researchers whose index studies were funded by the United States agreed on the same question. A much higher percentage (88 percent) of nonphysicians versus 59 percent of physicians stated that prevalence of disease in question is much greater in the host developing country than in the United States ($p = .040$).

Seventy-six percent of the survey respondents agreed that the intervention being tested is more relevant to the host country than to the United States. Seventy-seven percent of the U.S.-funded developing country researchers agreed. A much higher percentage of nonuniversity respondents (89 percent) versus university respondents (67 percent) agreed that the intervention being tested is more relevant to the host country than to the United States ($p = .053$).

Table D.3.1: Reasons for the Study Being Carried Out in the Host (Developing) Country as Opposed to in the United States

Question	Developing Country Researchers*		Developing Country Researchers (U.S. Funded)**	
	Number (n)	% Yes	Number (n)	% Yes
Prevalence of disease in question is much greater in the host country than in the United States	80	66	63	64
Intervention being tested more relevant to host country than to the United States	82	76	62	77
Easier to identify a cohort of patients relevant to research	69	55	54	54
Recruitment of patients more rapid in host country than in the United States	60	52	49	53
Less expensive to do study in host developing country than in the United States	60	62	47	60
Host country researchers asked for U.S. collaboration	85	69	66	67
Research question relevant to U.S. strategic interests in the region	70	49	55	45
Marketing approval for drug or device will be sought in host country	53	25	41	24
Interest in addressing global inequalities	80	71	63	71

*Survey respondents from developing countries.

**Survey respondents from developing countries whose index studies are/were funded by the United States. In the survey questionnaire, although only those researchers who received U.S. funds for their index studies were asked to respond to this question, additional numbers of researchers also responded to the question. It is possible that U.S. funding may have been involved as part of bilateral funding or other arrangements that could not be determined from the survey data. The responses are to be based on index studies, and it is possible that responses may have been given based on general experiences and personal opinions.

Over half (55 percent) of the respondents agreed that it was easier to identify a cohort of patients relevant to research in the host country. Fifty-four percent of the U.S.-funded developing country researchers agreed.

Half (52 percent) of the respondents also agreed that recruitment of patients is more rapid in the host country than in the United States. Fifty-three percent of U.S.-funded developing country researchers agreed. About one-third (62 percent) of the survey respondents agreed that it is less expensive to do the study in the host developing country than in the United States. Sixty percent of the survey respondents with U.S.-funded studies agreed.

Sixty-nine percent of the developing country researchers agreed that they asked for U.S. collaborations. Similarly, 67 percent of the U.S.-funded developing country researchers also asked for U.S. collaborations. Half (49 percent) of the respondents agreed that the research question is relevant to U.S. strategic interests in the region. Forty-five percent of U.S.-funded developing country researchers agreed. Sixty-three percent of the female survey respondents agreed, while a smaller percentage (41 percent) of male survey respondents agreed that the research question is relevant to U.S. strategic interests in the region ($p = .098$).

One-quarter (25 percent) of the survey respondents (as well as 24 percent of the U.S.-funded researcher respondents) agreed that marketing approval for the drug or device would be sought in the host country. More than twice as many (38 percent) of IRB-member respondents agreed versus 17 percent of non-IRB member respondents that marketing approval for drugs or devices will be sought in the host country ($p = .115$).

Seventy-one percent of the respondents agreed that interest in addressing global inequalities was one of the reasons for the study being carried out in the host country as opposed to in the United States. The same percentage of U.S.-funded developing country researchers also agreed. It is of statistical significance that as many as 94 percent of nonphysician respondents versus physician respondents (64 percent) agreed that interest in addressing global inequalities was one of the reasons for the study being carried out in the host country as opposed to in the United States ($p = .016$).

Standard of Care in Host Country

Sixty-one percent of the respondents agreed that it is true or sometimes true that medical care provided to participants generally is not available outside the study (Table D.2.3 in Section D.2). Almost three-quarters (74 percent) of the U.S.-funded researchers said it was true or sometimes true versus half (52 percent) of the non-U.S. funded researchers that medical care was generally not available outside the study ($p = .031$). A higher percentage (65 percent) of male respondents agreed versus female respondents (49 percent) that medical care provided to participants within the study generally was not available to local populations outside the study ($p = .084$).

Two-thirds (66 percent) of the developing country researchers agreed that it is true or sometimes true that the standard of medical care in the host country may be much lower than that of the funding country, creating difficulties in establishing appropriate procedures for the control group. Fifty-five percent of the respondents said that it is true or sometimes true that study participants have unrealistic hopes about personal benefits from study participation.

Sixty-three percent agreed that it is true or sometimes true that study participants join because of the desire for compensation, medical care, or other benefits. Response of male survey respondents differed significantly from the female respondents. Sixty-eight percent of the male respondents versus 58 percent of female respondents stated that it is true or sometimes true that study participants join for the benefits ($p = .033$).

Slightly more than half (58 percent) of the respondents agreed that it is true or sometimes true that research priorities of funding agency are not congruent with priorities in developing country. Half (48 percent) of the respondents said that it is true or sometimes true that treatment or intervention being tested is unlikely to be available to most citizens of the developing country in the foreseeable future. For those researchers whose index studies are related to HIV/AIDS, they appear to be more optimistic. As many as 82 percent of them disagree,

compared to the other researchers working on other issues (53 percent), that the treatment or intervention being tested is unlikely to be available to most citizens of the developing countries in the future (p = .034).

Recommendations

Survey respondents were asked for their recommendations in the area of standard of medical care for the study participants and availability of intervention if research is found to be successful. Responses from all the researchers versus only those whose studies are/were funded by the United States are compared in Table D.3.2.

Seventy-seven percent of the developing country researchers agreed or strongly agreed that the issue of what standard of medical care to provide to study participants should be decided on a case-by-case basis, while 16 percent disagreed. Similarly, 77 percent of U.S.-funded researchers agreed, while 19 percent disagreed.

More than three-fourths (78 percent) of the developing country researchers agreed that research to test an intervention should not be carried out in a developing country unless the intervention, if found to be successful, will be made available to that country at the conclusion of the study.

D.3.2 Results from Qualitative Research

Access to Health Care

Local health care services in study communities are typically described as "not functioning," "understaffed," and "lacking in supplies." Several respondents remarked that people must seek care outside of the communities where they live, often at a great distance. Family planning services are often not readily available in the community, particularly access to a broad range of family planning methods.

Some respondents claimed there was an underutilization of services due to "lack of awareness" and poor quality of care. Lack of utilization of health care services in one country was explained as due in part to village health workers selling pharmaceuticals from shops adjacent to their homes or the health center. Often, community members preferred purchasing these drugs to seeking care at the health center because the health center itself often did not have pharmaceuticals in stock. In terms of HIV, antiretrovirals and other more basic drugs used in the treatment of HIV and AIDS are typically inaccessible. In some countries, only the wealthy upper class are able to purchase HIV medications including antiretroviral therapies.

Table D.3.2: Recommendations

	Developing Country Researchers*				Developing Country Researchers (U.S. Funded)**			
Recommendations	n	% Strongly Agree and Agree	% Neutral	% Strongly Disagree and Disagree	n	% Strongly Agree and Agree	% Neutral	% Strongly Disagree and Disagree
The issue of what standard of medical care to provide to study participants should be decided on a case-by-case basis.	182	77	7	16	79	77	4	19
Research to test an intervention should not be carried out in a developing country unless the intervention, if found to be successful, will be made available to that country at the conclusion of the study.	187	78	9	13	81	32	17	51

*Survey respondents from developing countries.

**Survey respondents from developing countries whose index studies are/were funded by the United States.

Relevance of Research

Respondents generally felt that research should not be conducted without giving something back to the study community. A respondent expressed this point as follows:

> At times you have to do this kind of study with controls for the benefit of the people at large. To me the real issue is working in a community and later pulling out of it. You benefit from the community but what had you given them in return.

While most respondents acknowledged that much of the research benefits the "greater good" and not the individual, some questioned who the "greater good" might represent. These respondents strongly opposed research in resource-poor countries that will only benefit those living in developed countries:

> U.S. investigators should not be allowed to test hypotheses in developing countries that would tend to benefit primarily subjects in the United States. The justice principle of ethics would be violated. The argument that a technology, be what it may be, has already diffused and is already standard therapy in the United States is just not acceptable.

This debate was most often illustrated through examples of drug trials and drug companies conducting what some respondents considered unethical research. Another respondent remarked:

> I know that's being very radical, but the point is that there are drugs that are dumped on developing countries. There are things that are done wrongly to people, and you don't know what the effect is down the line. Are they carcinogenic? Are they toxic? Nobody knows, and they just bring it. If they're doing drug clinical trials and if the Ministry [of Health], you bring your drug, I'll ask you, did you try these drugs on your own people? If they say no, then don't bring it here, period.

Compensation and Incentives

Medical Care Compensation. Many respondents acknowledged that people who do not have access to health care, who have less education, and who are poor want to participate in the research so that they may receive health care or other services. By participating in studies, they hope to gain access to at least some benefit for themselves or their families, as this respondent said:

> …the low income class they really don't know what is going on…they [are] willing to answer whatever it is. Or if that's a treatment [that] might help them but doesn't cost any money, they don't care. Just to go through the benefits of whatever…is offered. But when the thing goes to a high level of…socioeconomic level with education, you might get more questions…and…they might be unwilling to participate.

Other respondents agreed and felt that providing medical care as an incentive was undoubtedly coercive:

> …I don't think the informed consent forms add anything or do anything ethical to the whole research process because if a mother is in the hospital and to bring their child.…What do they tell them? What do you have to say? Treat the children. They wouldn't bring them there in the first place. How would they refuse to take any form of treatment they are offering to them? It's hypocrisy, I think. I think researchers ought to think about what they are doing and then do it with the interest of the patient at hand rather than go through some bureaucratic process and call it informed consent.

> …I don't think it mattered to the people [initiating consent forms]. They just wanted help and they expected that they would be investigated and they would get assistance somehow.

Despite these opinions, generally, respondents did feel that medical care was an acceptable incentive, or rather benefit, for study participation. Many respondents viewed the provision of medical care including diagnostic testing, as acceptable incentives for study participation:

> What we have done in terms of incentives in the project is provide medication...to the people in their communities. We provide more clinics to the people.

> One of the things that—we went to do research, but one of the things that we had to do was really establish a lab where we were providing diagnosis, just diagnosis and screening and confirmation of HIV disease to anyone who wanted it, and that was, you know, kind of part of an incentive for, you know, participating in the study.

However, at least one respondent did not agree that receiving knowledge of a positive test result for syphilis, in that case, could be considered an incentive, because the disease cannot be treated locally and the clinic referral is meaningless.

When respondents were asked if they knew why people participated in their studies, it was found that most did not typically document this information. However, several respondents felt that study volunteers willingly participated in research knowing that it would not directly benefit them beyond gaining some new information or, as in one case, an opportunity to socialize with their friends and neighbors.

For many respondents this broadened the discussion to the more difficult issue of determining the limits of treatment of infections or health problems unrelated to the study that are diagnosed during the study. Several respondents shared experiences of procuring treatment or the funding to make medications available to treat infections diagnosed during the study. One respondent researching diabetes was concerned about whether study volunteers would be able to access health care when the study ended. Medical supplies were given to study volunteers, but the research staff also provided their personal telephone numbers so study participants could reach them in case of emergency.

Monetary Incentives. Monetary compensation for travel to the study site or for loss of income from paid work or other costs incurred in relation to study participation was acceptable to most respondents. However, several individuals spoke out against distributing monetary incentives to study participants. As one respondent explained:

> They want to see taps in their houses with running water but we do not pay them anything. We never pay for anything. I am dead against that, but some organizations are paying.

Another respondent stated that this was a national level concern because many community-based organizations provide services similar to those of the studies, but do not offer monetary incentives to participants. In the long run, monetary incentives were viewed as jeopardizing the activities of community-based organizations. Financial incentives were used in some studies, but the amount of the incentive was so low that it was not used as an incentive per se, but rather to cover the costs of study participation.

Study Staff Incentives. Providing incentives for study staff was typically not commented on, as it seems staff are generally not offered any incentive for recruiting study volunteers. However, one participant reported this to be a very controversial topic in his country where study staff have been provided monetary bonuses for recruiting volunteers. This has created a "conflict of interest" for study staff who have low incomes and who genuinely feel that participation in the study is "the right thing" for the volunteer. In their eagerness to recruit volunteers, the conditions of participation were not clearly explained. When some of the volunteers wanted to leave the study early, the staff who feared losing their bonuses persuaded the volunteers to stay.

Standard of Care

The term "standard of care" was used by many respondents in discussing the issue of the best treatment locally available. As this respondent explains, the best treatment available is typically less than what is available in the United States and often is no treatment at all:

> I think the central issue is 'standard of care.' Is there a global standard of care, which is decided upon the best evidence available or is the standard of care flexible and dependent on what is the usual practice in a particular country. This is a very difficult issue. For instance in [African country] the government policy would probably support the use of antiretrovirals to prevent mother-to-child transmission of HIV, however, the usual practice is to do nothing because of cost. However, the affluent minority would be given state-of-the-art prophylaxis by their private physicians. This is complicated by the fact that standards of practice in different industrialized countries are different—more anti-retroviral use in the United States versus in the United Kingdom, for instance. I would argue that there is a global standard of care—the best therapy or prevention that is available.

This same respondent also felt that the ethical issues change—that they are dynamic, as the nature of the research changes.

Another respondent remarked on the potential barriers to research if investigators are required to provide the best-known treatment for study participants. Screening for HIV in countries where most people do not have access to care would be prohibited as this respondent commented:

> …it is seen as an issue of North and South. They have no therapy, but you must provide it because you are doing research in that country. It gets to ridiculous limits. You know you might say, well, we can't ever screen for HIV in any country where therapy is not available. It's a very confusing and contentious issue.

Respondents also mentioned experiences with IRBs raising the issue of the level of care available in treating specific diagnoses. One respondent reported that a study on anemia was rejected by the local IRB because local treatment was not available. In this case a pamphlet was prepared describing the management of anemia by eating locally available foods. However, these foods were not normally consumed in this population, and the respondent in part related the rejection of the study to a lack of trust.

Another researcher described a nutrition study in which acutely malnourished patients had been recruited in order to have a more representative sample of the population, rather than recruiting only stable patients. A high incidence of death at the initiation of the study caused the U.S. sponsors to halt the study to investigate. Because the hospital had no respirators to provide intensive care to these patients, there were more deaths than what is typically seen in U.S. hospital settings. If the study had taken place in the United States, the patients could have been put into an intensive care unit and possibly have been saved with the help of a respirator. As this respondent explained:

> If you don't have a ventilator, does that mean you do not do any research or interventions.…No, I believe some of the work that you did and were able to publish has actually tremendously improved case management for many of those children.…

This respondent felt that although the best-known treatment was not available for study participants, results of the study were beneficial to many children locally.

Another respondent agreed that requiring the best-known treatment prohibited research from occurring:

> We can't do diabetes research in the developing world because we can't provide kidney transplants for diabetic neuropathy. It's a silly standard.

A distinction was made in one focus group between prevention and intervention research. Several respondents contended that provision of the best-known treatment should not be an issue in prevention studies. One respondent could not screen for pediatric HIV because the country did not have pediatric HIV treatment available. The respondent felt that any requirement for best-known care would be too limiting for prevention research, where best prevention is the focus of study and not best treatment.

One respondent suggested that a unilateral requirement for treatment standards could not be applied in all countries, but that a case-by-case review was more appropriate:

> But my feeling is that there is no standard procedure that applies to all countries. You really have to go to the country and then see what happens and see how things go in a particular place.

Clinical Trials and Control Trials

A great deal of debate has been sparked by recent AZT and placebo drug trials in developing countries aimed at preventing mother-to-child transmission of HIV. Respondents made emotional comments in regard to these debates and were clearly concerned with how these issues are resolved. One respondent felt that the complexities of drug trials in developing countries have yet to be fully and honestly debated.

Many feared exploitation of unwitting populations who did not know the circumstances of their participation or who were used as "guinea pigs" for the benefit of those living in developed countries:

> I think the researchers from economically developed countries should apply the same rules and regulations as they apply in their own countries. I think if they are not doing that, they are not doing justice. Lots of drug trials [that] are being carried out in sub-Saharan Africa and in other developing countries are not ethical. I think it's beyond ethics and totally unjustified.

Others argued that control trials are necessary to discover unknown benefits of drugs and is an opportunity to research the "second best" drugs while the best-known treatments remain economically out of reach:

> I am aware of the…criticism of studies not using best standard of care in control groups…. Applying this standard to developing country research [when treatment is aimed at citizens of that and similar countries] prevents them benefiting from second best which might be a big improvement on nothing at all.

Several respondents expressed concern that developing country nations are able to define for themselves what they want from research and what they can accept. Each country has its own values and needs in regard to research participation:

> ...you cannot resolve the points of confusion for countries. They really have to understand what their needs are in relation to research.

Several respondents described how both intervention and control groups would receive the intervention when the study was over. Specific examples provided by respondents included studies in education and communication involving counseling, training, and nutritional education. However, one respondent was concerned that the control arm in one study was not going to receive treatment. Another respondent noted how their study was halted more than once because the intervention was proving to be so effective that it was unethical to continue withholding treatment from the control group.

One respondent said that the issue of how to treat the control arms of studies did emerge in discussions among investigators, but that he was opposed to using controls:

> A couple of times this issue was raised in our department. I personally feel the controls are unacceptable.

In terms of drug trials, another respondent did not oppose placebo-controlled trials:

> I am aware of the Angell/Lurie criticism of studies not using best standard care in control groups. I feel this is making the best the enemy of the good. If applied widely this principle prevent[s] testing of cheaper, i.e., affordable, almost as good as the best, interventions. And it prevents them being evaluated against usual care, which is often nothing.

Other respondents did not necessarily oppose control trials but did raise issues of informed consent and the importance of ensuring participants understand the conditions of the controlled trial:

> I think participants should be clearly told we are not sure about the benefits [and] that's why we are doing the research.

Another respondent felt control trials were acceptable, but asked:

> …controls benefit [the] greater good, but what do you leave [with the] study participants?

Another respondent felt that providing some benefit to the study community was absolutely necessary:

> I believe every research must have an intervention to follow. After our last research when we analyzed the problems of the community there were so many that we could not deal with them. For instance, we went to the community and women's group told us that two women died last month, I would immediately think of providing antenatal care to women rather then walking out of the communities without any follow up services [which] is unethical.

This same respondent felt that pre-study agreements are critical in providing benefits to the study community. The interventions described by this respondent were not necessarily the treatments under investigation, but are interventions selected for implementation by the study team based on available resources and the expertise of the participating investigators and needs of the community.

Several respondents commented on the lack of control over the drug trials the pharmaceutical industry is conducting in developing countries. One respondent thought the "pharmaceutical industry is very strong and important" in the United States and therefore more loosely controlled. This respondent commented:

> Pharmaceutical industry puts pressure on researchers to conduct research on their drugs and we are acting as guinea pigs for the first world. This industry is actively participating in unethical research which could never be carried out in other developed countries or the United States.

Some felt that the United States did nothing to stop unethical research even when it was aware that it was taking place. This respondent commented as follows:

> ...before AZT was found to be useful in preventive perinatal transmission, it was not thought that it was a useful single drug for HIV-infected individuals, but there were areas that were using that and they're not doing it on their own. They had somebody that was providing them with the drugs. So when I go to some of the meetings…where the head of USAID is saying, Well, a list of the official legal vaccines that we know of…that really disturbs me because it means there are some unofficial or unethical things happening and it's a huge problem for [African country]….

Recommendations

Compensation and Incentives. Many respondents had very clear concerns in regard to how the community will benefit from research, particularly the study participants themselves. Monetary incentives were not recommended except at low enough levels to be considered as compensation to cover the costs of study participation and not as the primary reason for participation. One participant suggested "more creative, nonmonetary incentives" need to be developed for study participants, particularly in areas of poverty or low employment. Providing monetary incentives to research staff also was not recommended due to the potential for conflict of interest.

Study Design. There were dissenting opinions on the ethics of using control and placebo arms in research in resource-poor countries. Some felt that these arms were important in discovering second-best treatments while others warned of the potential to treat people as guinea pigs. Generally, respondents felt that the intervention under investigation had to be relevant to the population and that there needed to be some provision of direct benefit to the study population. Respondents also felt that the control groups should receive the intervention at the completion of the study. Some respondents felt there should be specific requirements regarding these issues, while others felt that a case-by-case review was more appropriate.

Much of the disagreement regarding benefits to the study community related to drug trials and use of control or placebo arms. One respondent felt that U.S. guidelines should include special restrictions for U.S. researchers conducting research in developing countries that could not be conducted in the United States. The respondent explained that the restrictions should not result in prohibition, but that a set of processes should be required to justify the research. Another respondent recommended restricting drug testing in developing countries to only those drugs that previously have been tested in a developed country.

There also was a discrepancy between the responsibilities in terms of treatment during the study for treatment intervention research and prevention intervention research. Several respondents argued that requiring the best-known available treatment for prevention studies is not appropriate.

Pre-Study Agreements. A pre-study process was recommended for determining which interventions will be provided to the study community after the study is completed. Specific organizations providing these services or interventions should be included in the pre-study agreement negotiations.

Cultural Sensitivity. Two respondents mentioned cultural insensitivity among researchers involved in a study on breastfeeding and breast cancer, respectively. In both cases, respondents felt that the investigators lacked awareness of the significance and meaning of the breast within their particular cultural setting. The respondents called for more cultural awareness on the part of the investigators in designing and implementing their studies.

In terms of study design, the issue of religion was raised in one focus group and is an example of how contextual factors were considered in developing a study. Investigators were concerned with whether or not drawing blood would break the fast during Ramadan. A group of Islamic scholars was consulted to resolve the issue.

D.4. Obligations to Subjects, Communities, and Countries

D.4.1 Results from Survey

This section covers the issues related to the conclusion of research studies. Based on the survey findings, the section addresses the implementation of interventions after research studies are completed and capacity building and partnerships between the sponsors of the study and the developing country researchers.

Research Priorities

Fifty-eight percent of the developing country researchers responded true or sometimes true that "research priorities of outside funding agencies that are funding the study are not congruent with top priorities of the developing country" (Table D.2.3). Among those researchers funded by the United States, 55 percent of them responded true or sometimes true on the same question. These responses relate to either the reality of the situation or a perception of the researchers' priorities.

Intervention Studies as Human Subjects Health Research

Less than half (44 percent) of the developing country researchers described their "index study" (on the survey questionnaire) as being an intervention study. Among physician respondents, almost half (48 percent) of them had intervention studies as part of their human subjects research. Only 30 percent of those researchers who were nonphysicians had intervention studies ($p = .032$). Of those researchers with intervention studies, almost all (94 percent) of the respondents reported that their particular studies had shown the intervention to be efficacious.

Implementation of Interventions After Research Studies

Most (92 percent) of the developing country researchers responded "yes" to the question "Was the intervention provided, or, will it be provided, if successful, to study participants or any other host country residents at the conclusion of the study?" Six percent responded "don't know," while 2 percent responded "no."

To the question, "To whom was (or will) the intervention be provided?" the responses are as follows (Table D.4.1):

Table D.4.1: To Whom Was (or Will) the Intervention be Provided? (Respondents could check more than one option)

Group	Percent
Community from which the study population comes	38
Entire study populations	32
Certain regions of host country	28
Entire host country	22
Placebo or control group of study	20
Others	8

For the above groups of respondents, a difference ($p < .10$) was found upon further analysis by type of researcher (i.e., by gender, age, and IRB/non-IRB membership status) for the "entire study population" category. The differences are presented in Table D.4.2.

Table D.4.2: If the Intervention in the Research Study was Successful, Will It be Provided to the Entire Study Population?

Gender of Survey Respondents	% Yes	% No	P-Value
Female (n = 16)	50	50	0.057
Male (n = 38)	24	76	
Age of Survey Respondents	**% Yes**	**% No**	**P-Value**
45 years or less (n = 26)	19	81	0.075
Greater than 45 (n = 25)	44	56	
IRB Member/Nonmember	**% Yes**	**% No**	**P-Value**
Members (n = 25)	44	56	0.066
Nonmembers (n = 29)	21	79	

Table D.4.3: What Parties Were (or Will Be) Part of the Arrangement to Provide the Intervention? (Respondents could check more than one option)

Category	Percent
Host country institution	55
Host country government	53
Host country research team	47
International agency (e.g., WHO, UNICEF)	24
Foreign funding agency for this study	19
Foreign research team carrying out this study	14
Foreign institution carrying out this study	10
Other	7
Private foundation	5
Private for-profit agency	3

Table D.4.4: How Long Was (or Will) the Intervention Be Provided?

Duration of Post-Research Intervention	Percent
Two to five years	39
Greater than five years	33
Less than one year	26
Other	2

To the question, "What parties were (or will be) part of the arrangement to provide the intervention?" the responses leaned heavily towards host country categories (Table D.4.3). The researchers identified the host country institution (55 percent), the host country government (53 percent), and the host country research team (47 percent) as the parties who were/will be part of the arrangement to provide the intervention.

Further analysis was made among the survey respondents regarding host country government arranging for the provision of the intervention. The results indicated that 72 percent of nonuniversity respondents said the host country government did or will do so, while a smaller percentage (43 percent) of university respondents say the host country government did or will arrange for provision of the intervention ($p = .080$).

The U.S.-funded researchers (19 percent) were more likely to state that the "foreign institution carrying out the study" should be involved in arranging the provision of intervention than non-U.S.-funded researchers (3 percent, $p = .096$).

The developing country respondents were also asked the question, "How long was (or will) the intervention be provided?" Their responses are organized in descending order in Table D.4.4.

Fifty percent of non-IRB members indicated that the intervention was (or will be) provided from two to five years, whereas 50 percent of IRB members indicated that the intervention was (or will be) provided for more than five years (Table D.4.5).

Table D.4.5: IRB Versus Non-IRB Survey Respondents on Duration of Intervention Provision

IRB Members/ Nonmembers	<1 year	2-5 years	>5 years	Other
Members (n = 24)	25	25	50	0
Nonmembers (n = 24)	29	50	17	4

p = .050

Table D.4.6: University- Versus Nonuniversity-Employed Survey Respondents on Duration of Intervention Provision

University/ Nonuniversity	<1 year	2-5 years	>5 years	Other
Nonuniversity employed (n = 17)	18	23	53	6
University employed (n = 30)	33	44	23	0

p = .069

Table D.4.7: How Was (or Will) the Intervention Be Paid for? (Respondents could check more than one option)

Source of Funding	Percent
By host country government	46
By research grant for this study	39
By foreign funding agency for this study	25
By host country institution	21
By international agency	11
By private foundation	9
Other	7
By private for-profit company	5
By foreign institution carrying out this study	4

Among respondents employed by nonuniversity settings, the majority (53 percent) stated that the intervention was (or will be provided) for more than five years (Table D.4.6). In contrast, most (44 percent) of the university-employed respondents stated that the intervention would be provided for two to five years; one-third (33 percent) of them stated that it would be provided for less than a year. Only 23 percent of them said the intervention would be provided for more than five years.

The developing country researchers responded to the question, "How was (or will) the intervention be paid for?" as shown in Table D.4.7. The host country government (46 percent), followed by the research grant for the study (39 percent), was mentioned most often as being the source of funding for the intervention. Upon further analysis, statistical significance was found between IRB members (64 percent) and non-IRB members (31 percent) stating that host country government would pay for the interventions (p = .014).

The above data suggest optimism in the provision of interventions at the conclusion of the study to study participants or any other host country residents. However, the researchers appear less optimistic when asked if the treatment or intervention being tested will be made available for most citizens of the country in the foreseeable future (Table D.2.3). Almost half (48 percent) of them agree that it is true or sometimes true that the treatment or intervention being tested is unlikely to be available for most citizens of the country in the foreseeable future.

Capacity Building and Partnerships with Developing Country Researchers

The Involvement of Developing Country Researchers in Research Tasks. According to the developing country researchers, they participate in various research tasks with foreign research collaborators. The tasks are ranked according to perceived level of involvement (see Table D.4.8). In terms of involving field staff on the topic of ethics issues, 39 percent said that it is true or sometimes true that it was rarely discussed. See Section D.6.5 and Section E.4 for further discussions on this topic.

Table D.4.8: Developing Country Researchers Were/Are Included in the Following Research Tasks

Option	% Yes
Listed as authors on papers	95
Training of research personnel	92
Change in study design	87
Drafting manuscripts	86
Initial study design	86
Data analysis	86
Recruitment of participants	86
Drafting consent form	84
Consent discussions with participants	84
Grant writing	72

Table D.4.9: Resources or Research Infrastructure That Will Remain After the Study Has Ended

Question	% Yes
Will some of the resources or research infrastructure established for this study remain in the developing country after the study has ended?	92
Personnel who were trained or who acquired skills on this research project	95
Medical, laboratory, or office equipment	90
Computers or data management system	86
Medical, laboratory, office, or pharmaceutical supplies	79
Organizational structure for health care or research	70
Power generating equipment, water system, or motor vehicles	48
Buildings, laboratory facilities, or renovations	44
Other	37

Resources and Research Infrastructure for Host Countries. As many as 92 percent of the developing country researchers say that some of the resources or research infrastructure established for their studies will remain in the developing country after the study has ended. The type of resources and infrastructure are ranked in descending order in Table D.4.9.

Recommendations

Survey respondents were asked for their recommendations in the area of intervention implementation at the conclusion of research studies. Responses from all the researchers versus only those whose studies are/were funded by the United States are compared in Table D.4.10.

Three-fourths (77 percent) of the developing country researchers agreed that the issue of what standard of medical care to provide to study participants should be decided on a case-by-case basis. Eighty percent of the U.S.-funded developing country researchers agreed.

Eighty percent of the respondents agreed that researchers should be required to make data from the research study directly available to study populations after the study is over. A slightly higher percentage (87 percent) of U.S.-funded developing country researchers agreed that researchers should be required to make data from the research study directly available to study populations after the study is over.

Seventy-eight percent of the respondents agreed that research to test an intervention should not be carried out in a developing country unless the intervention, if found to be successful, will be made available to that country at the conclusion of the study. The same percentage of U.S.-funded developing country researchers agreed.

Seventy-nine percent of the respondents agreed that international policy regarding research should require researchers to establish a mechanism for continuing delivery of medical care after completion of the study. Seventy-five percent of U.S.-funded developing country researchers agreed.

Table D.4.10: Recommendations

Recommendations	Developing Country Researchers*				Developing Country Researchers (U.S. Funded)**			
	n	% Strongly Agree and Agree	% Neutral	% Strongly Disagree and Disagree	n	% Strongly Agree and Agree	% Neutral	% Strongly Disagree and Disagree
The issue of what standard of medical care to provide to study participants should be decided on a case-by-case basis.	182	77	7	16	79	80	5	15
U.S. researchers should be required to make data from research study directly available to study populations after study is over.	176	80	13	7	76	87	9	4
Research to test an intervention should not be carried out in a developing country unless the intervention, if found to be successful, will be made available to that country at the conclusion of the study.	187	78	9	13	81	78	9	13
International policy regarding research should require researchers to establish a mechanism for continuing delivery of medical care after completion of the study.	185	79	12	9	80	75	14	11

*Survey respondents from developing countries

**Survey respondents from developing countries whose index studies are/were funded by the United States.

D.4.2 Results from Qualitative Research

Provision of Effective Intervention

Generally, as mentioned in the previous section, "cowboy research," where researchers go into a community, collect data, and leave, is not acceptable:

> They [study participants] need to be informed and something needs to go back to them. You can't just do the research and take the results and run. Intervention has to come through, and this is happening now.

However, the issue of requiring implementation of interventions found to be effective during the study was debated. Some respondents felt that effective interventions should be implemented in the study community after completion of the study, as this respondent stated:

> …I give an example of [study in an African country]…where they…found that treating STDs can reduce HIV 42 percent…but after that what has really happened? Has the government got the money to…implement the findings? What do we really need from these countries [developed countries]…the drugs for treating STDs and the training…you can provide international presentation and publication but so what?

One respondent felt that an essential part of a "research contract" between the government and the researchers should be to make the product of the research available to the study volunteers if proven effective:

> As an example for HIV vaccine, I wouldn't be surprised if we finally get a very good result…we should have some kind of consent that says this vaccine…should be available first for those people…for free because they…risk their life in something they don't know.

One respondent suggested provision of the intervention be written into the guidelines as a requirement:

> It should be made a requirement that research involving testing of drugs and other interventions, if found efficacious, the participating populations should be among the first ones to benefit, at affordable costs.

However, another respondent felt that this was beyond the scope of research and that providing effective interventions was a policy decision of the Ministry of Health or host country government:

> We think more or less to do the research and hand the results to the Ministry and it's their objective to implement and mandate.…

Economic Feasibility

The feasibility of making effective vaccines available was considered low unless some pre-study negotiation had been achieved. In terms of other interventions, such as information, education, and communication interventions aimed at preventing maternal mortality, respondents felt these decisions were up to their governments to provide the funding. Some respondents felt that their role was limited to making national health policy recommendations, not funding decisions. Several others spoke of potential funding sources with private donors or research institutions. Others mentioned built-in research funding to implement successful interventions. Respondents in one focus group agreed that typically after the study is completed, all interventions end.

Another respondent agreed that interventions should be made available to the study community, but cautioned:

> This is an issue that needs to be studied further to see how it can be implemented. It is indeed important for equity and justice. However, it is difficult to require this for ERB/IRB approval in the case of new drugs/tools, having little idea yet of its efficacy, market price, etc. This needs continuing negotiation and discussion as the study proceeds. At least, if found efficacious, the new drug/tool should be made available to the study community.

The quality of the health care delivery system and efforts in changing government policy were also mentioned as considerations in the provision of effective treatment:

> We can never be sure that an intervention would be available all over the country, even successful. It depends on the cost of drugs, government policy [national] and health system possibilities to do it. We have to test interventions that make sense for the country where they are done but availability after the results depends on our common fight as a society to implement those [interventions].

In terms of HIV, the drugs are more expensive. Several respondents felt that it was not realistic economically for studies to provide the drugs for an unlimited time period. This respondent remarked:

> …our general…what we call opinions from us as locals [local investigators] from local countries, we actually thought it [provision of effective intervention] was quite unreasonable because you couldn't, we couldn't—even if you gave the drugs during the study, but you couldn't continue giving the drugs after the study.

Recommendations

Respondents clearly felt there is a need for the study community to benefit from the research. Whether or not to make the provision of effective interventions a requirement was debated. In some cases, respondents felt it was prohibitively costly to provide the treatment, particularly in HIV research. Other respondents mentioned that the decision to provide effective interventions in the study community was a public heath policy decision that should be made by the host country government and not the investigators themselves.

Pre-study agreements were clearly recommended where provision of the intervention is considered. One respondent felt that such "contract" agreements require continuous negotiation, particularly in terms of providing drugs or vaccines that were proven effective.

D.5 International Collaborative Research

D.5.1 Results from Survey

This section covers the survey findings in the area of U.S. as well as developing country (host) IRBs and human subjects research regulations.

U.S. IRBs Versus Developing Country IRBs

The developing country researchers were asked to respond to the frequency in which the U.S. IRBs raised the following issues, as well as the frequency with which the same issues were raised by the developing country's IRBs or ethics board in its review of the same index study (Table D.5.1).

Table D.5.1: Comparison of Responses to Issues Raised by U.S. IRB(s) vis-à-vis Issues Raised by Developing Country IRB(s)

Option	Raised by U.S. IRB(s) in Its Review of the Index Study % Yes	Raised by Developing Country IRB(s) or Ethics Board in Its Review of the Index Study % Yes	Test of Statistically Significant Difference P-Value
Relevance of research question to country where research is conducted and/or rationale for doing study outside the United States	52	54	0.8426
Complexity of language on consent form	64	45	0.0699
Cultural appropriateness of study procedure	63	59	0.6876
Need for local language consent form	84	58	0.0065
Need for letters of approval from developing country representatives	79	47	0.0011
Intervention was considered too risky	15	11	0.4656
Appropriateness of procedures for control group	50	39	0.3254
Confidentiality protections for participants were not adequate	42	18	0.0045
Participant voluntaries may be compromised because of benefits study provides	20	24	0.6446
Use of placebos	22	26	0.6949
Availability of intervention (if successful) to host country after study is over	46	54	0.4832
Political considerations	17	16	0.9052
Others	8	12	0.000

In comparing issues raised by U.S. IRBs versus those raised by developing country IRBs or ethics boards, significant differences ($p < .01$) were observed in the response of the researchers on the following three issues:

- The need for local language consent forms.
- The need for letters of approval from developing country representatives.
- Confidentiality protections for participants.

Further analyses were conducted to determine whether or not there was statistical significance depending on the various categories of the researchers (e.g., age, gender, university/ nonuniversity employed, physician/ nonphysician, and IRB/non-IRB member). Significant findings are reported below.

Need for Local Language Consent Forms. The issue of the need for local language consent form was brought up by 84 percent of the U.S. IRBs versus 58 percent by developing country IRBs or ethics boards ($p = .0065$) (Table D.5.1). With regard to developing country IRBs or ethics boards, one-third (30 percent) of the researchers over 45 years of age disagreed that there is a need for a local language consent form, whereas slightly more than half (55 percent) of those researchers age 45 or less disagreed ($p = .006$).

Need for Letters of Approval from Developing Country Representatives. The need for letters of approval from developing country representatives was brought up more often (79 percent) by U.S. IRBs than the local IRBs or ethics boards (47 percent) ($p = .0011$) (Table D.5.1). With regard to developing country IRBs or ethics boards, older researchers (>45 years of age) were more likely (59 percent) than younger researchers (35 percent) to agree that the local IRBs/ethics boards raise the issue of needing letters of approval ($p = .015$). In addition, nonacademic researchers (60 percent) were more likely to agree than academic researchers (38 percent) on the same issue ($p = .020$).

Confidentiality Protections for Participants. The U.S. IRBs raised the issue of confidentiality protections for participants not being adequate, more often (42 percent) than by the developing country IRBs/ethics boards (18 percent, $p = .0045$). On the issue of confidentiality protections for the participants being inadequate, only 10 percent of the researchers funded by the U.S. stated that it was brought up by the developing country IRB or ethics board reviews of their studies. A much higher percentage (25 percent) of non-U.S. funded researchers said the same issue was brought up ($p = .042$).

Other issues that arose during *developing country IRB reviews* only that were noted to be significant are as follows:

Appropriateness of Procedures for Control Group. Forty-four percent of the older researchers (>45 years of age) versus 15 percent of younger researchers said that issues related to the appropriateness of procedures for control groups were brought up during their index studies ($p = .001$).

Use of Placebos. On this issue, a significant difference was observed between researchers over age 45 versus researchers 45 or less. As many as 41 percent of the older researchers said the placebo use was brought up by the developing country IRB or ethics board review. Only 6 percent of researchers 45 or younger said the same issue was brought up ($p < .001$).

Availability of Intervention (If Successful) to Host Country After Study Is Over. When the research studies involved vaccine development and/or testing, all five researchers (100 percent) stated that the issue of availability after the study was brought up by the country's IRB or ethics board review ($p = .058$). No statistical significance was found regarding the same issue, by the U.S. IRB. When the research studies were on health systems or services, 80 percent of the time the availability of intervention was brought up by the country's IRB or ethics board review ($p = .010$).

Political Considerations. When the research studies involved HIV/AIDS, political considerations were raised 35 percent of the time ($p = .016$). No further information on the nature of this issue was available from the survey.

U.S. Human Subjects Regulations

Table D.5.2 describes the developing country researchers' experiences and attitudes regarding U.S. and international human subjects regulations and guidelines. Thirty-seven percent of the survey respondents said that U.S. human subjects regulations were "never" flexible where they needed to be, while 7 percent said they were "always" flexible, and 56 percent said "sometimes." More than half (57 percent) of the developing country researchers agreed ("sometimes" or "always") that U.S. IRBs were more concerned with politics than with protecting the interests of research subjects, while 43 percent disagreed. Seventy-seven percent of the researchers responded that "sometimes" U.S. IRB regulations are insensitive to local cultural norms, while 6 percent responded "always" (cumulative percentage is 83 percent for "sometimes" and "always"). No association was found when the researchers were further classified by gender, age, physician/ nonphysician, IRB/non-IRB member, U.S./non-U.S. funded, or academic/nonacademic.

Table D.5.2: Researchers' Beliefs/Attitudes About Ethical Guidelines and Regulations in Human Subjects Research

Options	% Always	% Sometimes	% Never
U.S. human subjects regulations are flexible where they need to be.	7	56	37
Developing country collaborators rely on U.S. ethics regulations for guidance.	14	77	9
U.S. IRBs are more concerned with politics than they are with protecting the interests of research subjects.	3	54	43
The current U.S. rules and regulations governing human subjects ensure high ethical standards in research.	59	36	5
U.S. IRB regulations are insensitive to local cultural norms and traditions outside the United States.	6	77	17
Developing country IRBs are more concerned with politics than they are with protecting the interests of research subjects.	3	60	37
Developing country IRBs have voiced concerns to me about the costs associated with the IRB carrying out its work.	7	38	55
National guidelines in developing countries are effective in protecting research subjects.	21	71	8

A very small percentage (6 percent) of the researchers agreed that they have ever had to abandon a research project because it was impossible to get U.S. IRB approval, despite modifications.

Single Project Assurance. Forty-four percent of the survey respondents had index studies that are/were funded by the United States. Based on those who responded, from this category, 44 percent reported that they did obtain SPAs (p = .72). According to the majority (almost three-quarters) of them, it took between one and six months to obtain the SPA. Only 2 percent of the researchers agreed that they have ever had to abandon a research project because it was impossible to obtain an SPA. A small percentage (15 percent) of these survey respondents (n = 26) encountered resistance on the part of developing country officials to agreeing to a SPA (Table D.5.3). At the same time, as many as 84 percent of them (n = 25) considered the SPA process to be valuable in ensuring that a developing country ethics review was carried out.

Besides SPAs, 12 percent of the researchers reported that they encountered resistance on the part of developing country officials to U.S. requirements for (host country) IRB composition (Table D.5.3).

In the area of DSMBs, all the researchers who have studies involving greater than minimal risk (n = 3) stated that they had a DSMB (p = .015). (See Table D.5.4 for additional information.)

Table D.5.3: SPA Information

Option	% Yes	% No
Encountered resistance on the part of developing country officials to agreeing to an SPA (n = 26)	15	85
Encountered resistance on the part of developing country officials to U.S. requirements for IRB composition (n = 25)	12	88
Considered the SPA process valuable in ensuring that a developing country ethics review was carried out (n = 25)	84	16

Despite the relatively high percentages of agreements that U.S. human subjects regulations are not flexible, are concerned with politics, and are insensitive to local cultural norms, there are also higher agreements of the positive contributions of the regulations. As much as 59 percent of the developing country researchers responded "always," while 36 percent responded "sometimes" (combined percentage of 95 percent), that the current U.S. rules and regulations governing human subjects ensure high ethical standards in research. Over three-quarters of the researchers (77 percent) relied on U.S. ethics regulations for guidance "sometimes," while 14 percent said "always" (cumulative percentage for "always" and "sometimes" is 91 percent). A much higher percentage (97 percent) of academic respondents said that developing country collaborators rely on U.S. ethics regulations for guidance "sometimes" or "always" versus 81 percent of nonacademic respondents (p = .018).

Table D.5.4: DSMB Information

Question	% Yes	% No	% Don't Know
Study had a DSMB (n = 84)	22	58	20
Ethic issues arose in DSMB review of study (e.g., medical care offered to participants)? (n = 19)	37	58	5
	% Never	**% Sometimes**	**% Always**
Aware of results of DSMB meetings (n = 18)	17	33	50

Host Country (Developing Country) Human Subjects Regulations

The developing country researchers were equally critical of their countries' IRBs as they were of the U.S. IRBs, when asked if their IRBs are more concerned with politics than they are with protecting the interests of research subjects. Sixty-three percent of them agreed ("sometimes" or "always"). (Fifty-nine percent of them had agreed about U.S. IRBs, on the same issue.) Nonphysician researchers as a group were more critical about their countries' IRBs on this issue (82 percent) ("sometimes" and "always" combined) than the physician researchers (57 percent) ("sometimes" and "always" combined) (p = .008).

When asked whether the developing country IRBs have voiced concerns about the costs associated with an IRB in carrying out its work, 45 percent (cumulative percentage for "always" and "sometimes") of researchers stated that it has been brought up. The majority of the researchers (92 percent) agreed that "sometimes" or "always" the national guidelines in the developing countries are effective in protecting research subjects.

Seventeen percent of the researchers responded that they have had to abandon a research project because it was impossible to get developing country IRB approval despite modifications. In contrast, only 6 percent of them reported having to abandon their project because it was impossible to obtain U.S. IRB approval. More IRB-member researchers (62 percent) had to abandon their research because it was impossible to get developing country IRB approval despite modifications, compared to 38 percent of researchers who are not IRB members (p = .029) (Table D.5.5).

Table D.5.5: Developing Country IRB Approval

Have you ever had to abandon a research project because it was impossible to get developing country IRB approval despite modifications?	Yes	No
IRB member %	62	38
Non-IRB member %	40	60

p = .029

IRB and Ethics Review at the National or Local Level

Forty-four percent of the survey respondents reported that their studies did not undergo review by the Ministry or Department of Health in the country where the research is/was conducted (Table D.5.6). Twenty-five percent of the respondents also reported that their studies did not undergo some type of ethics review by an IRB, ethics board, or Ministry/Department of Health in the country. Further analyses show that a potential 15 percent (28 studies) of the studies being described in the survey were *neither* reviewed by the Ministry/Department of Health *nor* by any IRB/ethics board. Of these studies that were *neither* reviewed by the Ministry/Department of Health *nor* by any IRB/ethics board, 36 percent (10 studies) were funded by the United States.

Table D.5.6: Developing Country IRBs and Other Ethics Review

Studies That Did Not Undergo Reviews	%	n
The study did not undergo review by the Ministry/Department of Health in the country where the research is/was conducted.	44	82
The study did not undergo some type of ethics review by an IRB, ethics board, or Ministry/Department of Health in the country where the research is/was conducted.	25	46
Studies that were neither reviewed by the Ministry/Department of Health nor by any IRB/ethics board.	15	28
Studies that were neither reviewed by the Ministry/Department of Health nor by any IRB/ethics board and were funded by the United States.	36	10

Source of Ethics Review Requirements. Of those researchers whose index studies are/were funded by the U.S., 69 percent of them responded that the developing country ethics review was required by U.S. institutions/regulations (p = .001) (Table D.5.7). Further, 95 percent of this category of researchers reported that the developing country ethics review was required by developing country institutions/regulations.

Table D.5.7: Source of Ethics Review Requirements

	U.S.-Funded Researchers		
Question	n	% Yes	% No
Was any of this developing country ethics review required by U.S. institutions/regulations?	55	69	31
Was any of this developing country ethics review required by developing country institutions/regulations?	61	95	5

Table D.5.8: Developing Country IRBs and Other Ethics Review

Did this study undergo some type of ethics review by an IRB, ethics board, or Ministry of Health in the country where the research is/was conducted?	Response of the Researchers		
	% Yes	% No	P-Value
Discipline of index study: epidemiology	82	18	0.013
Discipline of index study: clinical care	89	11	0.016
Discipline of index study: anthropology	48	52	0.002

Types of Studies and Ethics Review. Compared to other study methods, half (52 percent) of the anthropological studies did not undergo any type of ethical review by an IRB, ethics board, or Ministry of Health (p = .002) (Table D.5.8). In addition, 11 percent of studies conducted by researchers in clinical care also did not undergo ethical review (p = .016); 18 percent of epidemiological studies did not undergo ethics review (p = .013).

Table D.5.9: Developing Country IRBs and Other Ethics Review

Did this study undergo some type of ethics review by an IRB, ethics board, or Ministry of Health in the country where the research is/was conducted?	Response of the Researchers		
	% Yes	% No	P-Value
Topic: infectious diseases, non-HIV/AIDS	86	14	0.016
Topic: HIV/AIDS	93	7	0.017
Topic: health systems/services	61	39	0.013

The following types of research studies did not undergo ethical review: 39 percent of health systems/services types of research studies (p = .013); 14 percent of infectious disease (but non-HIV/AIDS) research studies (p = .016); and 7 percent of HIV/AIDS studies (p = .017) (Table D.5.9).

In the country where the research was conducted, the respondents stated that the study was reviewed by the following institutions (Table D.5.10):

Note that the majority of studies (92 percent) were being reviewed at the local institution level. In terms of community representation, 61 percent of the researchers say that there is inadequate community representation on the local IRBs/ethics boards.

Table D.5.10: Developing Country IRBs and Other Ethics Review

Review Board	Percent of Responses	
	% Yes	% No
A national IRB /ERB (n = 115)	49	51
State/provincial IRB/ERB (n = 93)	27	73
Collaborating local institution IRB/ERB (n = 130)	92	8
Other in-country ERB (n = 70)	14	86

Recommendations

Survey respondents were asked for their recommendations in the areas of U.S. IRBs, developing country IRBs, SPAs, ethical reviews and international guidelines. Responses from all the researchers versus only those whose studies are/were funded by the U.S., were similar when compared (Table D.5.11).

The majority (85 percent) of survey respondents agreed that research funding agencies should provide funding to support the work of developing country IRBs. More than three-quarters (77 percent) of the survey respondents recommended that international guidelines (e.g., CIOMS) should be used instead of U.S. rules and regulations. According to 85 percent of the developing country researchers, a developing country ethical review should be required for all studies. Ninety-two percent of them also stated that the composition of ethics review boards used in developing countries should not be dictated by U.S. regulations. Forty-six percent were neutral, while 28 percent agreed and 26 percent disagreed that the SPA requirement should be eliminated. Seventy percent of the researchers agreed that some research funds for piloting consent forms should be released before final IRB approval is obtained.

Table D.5.11: Recommendations

	Developing Country Researchers*				Developing Country Researchers (U.S. Funded)**			
Recommendations	n	% Strongly Agree and Agree	% Neutral	% Strongly Disagree and Disagree	n	% Strongly Agree and Agree	% Neutral 1	% Strongly Disagree and Disagree
Research funding agencies should provide funding to support the work of developing country IRBs.	191	85	7	8	82	89	6	5
International guidelines (e.g., CIOMS) should be used instead of U.S. rules and regulations.	171	77	22	1	75	76	23	1
A developing country ethical review should be required for all studies.	190	85	6	9	81	89	2	9
The composition of ERBs used in developing countries should not be dictated by U.S. regulations.	191	92	7	1	82	85	14	1
The SPA requirement should be eliminated.	116	28	46	26	82	26	41	33
Some research funds for piloting consent forms should be released before final IRB approval is obtained.	182	70	21	9	54	70	18	12

*Survey respondents from developing countries

**Survey respondents from developing countries whose index studies are/were funded by the United States.

D.5.2 Results from Qualitative Research

Local National IRBs in Host Country

Adequacy and Effectiveness. Respondents felt that a local institutional review process was necessary for regulating research and was described as bringing "some sanity to the researchers." However, the perceived functioning of these review systems varied greatly. Some countries do not have local IRBs, while others have well-established IRBs that have been in operation for many years:

> Most of the issues did not arise at the local review because they were already addressed in the application. My institution has a strong ethics board, which has been active for several decades. Thus, formal ethics review is an essential part of the tradition and teaching in research.

Respondents felt that local IRBs were strengthened over time as they gained experience and exposure to various research and ethical issues. Several respondents described the process of building up the IRB. This respondent commented as follows:

> Once we got it set up in the university then we moved on to the Ministry [of Health] and it took a while….I'm not saying that all Ministry people are bad, but some people…[the government] took money from, these researchers, and turned their backs, so whatever happens to the patients, they don't care too much.

This same respondent felt that these issues are beginning to be dealt with now:

> In [African country] there was no ethics or research committee by the time I got there and when there were a lot of researchers coming from abroad and calling themselves researchers who just came to the country and they did what they wanted to do and left. It took a while for us to push the government to the point [of addressing the situation]. The university first approached the issue. Once we had it set in the university we moved on to the Ministry and it took a while and there are many, many reasons for that. This has been addressed in most African developing countries by now because the patient is extremely important.

One respondent remarked that other than official IRBs, there were many private advocacy organizations that served minorities groups, human rights, and women, among others. These groups were vigilant of research activities and the protection of human subjects.

Urban areas where university or research institutions are generally located were more likely to have established review processes that were better functioning and more effective than in rural regions. Outside of larger cities there was reportedly less familiarity with the IRB process and the government had more difficulty in regulating research. However, where there is a history of research or more recent research activity, there is more capacity and familiarity with the process. Several respondents mentioned that IRBs are "routine" for rural districts where research activity has been at a high level. Any investigator arriving in those areas will be required to go through a review process, but rural districts with less research activity do not share in this level of experience with the local IRB process and do not know how to advise incoming investigators. Other respondents noted that although their local university has an established review system, investigators, both nationals and non-nationals, who are not aware of its existence, bypass it. Some of these respondents also felt that research was in its infancy in their country, that ethical considerations are not taken seriously, and that review processes are sometimes simply ignored. Other respondents also felt that seeking ethical approval was the investigator's responsibility, particularly for projects to be implemented in rural districts where review processes are not well established.

Several respondents felt the review process at the government level was slowed considerably by bureaucratic procedures:

> …when it gets to the Ministry [of Health] it just drags on forever. So you have to follow it all the time because the committee will tend to not meet regularly and you have to push the chair person to call a meeting…it takes four to six months.

Citing a long history of research in collaboration with a U.S. university, one researcher referred to the "tradition of research" that exists at the university level, but is absent at the government level Ministry of Health, which was described as:

> …More concerned about the money than [whether the study is] for the people or not.

Frustration was frequently expressed over the inadequacy of the national governments to regulate research and to enforce ethical guidelines for all research projects implemented within national boundaries. This respondent commented:

> …Institutions that have universities attached to it and have a lot of people that have been outside and are [also] used to the developing world system, it's more probable that you will have something comparable to what you have in the developed nations…moving from those cities that have universities and just set up a collaboration with some private medical practitioner or some small group somewhere…you might find…that they have no control at all, and that is a huge problem for the government.

Another respondent explained that when they began research in the early 1980s in (a Caribbean country), the Ministry of Health had a review board, but its role and mission were unclear, and it operated without guidelines. A regional research institution, which already had an IRB and served several countries in the region, began to review proposals for the respondent's projects sponsored by the United States. This was a feasible solution for the investigators so that they could fulfill U.S. requirements of local IRB approval. Such creative solutions with partnering and twinning of institutions could be effective in the design phase of research.

Emphasis of Review. Most participants reported their university review boards as serving dual functions of both technical and ethical review. One participant remarked that U.S. investigators have been rebuked at the questioning of local IRBs on the technical merit of their studies because their expectation is that the review will be based solely on ethical concerns. But as this respondent said, the philosophy behind the dual role of the local IRB is that you cannot have ethical research without "good science."

Ethical review of study proposals has been a more recent occurrence in some countries, a process many respondents described to have developed within the last ten years. In some countries the local review continues to emphasize scientific, political, or funding concerns versus ethical considerations:

> They [local IRBs] are not really concerned about ethical issues, they are looking [at] technical [issues]. And you know, and who [is] giving you money, how much are you getting….But now [we need to look at] the ethical aspects, what people are doing, is it right.

Particular instances were mentioned of IRBs considering the political sensitivity of the potential proposals primarily, while the scientific and ethical aspects of the study are judged secondarily. Generally, funding concerns were more often associated with governmental IRBs than university IRBs. Several respondents mentioned the political nature of local IRB decisionmaking. One respondent remarked:

> …it is a political approval. It is not an approval that is about ethics. It was more about whether we would be spies or we would be real researchers that would benefit [Asian country].

In resource-poor countries, the issue of corruption and "kickbacks" for government officials was a concern in establishing and, particularly, in enforcing standards for research ethics at the national level. These concerns were relevant for all respondents. One respondent expressed their concern that external organizations took advantage of the resource-poor countries in that they could dictate what they wanted by finding government officials that they could control. Where specific regulations do exist, enforcement of those regulations is a problem. Several participants specifically referred to pharmaceutical companies looking for new markets for their drugs:

> …they [pharmaceutical companies] get an institution somewhere that has a half-controlled person that would be willing to just take them in and do…whatever kinds of studies they want to do.

> …the companies when they want to market the new drug in a new market…they would promote those trials, and for them to get into the market was to get the approval of the Ministry of Health and then find collaborators at the universities and then move on.

Other participants felt that the lack of standards or guidelines came from their government officials' lack of familiarity with principles of ethics, scientific expertise, or commitment to developing or enforcing ethical guidelines because of the strong desire to build links with international organizations. One respondent commented:

> …they would have anything any foreign government body would require, so that they would make a link with [Asian country] or WHO…but in terms of who is running these bodies and who is controlling what's really happening, you will be amazed. It is mostly people who have no idea about this. They just know it is a word. So if it's human rights abuses, it will be OK, we won't abuse anyone. That is the context.

Several respondents felt that the unequal power relationships between the United States and developing countries created a paternalistic environment in which to negotiate the terms of research. When the United States brings funding, a research proposal, and specific technical expertise necessary for implementing a study, the developing country governments have difficulty in refusing the opportunity. Given these power differentials, respondents felt that decisionmaking regarding research was unfairly influenced:

> The biggest problem in developing countries is that our poverty puts us in a situation [where] the beggar has no choice.

Composition of Review Boards. The composition of review boards was mentioned in a few cases and included scientists, lawyers, faith leaders, doctors, and community members. One respondent remarked that the local university IRB would not approve research proposals unless a community representative is serving on the review board.

The issue of community representatives was important to another respondent who said it would ensure diversity and democratic composition of the board. In the university setting, one respondent mentioned the issue of conflict of interest. It was customary to have both departmental and nondepartmental faculty review each proposal to reduce the possibility for conflicts of interest to arise. Some of the respondents served on review boards, and several commented on the difficulty in finding appropriate individuals with adequate familiarity with ethics and enough experience to serve on review boards. It is frequent that the review boards are set up ad hoc to satisfy the requests of U.S. donors or collaborators, which is found to be "paternalistic" by some respondents, particularly in areas that already have established IRBs. One respondent had the experience of an ad hoc committee being set up because the composition of the local IRB was "not equal to that in U.S. institutions." This respondent added that this created a problem because the U.S. IRB felt that the local IRB was not "appropriate."

External Influence. External influence in the establishment of review processes was met with both support and skepticism. Several respondents felt that high-quality review processes could be developed through learning and borrowing from external review systems. As one respondent stated:

> I guess you learn from outsiders how research is conducted and then try to apply those standards to our situation.…

This was reiterated by another respondent, who described the process of starting with no guidelines at the university and having to build a system for ethics review:

> I think if we are both self-directed and also directed by the requirements of any agency, you learn from it the right way.…Initially it was very difficult for us as there was no board. We had to take our guidelines from various agencies, the [local] college…NIH, [local research institution].…We had to go through four IRBs. There was no regulating body.

Others clearly felt that while the review process was important, they were critical of external regulations. As one participant explained:

> So the thing for us [as] a country [is that] we don't really care about the other country's approval…we really want to make [sure] that everything is OK according [to] our standards and not with the outside standard because they might have another agenda to pursue.

This reflects the same skepticism of how effective external review requirements are in protecting human subjects in the consent process.

However, several respondents saw these "outsiders" as positive forces in motivating change for better research through more control over the type and quality of research conducted in their respective countries. Two participants mentioned specific examples of how their governments were guided and motivated by WHO and NIH to establish a process of review for research proposals in their respective countries. They felt that these external organizations served as catalysts in prompting their governments and universities to improve standards in research:

> …it was WHO that was…behind the whole study.…And they were very insistent that they cannot start the study or do anything without being invited by the Ministry of Health.…And they try to push and empower them….

Other respondents said that while the NIH guidelines were "comprehensive" and provided a good "basic format," some of the regulations are irrelevant and do not apply in their particular setting. Respondents felt there were distinctions between the U.S. cultural context and that of other countries, making some requirements irrelevant.

Several respondents commented on the lack of monitoring of research in the field. Review systems are important, but where activities are not monitored, efforts of the IRBs are negated:

> Now, what this mechanism does is to have on paper something that is acceptable. That doesn't mean that that's the way it is going to be implemented. As to what happens out there in the field, nobody knows, because there is no mechanism for follow-up to make sure that people are doing what they put down on paper.

In some cases, the sheer number of IRBs requiring approval complicated the process. Each research institution, donor organization, national government, and collaborator's institution has requirements and boards, each with several steps of approval depending on the level of risk involved for study participants, the number of collaborators involved, and the level of collaboration. Considerable time was reportedly spent in seeking IRB

approvals. Another respondent felt that the IRBs were too stringent and that some of their requests were quite "illogical."

Gaining IRB approval was described as faster and easier for international organizations than for individuals or for local NGOs because negotiations are said to occur at higher levels. One respondent felt it was advisable to gain funding before seeking local approval because the local clearance will depend on whether or not the project has financial support.

Capacity Building. One cultural dimension discussed by some respondents was that of the local power dynamics and hierarchies in the government. For one participant, it was important to sensitize U.S. investigators and donors to the "power structures" of the government so that they deal with the government officials who are not corrupt and are making decisions in the citizens' best interest.

However, more often participants emphasized capacity building of government officials as the important issue, sensitizing them to ethical concerns and broadening their understanding of how they can be active players in regulating the type of research implemented in their country.

The main issue for most participants was not one of speaking to the "right people" in the government, but rather one of raising awareness and empowering the government to take ethical issues under their control, to negotiate the terms of the research, and to actively protect their communities. Many referred to this capacity building as their responsibility as investigators who have been "trained outside," but who also have local cultural knowledge in developing appropriate ethics guidelines for their particular setting and in building the capacity of their local governments to deal with donors in negotiating research proposals:

> Where I think we have a role to play from developing countries not to be persuaded…not to be taken off by monetary matters. We need to take the interest of the people and the country at heart…it's our duty who know how to do this type of research to guide the country to make sure that whoever comes to do research…does it the way the government wants it to be done, the country wants it to be done.

These respondents felt that not only do they have familiarity with Western ideas, they also have an understanding and knowledge of their own cultures. As investigators with this dual knowledge, including an understanding of the local health care situation, many saw themselves as responsible for raising awareness of ethical principles and adapting them to their cultural setting. In this way, they are able to build the capacity of their governments to actively participate in research regulation within the local and national governments in particular, but also at the university level.

One respondent described research as "a very new [option] for recent medical school graduates in [Asian country]." While there is a dependency on outside researchers to conduct research, this respondent felt a strong obligation among them to develop capacity in the country where the research is conducted:

> Whenever you are doing research in a developing country, you have to have the mentality that we are going there because the research capacity is not there so we are going to develop something when we leave there is something left there…and also not carrying out the research but the reporting and the presenting and also the…capacity building it's not there.

The publication and dissemination of study results was also considered an important area of training for developing country researchers. Respondents wanted to be equally included in the publication and presentation of study results. Other respondents felt that this was already integrated into collaborative research activities and reported having been involved in the research process from the study design to the dissemination of results. Providing training of local health providers in how to diagnose, treat, or otherwise provide specific care was also considered a key issue in capacity development.

Another area of capacity development mentioned repeatedly throughout the discussions was infrastructure. Many respondents felt it very necessary to begin to provide physical structures and equipment, particularly laboratories for diagnostic testing, in the country where the research is being implemented. Respondents viewed this as a way to offer something back to the study communities after completion of the study. This has been a point of conflict between sponsors and collaborators, as this respondent commented:

> …I find unless you are the collaborating body or the government forces your donors or sponsors think of things that they can leave behind after the study, or benefits during the study that would benefit your own people, its very difficult. Its very generic…that way of thinking, and some of them actually accept your suggestion, but some are...like, Oh we know what we should leave behind after the study that can help you…it would be nice if they would ask.

One respondent felt that donors should send laboratory equipment directly to developing country study sites instead of providing the money to procure the equipment. Another respondent included provision of infrastructure in the "ground rules" agreed to by the collaborators before the study began:

> I like people to come and take samples, but after a few years I want the work to be done at home because not only are we getting the treatment, we are [getting] people trained to be able to do the work and carry on the work when I'm not there or somebody else is not there.

For another respondent, capacity development included the relationships that had been established between health workers and the researchers. This respondent described how health workers continue visiting the researchers "every now and then as they have the confidence" to interact with the researchers as a direct result of their involvement in a study. Several respondents made comments regarding the actions of their local government IRBs in stopping research activities that were viewed as unethical. One respondent discussed how the government refused a drug trial testing the effectiveness of Aquamarine as a birth control method. Another respondent related a case where the Ministry of Health rejected the research proposal of an investigator who falsely claimed to have found a cure for AIDS.

U.S. IRB Review

U.S. Regulations. U.S. guidelines were generally thought to be acceptable in terms of their basic premises. This respondent remarked:

> …it [present U.S. human subjects regulations] is all right in principle and in spirit, as they want to protect the rights of the participants.

However, several respondents viewed U.S. guidelines as inappropriate because they are based on the U.S. legal system and issues originating from concerns of protection and liability that are only relevant in the United States. Respondents typically felt that the manner in which these guidelines were applied should reflect the cultural and social distinctions found across all countries:

> It is offensive that U.S. funding agencies impose IRB requirements on developing countries that exist because of tort liability concerns in the United States…as if other countries were additional states of the United States. Protection of research subjects is, or should be, of paramount concern everywhere, but the individual nature of that protection as practiced in the United States is not necessarily the best model for other social/cultural settings.

This same respondent also felt that instead of U.S. institutions focusing on a U.S. review, they should rather ensure a proper, relevant, and complete local review. Others charged that their local review processes were highly functioning and adequate, as one respondent noted:

> …at least at my university the IRB, etc., procedures are by no means inferior to those in the United States, and it is not necessary for them to be superceded or made consistent with U.S. regulations.

Another respondent agreed:

> There are too many review boards. The U.S. and developing country's national review boards duplicate the work as they have similar guidelines by and large.

The need for multiple approvals created difficulty in coordinating review schedules and funding cycles. If local IRBs do not meet regularly, there may be a considerable time lag between getting approval and start of funding. Conflict was noted in trying to seek local approval first, making changes per the U.S. IRB process and then having to return to the local IRB to seek approval again. Some felt that IRB regulations were too stringent and impeded important research.

Respondents frequently mentioned that U.S. guidelines were applied unequally to research conducted within the U.S. and outside the United States. One respondent did not feel it was appropriate for studies that are not approved for implementation in the United States to seek approval in countries outside the United States.

One respondent felt that the U.S. government or U.S. universities seeking local approval before a study may be implemented is "healthy." Similarly, others felt that the local IRB having the last review approval was more appropriate because they were more familiar with the local cultural landscape and what would work best in terms of specific consent processes and seeking permission from the local community. Another important issue in this regard is reviewers' understanding the *level of health care* available in the local setting. One respondent remarked that there is a

> …need for a broader knowledge of the health system, availability of treatment, and resources in the host country [which] should be reviewed before making negative decisions about important research impossible to develop without international funding.

Ethical Responsibility. Respondents identified individual researchers, donors, and local and U.S. governments as having a role in maintaining ethical standards. As one respondent noted:

> I find the process as mandated by the NIH overly bureaucratic…the SPA is a good example.…I don't think the process…adds anything to the safety of studies. While I appreciate the need for standards, in the end the only guarantee for protecting human subjects are the researchers and the research team.

Donors were viewed as having a role in maintaining ethical standards in research by providing education and allowing government officials to negotiate their ethical concerns and needs. This respondent referred to capacity building with government officials and encouraged discussion of ethical concerns and issues with the local IRB for a more meaningful review process:

> There are a lot of donors who will strictly deal with only the government and the government will get away with pure murder because part of the problem is they don't even understand it…they're [the donors] surprised when you have the Ministry of Health who does not know…about a live virus…given in a vaccine…He doesn't [Ministry official] care a hoot, but he's interested in getting a kickback…we're talking about developing countries…if he is able to line his pockets he will do that…some of those kinds of information [ethical issues] should be getting to the government…let them filter through their hierarchy so that at least they will

> begin to ask questions, they will know that they can bargain for incentives, bargain for making the vaccines available if we participate in the studies, be active participants.…A lot of them [Ministry officials] are really very positive.

Another respondent felt that collaborators shared in the responsibility to maintain ethical standards:

> Along the same lines, I think that the responsibility should not be solely on the developing country researchers, but on the collaborators as well because a lot of things, researchers in developing countries are low with money, I mean, the funds are low, and so they lose interest in the people they're treating, but I think collaborators should also have some level of credibility.

Monitoring. Several respondents felt that the United States did not pursue investigation or take any action against ethics violations of which it was fully aware:

> [The] United States should also—to the extent possible—curb unethical research done by U.S.-based firms which do not follow existing U.S. and international policies and regulations.

Respondents related examples of ethics violations, which ranged broadly from physicians not participating in the training for implementing the study intervention to failing to treat the placebo arms of a control trial once the study concluded. In this latter example, after the study ended, the investigators not only did not treat the placebo control group but also did not acknowledge their departure to the Ministry of Health.

Another incident involved data collection on Lassa fever and at the same time, but unknown to the study volunteers, on HIV. The HIV data was published in a well-known journal without the knowledge, much less consent, of the study participants. In another case, a respondent commented that the government allowed for an HIV drug trial to be conducted. When controversy over the study created attention and debate in the community, the government was not able to defend its decision and could not rescind approval. Another respondent provided a particularly disturbing example of a Norplant study where implants were left in research participants' arms with no follow-up care provided after the study was completed.

One of the ethical concerns voiced by several respondents was the need for better enforcement of guidelines and monitoring of research as it is implemented to ensure review board recommendations are carried out:

> My humble submission is that there is no dearth of rules and regulations but there is no enforcement, the rules have to be implemented…So what I am trying to say is that there is so much talk on ethics and [the] third world is all the time exploited.

Several respondents made clear references to enforcement of the recommendations made by IRBs:

> As to what happens out there in the field, nobody knows, because there is no mechanism for follow-up to make sure that people are doing what they put down on paper.

> Sometimes the ethical board clearances are a mere formality and paperwork. Therefore a method should be devised to evaluate the process of clearance and the actual execution of the recommendations of the ethical board.

Cultural, political and economic pressures often greatly influence decisionmaking about research. Several respondents suggested that a monitoring system is needed to ensure that the changes suggested by the review boards are implemented in the field, as this respondent commented:

> Ways should be found to monitor U.S. research collaborators about details of their research activities in developing countries. Sometimes some of their activities go beyond what was approved by the IRBs in areas that might be unethical. The issues of carrying away human samples and their use should also be discussed.

One respondent commented that the current review system could be made a more culturally appropriate process by paying attention to the basic principles of ethics and justice, more specifically, the distribution of justice:

> I think there is no hard and fast rule. We have to respect our subjects. To my mind, the real issue is the exploitation or taking advantage of the decency of poor people. The issue is of distribution of benefits, power, money, and position.

Recommendations

Capacity Building

Workshops, discussion groups, and seminars were recommended for researchers in both developed and developing countries to raise awareness of ethics in research. U.S. funding was also suggested for supporting the establishment of local IRBs and developing ethics guidelines. One respondent suggested that specific funds should be included in research project grant money to support IRB reviews. Scholarships for researchers in developing countries to study bioethics should be made available to ensure ethical research is conducted. Regular and wider dissemination of results was suggested, which includes the participation of developing country collaborators in the publications and presentations of data. Other capacity building was recommended in terms of providing infrastructure and training in advanced scientific research methods. A very general recommendation was mentioned by one respondent to identify and include investigators from developing countries in all aspects of research.

One of the most frequent recommendations from respondents is that guidelines remain flexible and adaptable for application in diverse cultural settings and allow for integration of local policy, particularly in terms of informed consent. Many respondents recommended the establishment of a national, independent regulatory body that could develop guidelines for regional application. These respondents suggested the Ministry of Health take on this responsibility of forming the regulatory body and developing guidelines. Appointing an IRB representative from within the Ministry who could be the contact for U.S. IRBs was another recommendation from one respondent.

U.S. IRB

Many respondents recommended allowing more flexibility in the application of U.S. guidelines. Coordination with developing country IRBs should be compulsory for U.S. researchers. An individual from a developing country should be included on U.S. IRB committees. Equal application of developed country standards of ethics for research within both developed and developing countries was also suggested. One respondent called for the reduction in the level of coercive tactics used by drug companies to market their products, but did not provide specific details. One respondent suggested integrating peer review into the proposal review process. Another respondent suggested an attempt should be made to understand study participants' perspectives on being involved in research and to integrate their experiences into developing national guidelines for the local IRB.

An ethical "commissar" should be appointed in the United States for each developing country or region, and a counterpart should be identified in the Ministry of Health of all countries. After these "commissars" develop a "common language," then all projects could have these professionals conduct the basic work between the local and U.S. IRBs.

Gender perspectives should be integrated into the ethics of research, including adding a woman's health activist to IRB committees. One respondent did not recommend that representatives from the religious community serve on IRB committees.

Several participants felt that the ethical clearance and the informed consent process are symbolic, with no real enforcement by the ethics review board for the implementation of the recommended changes. The

establishment of a monitoring system to evaluate whether or not the study is implemented as it was proposed and to enforce implementation of IRB changes was recommended by several respondents. Other respondents suggested the application of international guidelines instead of U.S. guidelines.

D.6 Discussion of International Results

D.6.1 General

This empirical work reflects the expressed attitudes and opinions of the 203 researchers who were surveyed in the developing world and the 37 additional scientists who participated in focus group discussions or in-depth interviews. This work clearly has some limitations, especially with respect to the sample of researchers surveyed and the domains of inquiry covered in the survey. Yet, this first attempt to explore input from the developing world has provided a much-needed insight into the assumptions and myths that have been taken for granted in the ethical discourse within the developed world—especially in the United States. The analysis contained herein is intended to demonstrate the potential implications of the nature and application of ethical rules and regulations—primarily U.S. guidelines—in a developing world setting. It helps to further our understanding about the many issues that plague those in developing countries who are involved in research—researchers, health professionals, participants, observers—and about how these issues are viewed by those who conduct research.

The diversity in attitudes, opinions, and experiences that emerged reflect the complexity of ethical issues in health research. Across countries, there are tremendous differences in culture, medical practices, politics, and religion. Even within countries, these differences can create a challenging context within which to apply standard guidelines for ethics. The notion of applying a single set of guidelines universally has the potential of stereotyping cultures, which may have negative consequences for research. One of the most prevalent concerns among respondents to this survey was the need for flexibility in applying guidelines so that they can be adapted to specific settings.

In general, respondents did not criticize the basic premise underlying the present set of U.S. guidelines for international health research. However, respondents were concerned about how those guidelines have been applied and about the mechanisms needed to make them more relevant to other countries. The need for flexibility repeatedly emerged in the data. While opinions seemed most vocal regarding drug trials, specific recommendations typically focused on practical changes in operational elements, as further described below.

D.6.2 Informed Consent

Disclosure

One of the issues traditionally thought of as a challenge by health researchers is the extra burden posed by the informed consent process and the inherent risk of losing potential research participants through that process. A majority of the survey participants agreed that there is a risk of losing potential participants upon disclosure of study details (whether randomized controlled trials or observational studies) in an informed consent process. However, participants did not feel that the informed consent process promoted wider mistrust in the study population, indicating that these researchers are willing to conduct the informed consent process even though some risks are involved. University-based researchers were more likely to agree with the issue of informed consent raising distrust than were nonuniversity researchers, which may be reflective of their perception within the academic centers or a consequence of the nonuniversity researchers being closer to the communities. Or, it may be based on the experiences of academic researchers. In any case, further exploration of this issue may be warranted in future studies.

The basic premise of individual informed consent seemed to coincide with the cultural values of most of the respondents and their respective research settings. Community and individual education were emphasized as

important in gaining true informed consent, and many respondents were concerned that people need to truly understand what was involved in study participation. Full disclosure of the relevant risks and benefits was an essential element in ensuring informed consent and in protecting the integrity of the research and the credibility of the investigators. However, this appears to be a trend that has evolved from earlier research practices in which full disclosure was not always the norm. Several examples of previous recruitment efforts, which did not include full disclosure of risks and benefits, were described, a practice that reportedly could not be repeated in the current climate of greater sensitivity toward ethical research.

Procedures

Despite the oft-quoted "hesitancy" of using written and signed informed consent in the developing world, the majority (nearly two-thirds) of the survey respondents indicated that this was the most common form of informed consent procedure used in their index studies. This was used appropriately and significantly more often in populations defined by medium to high literacy (>20 percent) as compared to low literacy populations. In addition, the use of community meetings and approvals from leaders was also common in index studies for nearly half the respondents. This is reflective of several possible trends:

- That the process of written and signed consent is being thrust upon research participants by ethical guidelines and rules that the local researchers must follow.
- That there are secular trends occurring in these countries along with social and economic development, and that the hesitancy for a written and signed consent may be an historical carry-over.
- That local researchers actually supported the implementation of this form of consent procedure and have convinced community leaders to lend their support to the process.

In any particular developing country, a mixture of these and other factors may be at play. The appeal for greater flexibility in applying ethical guidelines and more legitimate options for informed consent would tend to indicate that the first option may be close to reality. However, it is likely that the actual prevalence of the perceived hesitancy to written informed consent is decreasing and that both the local populations and researchers are becoming more accustomed to the concept, even if this trend is catalyzed by external guidelines. This may be a case of "exporting" standards to the developing world over time.

Participants in the qualitative research arm of this study expressed a measured perception on this issue. They considered written consent forms, in general, to be appropriate in studies involving therapeutic interventions, especially those that were invasive (higher risk), such as surgery or the administration of drugs. For lower risk studies and observational studies, the perception was that they typically have not followed strict informed consent procedures. Serious concerns were raised regarding the ethics of social science research, health program evaluation, and development oriented projects that are not required to obtain consent from participants, particularly when sensitive topics are covered in data collection. In considering research of lower risk not involving sensitive subjects, respondents felt some kind of consent process was still necessary, with verbal consent mentioned as a possible option.

Where illiteracy is high, verbal consent with or without a signature should be acceptable. However, it was suggested that verbal consent with a third party witness' signature would preserve the individual consent process without requiring the individual participants' signature. The distinctions made between informed consents that are written alone, written and signed, oral alone, or oral and signed reflect the great concern among developing country researchers in this area. Obtaining signatures, as an independent activity for informed consent, was often considered inappropriate and difficult to obtain in many situations. Such sensitivities to obtaining signatures in developing world communities must be reflected in the search for a wider menu of choices for informed consent in research that is compatible with U.S. ethical guidelines.

The use of nonwritten media for informed consent was limited to less than one-third of reported cases, and the use of high technology media was rare, reflecting the capacity development of local researchers in these countries to conduct such procedures, as well as the availability of technology for use in research. Further analysis revealed that academic (university-based) researchers were significantly more likely to use such media than their nonuniversity colleagues, and senior (>45 years of age) researchers had more experience with such methods. This is consistent with their exposure to research projects and the availability of resources over their professional careers.

Testing of participants' understanding prior to informed consent was reported to occur in less than a third of the cases. There may be a need to increase the importance given to this process, regardless of the exact procedure used for informed consent. In fact, the need for testing such understanding is further enhanced in countries where informed consent procedures may be considered imposed by external guidelines, or new for the local situation. Under these conditions, the effectiveness of the procedures and their validity need to be evaluated, especially if background conditions—illiteracy and poverty—make the population more vulnerable. As mentioned by focus group participants, if informed consent procedures do not promote enhanced understanding and truly informed decisionmaking, then they are not achieving their intended purpose.

It was also disturbing to note that a minority of the survey respondents felt that research staff interfered in the informed consent process by shortening or simplifying the consent forms. This was expressed by a significantly greater proportion of university-based researchers, as compared to nonuniversity based researchers. Although significantly more researchers working with populations with higher literacy (>20 percent) agreed with the statement, the numbers of studies in low literacy populations were small. This may also reflect the inadequacy of the consent forms and the discomfort of field staff in using them without additional modifications. The length, tense, phrases, and use of language may all play a role; however, this issue was not explored further in the survey. On the other hand, the conduct of research staff, especially field staff, such as interviewers, is critical to both the scientific and ethical integrity of the project. As a result, any undue actions on their part within the context of research need to be carefully monitored. There may be potential here for the development of guidelines for research staff that could accompany the main research ethical guidelines.

Substantive Issues

Much has been said in the literature on ethical guidelines about the imposition of Western values on the developing world. In this context, one of the most commonly noted examples is the individual orientation of the informed consent process. A large majority (two-thirds) of the survey respondents in this current study support this notion as well. Academic researchers (university-based) were significantly more likely to consider the informed consent process as focused on the individual than were nonacademic respondents. This corresponds to the report that community approval procedures were used in nearly half of the cases, although we do not know whether they were used by the researcher on his or her own accord or as a result of specific ethical guidelines. Both community and individual consent can be accommodated by the combination of both procedures within the same study and mandated by ethical guidelines. This strategy will avoid the perceived stress on individual informed consent only, while still providing the same opportunity for each person to respond to the study.

The use of cultural and religious beliefs to support the notion that individual decisionmaking is not compatible with societies in developing countries is still reported by nearly half of the survey respondents. However, the other half were either not convinced or disagreed with that statement, making it difficult to reach a conclusion. Studies done in areas of Muslim faith were more likely to agree with the individual orientation of informed consent. Suffice it to say that the notion of individual decisionmaking is being currently used in health research in the developing world and may need to be strengthened *within* the context of community and family consent. Even for observational studies, the notion that individual informed consent may not be necessary was supported by less than half of the survey respondents.

In further analysis of the survey data, it was found that physician respondents used written informed consent more and community consent less than nonphysician respondents. This appears to be consistent with the individually oriented medical care that doctors provide and with their practice of taking consent for therapeutic regimes from one patient at a time. This potentially makes them more comfortable with individual consent even within the research context. It could also be the result of the greater exposure of these physicians to Western practices and a familiarity with the notions of individual consent. This is also a reflection of the scarcity of trained and skilled professionals in developing countries where it is very common for physicians to be health researchers for a smaller portion of their time. In other words, the concept of a full-time health researcher who gains all of his or her livelihood from that pursuit is rare in these countries.

Level of Understanding

Comprehension and understanding by participants of research is essential for a complete informed consent procedure. Respondents view the procedure as an opportunity for dialogue with both the participants and the research staff. This presents informed consent as an education tool within the research enterprise and enhances the value to the community where research is being conducted. This is a very creative and appropriate view of informed consent, as it also presents an opportunity for providing some benefit to the community.

Researchers report that participants are mostly aware that they are involved in a research study and also dispelled the notion that the overall language used in informed consent forms may be too difficult—a hindrance to understanding by participants. This may be a reflection of the involvement of developing country researchers within collaborative projects where their input in the development of the local consent form and any subsequent translation creates a more appropriate form. Despite this general understanding, research participants were thought to have "unrealistic hopes" regarding the research projects in terms of personal gain of any nature. These viewpoints are quite compatible with anecdotal experience within the developing world, where despite an understanding of health processes, impoverished conditions cause people to hope for some personal health gain. A strong desire for some relief from the challenging circumstances of every day life is held by people, despite a presentation of facts to the contrary.

Conveying specific information was considered challenging within the informed consent process. Technical, biomedical information was difficult to explain, particularly in areas where the local language did not have words for terms such as "research" or "virus." Understanding of other biomedical concepts by research participants, such as use of placebos (this was not related to literacy level of study population), was also acknowledged to be challenging by the majority of the respondents. Senior researchers (>45 years of age) were significantly more likely to agree with this observation than their younger colleagues, which may reflect their longer experience or their firmly held beliefs based on their experiences. Overall, this phenomenon in a community may have culture-specific variations depending on the understanding of the nature and the use of placebos for therapeutic purposes in such settings.

Voluntariness

The respondents, especially in focus group discussions, expressed the concern that the informed consent process must allow for voluntary decisions. The communal context of health issues, presence of strong family influences, deep social traditions, and previous provider-patient interactions, often create situations in which individual voluntariness may be compromised in a research context. Thus, refusal of persons to participate in research studies was considered a proxy for some expression of voluntariness. Researchers described situations (in focus group discussions) where the social rules of hosting visitors or the established rapport between patients and local physician-researchers made refusal very difficult for potential research participants.

Examples of national censuses and demographic/health surveys were quoted to illustrate how participation in "research" can sometimes be mandated by law and do not involve voluntary consent. One can argue that the

primary intent of a census is not research; rather, it can be used for research once completed. In the specific case quoted by one researcher, a census was a rare entity in two countries, and participation in a health survey was mandated by the government and involved a consent form without expression of voluntariness. Demographic/health surveys may be used for the same purposes as a census but are often conducted to get a better understanding of the disease burden, especially in children and women. Countries mandating participation in such surveys may need to revisit this issue based on the nature and type of information collected. This is an area for further empirical work with nations and organizations that are involved in the conduct of demographic/health surveys.

Recommendations

The recommendations expressed by researchers from the developing world call for more flexibility in the procedures for documenting and practicing informed consent within human subjects regulations. This is consistent with the call for requiring community leader's consent, as well as individual informed consent, both of which are considered important. Thus, the notion of informed consent as a principle is strongly supported, and its flexible application at both individual and community level is also supported. This empirical evidence dispels some of the assumptions that informed consent itself may either not be acceptable in the developing world or that the ethical principle of respect for autonomy may not be as universally held. However, the evidence strongly urges ethical guidelines to include more options for "acceptable" forms of informed consent, which are appropriate for diverse national situations and cultures.

An overwhelming support for testing participants' understanding was recommended by these researchers. This is an issue that may be seriously considered for any future modifications in the U.S. ethical guidelines. Such a "check" is also consistent with the scientific side of research, where the notions of pilot testing and certifying methods and design issues are quite prevalent. Therefore, formal inclusion of such a requirement into guidelines may be quite acceptable. Exploration of innovative techniques, such as video, small group discussion, and visual aids, should also be recommended for participants' understanding and for seeking informed consent. Translation of written consent forms should emphasize the basic concepts of the study in order to ensure greater understanding of the fundamental aspects of research.

It is important to note that the recommendations described above were supported by even higher proportions of those developing country researchers who had received funding from U.S.-based sources. This lends greater credibility to their potential implications for the U.S. ethical guidelines.

D.6.3 Risks and Benefits

Survey respondents categorized their index studies as "minimal" risk for participants in the overwhelming majority of cases (>90 percent). The participants in these index studies included men, women, pregnant women, children, and infants, and there was no relationship between the level of risk and type of participants. All of the "greater than minimal risk" index studies were reported in populations with medium to high literacy levels (>20 percent literacy). In general, the index studies are diverse and hopefully reflective of the vast majority of low-risk studies done in the developing world.

The survey also queried respondents on the sensitive nature of the information in their index studies. Half of the respondents indicated that their index study gathered sensitive information and that there was no association between the level of risk and the sensitivity of information gathered in the index study. The majority of studies for HIV/AIDS were reported to gather sensitive information as compared to one-fifth of the non-HIV/AIDS index studies. The interpretation of the word "sensitive," personal and professional concepts of sensitive information, and the examples written in the survey next to the question (HIV-positive status, domestic violence) may have influenced these responses. However, in general, the impression that emerges is that studies done in developing countries, especially those dealing with HIV/AIDS, are handling information considered "sensitive" and the need for appropriate ethical evaluations is very relevant.

Burden of Disease

One domain of inquiry within the survey dealt with the reasons for conducting the index study (the reference study—on the basis of which the respondents answered several domains of questions). The majority of respondents agreed with each one of the reasons written for conducting the study in a developing country: greater relevance to the country in question, interest in global inequalities, and requests by host country researchers were the most frequently cited reasons. This set of responses is a reassuring picture from the potential notion that the West thrusts all research on the developing world and is irrelevant to the local situation.

However, there may be some difficult response issues creeping in this section as evidenced by the following observations:

- Two-thirds agreed that addressing "global inequalities" was the reason for conducting research; physician responders were significantly less likely to agree to this statement. In a generic way, this could be considered true at some level in any research within the developing world; on the other hand, the generation of a research project specifically to address these inequalities seems unlikely in such a majority of cases. Most research projects would tend to arise from an interest on specific topics or discipline-related questions. The continuing stark global inequalities, even within research investments and research utilization, make this point very relevant (Hyder 1999a).
- Half agreed that a research study was conducted because it was relevant to U.S. strategic interests in the region. A trend was noticed that female respondents were more likely to agree with this statement, compared to male respondents. This reason was included in the menu of reasons for the respondent to consider, as it is not related to either the science of the research study or to the health issue under investigation—making it an important reason to note. Nonhealth and nonscientific reasons should not govern the conduct of health research, specifically if they reflect concerns of only one country. However, this question could have been answered from a variety of different perspectives—health research, broader science, geo-political, economic—and it is difficult to assess which one each respondent used in defining "strategic." It may also have been viewed as a provocative statement, and the respondents may not have wanted their experiences to be labeled under such a category.

Further analysis of this data revealed that those researchers funded by U.S.-based sources had the same pattern of response as the overall sample of researchers. In other words, the source of funding did not affect the way respondents perceived or responded to such issues, making these findings more widely applicable.

A significant finding was that marketing approval being sought for a drug or product in the host country was found to be a reason for conducting the research in only a minority of the cases. Even among those studies that tested interventions (n = 27), less than 30 percent were stated to be done for this reason. This could indicate one of the following:

- Generally, marketing approvals do not form a substantial component of research portfolios for academic or nonacademic, nonprofit researchers in the public or private sectors. This is also indicated by the portfolios of survey respondents, such that 30 percent were predominantly involved with health systems research, for example.
- Research before marketing is not traditionally done in the developing world.
- Marketing approval is not required in these countries, as the laws and regulations either are not stringent or approvals in other countries can be used to bring drugs on the market.
- These drugs will not be sold in these countries after the end of research, at least in the short- to medium-term, and, therefore, the need for market research does not exist. This is held true by the time-lag in making drugs and vaccines available in the developing world after their approval in the developed world (Hyder 1999b).

It is likely that although a mixture of these factors may play a role, the last bulleted item above has the greatest impact on the health and development of the people in the developing world.

Types of Care and Treatment Available in the Host Country

The nature and content of health care available in the developing world generally leaves a lot to be desired. This is consistent with countries' level of health and economic development and the extent of the infrastructure available. This situation presents a multitude of ethical challenges in a research setting, two of which are supported by the majority of respondents to this survey:

- Medical treatment made available within a study setting is not usually available in the country.
- The difference between the standard of care in the country of study and the donor country is usually significant, making the selection and treatment of controls a very challenging task.

Those researchers funded from U.S.-based sources were found to support these opinions more than non-U.S.-funded researchers. These statements also confirm the source of debate in recent literature and emphasize the stark inequalities between nations, although they do not provide insight into potential solutions. (Lurie and Wolfe 1997; Angell 1997).

Medical treatment available during a study is one form of benefit to those involved in the study (limited to those who actually receive it; for example, in the "treatment" arm of a randomized controlled trial). Treatment of conditions found during the study but not related to the research question may or may not be available during the study. These potential "benefits" have the advantage of giving something back to generally impoverished communities. On the other hand, they are usually not sustainable over the long term (post-study) and may be important enough to the local community to be considered "incentives" for participation in the study.

Differences between standards of care are relevant to intervention trials with control groups. The nature of the "control" has to be determined (or the comparative regimen) based on an understanding of the standard of care. Interpretations of international guidelines such as CIOMS (1991 and 1993) were taken to mean that the best-known treatment globally be applied to the controls. In recent years, especially with the conduct of HIV/AIDS trials, the notion of best-available standard has been propagated. In either event, the use of any standard needs justification on ethical grounds.

Issues such as this one prompted discussions of pre-study agreements in focus group settings. The intent of such agreements was considered to support the provision of benefits to the study population and community. Details of such pre-study agreements were not explored in this current work.

In focus group discussions, a unilateral requirement for the best-known standard of care was generally considered inappropriate, due to the range of available therapies and the variation in clinical practice from one country to another. More importantly, it was stated that the level of treatment during the study needs to reflect what was typically available so that interventions could be tested for that particular setting. Where best-known treatment is not available and will not be feasible for some time, respondents generally felt that the second best interventions should be researched. This was a contentious issue, and some felt that developing country IRBs needed to clarify their research needs and develop their capacity to advocate benefits for their communities. This issue highlights the need for additional global debate between nations on health research and subsequent benefits.

Incentives and Compensation

Despite procedures of informed consent and information about studies, participants tend to have unrealistic hopes about personal benefits. Although it was acknowledged that providing medical care to people living in very poor conditions may be considered coercive, medical care was typically thought to be an acceptable incentive for study participation and, in fact, a benefit for study participants who would otherwise not have access to medical care.

Monetary incentives, other than for reimbursing costs of study participation, were not recommended by the respondents, who expressed the concern that the value of any reimbursements should be appropriate to the local setting. New forms of nonmonetary incentives, particularly for poor and unemployed individuals participating in research, were recommended. In addition, any incentives for recruiters and research staff were strongly rejected and were viewed as a possible source of conflict of interest.

Background Conditions

Research is a precious enterprise in resource-poor settings, one that requires careful justification. A decade ago, a global call was made to ensure that research in the developing world was relevant and essential to the needs of such countries and to develop a mechanism for more equity in development (COHRED 1990). This requires that donors and countries jointly agree on research agendas, which has not been the *norm* in most cases. As a result, half of the respondents agreed with the statements that the priorities of funding agencies and countries often differ and that the products of research are not likely to be available in the country where research is being conducted. The conduct of research in a country where the research topic is not a priority (if national priorities have been defined) by political leverage of donors needs to be contested, based on the above rationale (COHRED 2000). The priorities of the local institutions involved in research, the national health research agenda, and priorities of donors and those of the foreign research institution may all differ, creating further complexities. Thus, any piece of research may fall within the priorities of one or more of these stakeholders and yet be outside the realm of others. Regardless of such categorization, an ethical review process should be able to identify the relevancy and potential benefits of a proposed study to the population of concern.

Recommendations

A majority of the respondents promoted the notion of reviewing studies on a case-by-case basis to evaluate the standard of medical care provided during the study. Four-fifths of those researchers funded by U.S. sources also supported this notion. This indicates that the issue is important enough to these researchers to warrant specific attention in an ethical review process of studies. Whether this reflects a suggestion towards defining standards of medical care or a discomfort with pronouncing a fixed rule to this effect is difficult to judge. Qualitative explorations also indicated a recommendation to further evaluate the potential use of pre-study agreements regarding the care to be provided during and after the study. Such mechanisms would allow for a careful consideration of issues related to the provision of benefits in the early planning phases of a study. This would assist with the study-population interaction, as the expectations from the study would become explicit and transparent.

D.6.4 Obligations to Subjects, Communities, and Countries

In the survey sent to developing country researchers, they were asked to focus on a specific study that they are most involved with or have been involved with within the past five years. In questions pertaining to a specific study that involved external collaboration, fewer than half of the respondents were focusing on studies that involved testing an intervention—which could be a drug, a treatment option, a treatment method, or a public health intervention. Of these respondents, a very high percentage indicated that the intervention being tested had been shown to be efficacious, and nearly all (>95 percent) indicated that the intervention will be provided to "the study participants or any other host country residents at the conclusion of the study." This comes as a surprise finding, and these numbers must be carefully interpreted.

It is clear that intervention testing is less common in the developing world, than other types of research. The results indicate that the respondents involved in intervention research:

- Were generally part of successful intervention studies.
- Were of the opinion that the intervention would be provided to the study participants and their community; fewer indicated that the intervention would be available to other parts of the country; female respondents,

those who were over the age of 45 years, and those who were members of IRBs were more likely to suggest that the intervention would be provided to the entire study population. No significant differences were found between the source of funding, the topic, or the discipline of research.

- Thought that provision of the intervention would be done by stakeholders within the host country—the researchers (themselves), their institutions, and the government; nonacademic researchers were more likely to indicate the role of government in this process than academic respondents.
- Responded that the intervention would be available for more than two years, in most instances.
- Reported that it would be paid for by both the host country government and the research institution, on the one hand, and the research grant, on the other; respondents who were members of IRBs were significantly more likely to indicate that the national governments would have to pay for the intervention, compared to those who were not members of IRBs.
- Reported that a minority (<17 percent) of all the intervention studies were funded by any private sector source; moreover, of those funded by the private sector, only half were intervention studies. These numbers indicate that the U.S., European, and developing country private sector are funding very few studies (<14 percent) in the developing world and that they do fund intervention and nonintervention studies.

This depicts a situation that is contrary to the expectation and experience usually described in the literature and one that is also different from the facts about intervention availability in the developing world.

In considering the intervention studies that are conducted in the developing world, some very important issues emerge as a result of these findings, including the following:

- Studies may yield positive results (in terms of efficacious interventions) in many cases, and as such the consequences of such findings need to be addressed in the design and ethical review of these studies. In other words, prior to the initiation of studies, such outcomes need to be anticipated and a response prepared.
- There is a great desire expressed by developing country researchers to provide the products of research to the populations of concern to them—the study participants, the communities within which the studies have been conducted, and the national populace. These products could range the whole gamut of therapeutic and diagnostic options interpreted to be an "intervention," including those within the public health domain.
- The reported high prevalence of actual provision may therefore be colored by this spectrum of interpretation. Thus, interventions such as bed nets for malaria, vitamin A for malnutrition, and oral rehydration therapy that have been provided in several parts of the developing world would be included with other options, such as new drugs for hypertension or new vaccines for childhood diseases. Since the former types of interventions would tend to dominate the research scene in the developing world, the positive statements reported by the researchers become more consistent with what is known of current health care delivery.
- With the above proviso regarding delivery of interventions, only one-fifth of the researchers reported that a placebo or control group received the intervention after completion of the study. Again, this seems to indicate the fact that randomized controlled trials with placebo groups were experienced by fewer developing country researchers than other types of study design (<28 percent). A similar proportion reported that the intervention was provided or would be provided to the whole country. Interpreting this is difficult, since, on the one hand, the provision of an efficacious intervention to the whole nation should be of concern from the beginning of the research enterprise. On the other hand, however, the actual provision of any intervention country-wide is a huge undertaking, and it is unclear how these researchers can be so sure or how they can commit to it.

- Even if the interventions are provided, the *responsibility* of providing them in most cases excludes the foreign stakeholders, the research team, institution, and donor. This reflects the lack of responsibility in this action that is faced currently by external agencies that conduct research in the developing world. Similarly the private sector has been largely left out in the responses to this survey as being active in the provision of interventions (the private sector funded less than one-fifth of the reported studies overall). These facts are important for the development of appropriate mechanisms that allow for a more equal sharing of responsibilities for providing the products of research in such settings. Leaving the burden on local agencies and national governments is impractical and futile and leads to the current lack of provision seen in the developing world. As mentioned by a researcher from Asia in one of the focus groups: "Even cheaper interventions are sometimes not feasible [in our settings]."

- On a similar note, the reported instances of intervention provision were at least in part *paid* for by institutions within the developing country. It is likely that such provision involved a multitude of funding sources, and yet there is a hint of an undue burden on the country within which the research is conducted. A small minority of the respondents indicated that an international agency was involved in the financing of the intervention provision, which is a surprising finding, as there is an assumption that often it is the international agencies that pick up the tab for financing interventions in the developing world. Again, there is a trend of enhanced burden on developing countries themselves to pay for these interventions when they are in no position to do so in the first place. It is interesting to note that there was a higher trend for U.S.-funded respondents to indicate that the foreign institution would be involved with financing the intervention, than those not funded by the United States.

- Time is of essence within the health care industry, and commitments to population health are not to be held for only the short term. As a result, the commitment to provide interventions needs to be done on a longer term and sustained basis. Initiation of this process may be time-limited, as the intrinsic capacity of these countries is further developed to respond to situations themselves. Two-thirds of respondents indicated that the intervention, when provided, was done for less than a five-year period.

These researchers believe, in general, that the products of research are *unlikely* to reach developing country populations; they appear to see the national governments and the research institutions as the bearers of this responsibility; and they consider the products of research to be a public health policy decision to be handled by the Ministry of Health or other such agencies.

Recommendations

The survey section on recommendations evoked a set of responses that further affirms the notion that respondents value and believe that the products of research need to reach the study population. This was further categorized as an explicit agreement on the part of a majority of respondents to the following:

- Data from the study, need to be made directly available to the study population; U.S.-funded researchers demonstrated a trend of agreeing to this issue more often than non-U.S.-funded researchers. Participants in focus groups further agreed by stating that any data emerging from studies should be in a "usable" format for both the people and the policymakers.

- The conduct of research needs to be questioned if the results of that research will not be available to the developing country; this is a further reiteration of opinions expressed at various points in the survey to the same effect.

- Mechanisms to enhance and facilitate the transfer of results need to be seen as a component of the research enterprise; this promotes the concept of planning for such a transfer of benefits at the start of the study; furthermore, it promotes the notion that ethical guidelines need to make explicit this requirement for demonstrating such a mechanism.

Analysis of these responses from those researchers funded by U.S.-based sources and the qualitative arm of this study both revealed complete consistency with these statements, only revealing even higher proportions. These findings are very significant as an expression of the beliefs and desires, as well as the practice of health researchers in the developing world. They need to be operationalized within international and U.S. ethical guidelines.

D.6.5 International Collaborative Research

IRB Review Results: Local and United States

The nature of true collaborative research means that the studies are reviewed in all of the countries within the collaboration. As a result, exploring the issues raised during reviews in the United States and in the host country provides an insight into the nature of such review processes. The types of issues raised indicate both the process of review and its recollection by the respondent.

In responding to their impressions of the ethical reviews conducted in the United States, developing country researchers indicated that the type and complexity of documentation related to the study was raised in a high percentage of cases; these include issues relevant to the letters of approval and informed consent forms. Procedural issues, such as selection of control groups, were also raised by U.S. IRBs; while others, such as political issues, were raised less often. Respondents who were IRB members demonstrated a trend to be more likely to state that the issue of the intervention being too risky was raised; while nonphysicians were more likely to state that the issue of participant voluntariness was raised.

These results are more interesting when compared to the issues reportedly raised by developing country IRBs. In general, respondents indicated that most issues were raised *more* often by the U.S. IRB than the developing country IRB. This was especially related to informed consent processes and the protection of confidentiality, where statistically significant differences were found. Other issues were either raised equally by both IRBs, or the differences were small. Senior researchers (>45 years of age) were more likely to state that issues related to consent forms, approval letters, controls, and placebos were raised by developing country IRB's. U.S.-funded researchers were more likely to state that issues related to relevancy of the research and confidentiality were raised. Cultural appropriateness of the study was reportedly raised by both IRBs; in the international component, women researchers were more likely than men to report this issue (as being raised by the developing country IRB).

These findings may occur for several reasons:

- Developing country respondents actually experience U.S. IRBs raising more of each issue; this could be due to the greater experience of U.S. IRBs in conducting such reviews (and therefore a greater ability to detect issues) or their ability to compare procedures with standards used in the United States (and therefore identify differences). Developing country IRBs may have had less experience in conducting such reviews or may lack any set standards for comparison.
- Respondents recall the U.S. IRB comments more than they recall those of developing country IRB review. This could be the result of paying more attention to understanding U.S. IRB comments and responding to them; or it could reflect their own internal sensitivity to the critique of the U.S. IRB.

- The U.S. IRB review may have been the first to occur chronologically, and, therefore, it may have had more issues to critique. This could also relate to the fact that issues pertaining to letters, language, and consent were significantly more frequent, as these comprise common procedural issues in proposals. Subsequent reviews in the developing world, therefore, were conducted upon a more developed proposal, with several of the issues already addressed.
- The additional experience, with seniority of age, seems to make older researchers more likely to note issues raised by the local IRBs; this may also be due to their knowledge of the local IRB experiences of colleagues and other projects.
- U.S.-funded researchers are clearly consistent with their heightened awareness of specific issues, even from their local IRBs, potentially reflecting their earlier experience with U.S. IRBs. Greater sensitivity to local IRBs was also mentioned in one of the focus group discussions.
- Women researchers displayed a tendency to indicate that the issue of cultural acceptability of research has been raised by an IRB review.

Although it is difficult to generalize from such a recalled response, it is important to note that:

- On the one hand, a review of the ethical aspects of a study are being done in both the United States and the host country, which comprise both substantive and process issues covering a wide spectrum of ethical questions. This upholds the impression that such reviews are being conducted on both sides with serious intent.
- On the other hand, the fact that such issues were reportedly raised is a *proxy* way of saying that they were presumably addressed. This is the more critical issue at stake: What happened after these questions were asked from the research team? The survey itself did not address this issue, and we can only presume that a satisfactory response was given to the IRBs by the researchers and that the response was then implemented.

The last point feeds into an important issue that was also raised during focus group discussions. The IRB reviews only determine in principle and on paper what should happen, since usually, there is no monitoring or evaluation of the studies after the ethical review process. This often creates a dilemma for those researchers who know that what they write to the committee will subsequently need some (slight) "modification" procedures once field work actually begins.

Focus group discussion revealed that there was little communication between local IRBs and U.S. IRBs. Appointing an IRB representative within the Ministry of Health was suggested to encourage communication and to provide a contact person for the U.S.-IRBs. Similar representatives were suggested from U.S. IRBs so that these individuals could work together with a more open exchange. Several respondents felt that the responsibility of establishing the IRB system should fall upon those who have been "trained outside," who have an understanding of the ethical principles on which U.S. guidelines are based, and who are also intimately familiar with the local culture. Building collaborative partnerships between local and U.S. investigators was also recommended in curbing the corruption of local IRBs by powerful countries or industries. Local universities should emphasize the importance of ethics among their students and faculty by establishing a university IRB, if one does not exist, and by insisting on project review and approval. However, one respondent cautioned that local researchers who have been trained in Western countries are as "delineated from our own cultural setting as any foreigner would be."

IRB Review: United States

A very interesting finding in the survey pertained to U.S. IRB reviews of studies. Nearly 40 percent of reportedly U.S.-funded studies were not reviewed by a U.S. IRB. Although respondents whose studies were not U.S.-funded were not supposed to respond to this question, one-fourth of the respondents to this question fell in this category, and approximately 45 percent of non-U.S. funded studies were reviewed by a U.S. IRB.

U.S.-funded studies were defined to be those with at least one source of funding being labeled as a U.S. source, but excluding bilateral organizations. So, if a study received funds from a USAID office (considered a bilateral organization), in a country, for example, the study may not have gone through a U.S. review process and may be controlled within that country only. Similarly, studies that were not labeled as U.S.-funded may have included funds from USAID (under the bilateral organization category) and therefore have undergone U.S. IRB review. The classification of sources of funding did not distinguish between USAID and other bilateral organizations, and this may be a source of potential misclassification in the survey.

In order to better understand this potential misclassification, the 30 studies that were reported to be U.S. funded and not reviewed by a U.S. IRB and the 10 studies that were not U.S.-funded and yet reviewed by a U.S. IRB were further explored for sources of funding. It was found that only 3 of the 30 studies and 5 of the 10 studies, respectively, were in the "bilateral organization" category. Excluding this potential misclassification still leaves these questions: Why were 27 of the studies that were U.S.-funded not reviewed by a U.S. IRB? Why did five studies not funded by U.S. sources still undergo U.S. IRB review?

- Is this an error by the respondents? Could it be either a recall error or a mistake made while completing the survey? For example, did they forget to check off the U.S. course of funding for the five studies? Or has the check for a U.S. source of funding been made in error or from mistaken knowledge?
- Were the 27 U.S.-funded studies not reviewed in the "exempt" category for IRB review (which is only given after a "review") but considered to be "not reviewed" by the respondent? Or were they funded and/or conducted on an "informal" basis and thus "slipped through" the system? Or, is it that the U.S. funds were routed in a very indirect manner through many intermediaries so that it would be considered a "subcontract" and be subsumed within an original IRB review?
- Regarding the five non-U.S. funded studies that reportedly underwent a U.S. IRB review: Were they incorporating some form of U.S. input, such as technical assistance, equipment, or personnel, so that the U.S. collaborators had to submit the proposal for a U.S. review? Or were they part of a larger study that was reviewed and funded by the United States (although the specific component that the respondent worked on was considered separate by him/her)?

It is difficult to predict which of the above played a greater role, and the survey itself is limited in providing additional explanations. It is clear that the system of ethical review is imperfect and that the process of appropriate review needs to be improved (as well as the content of the review).

IRB Review Process: Local

Slightly more than half the studies reported undergoing a review by a governmental body. This may have been an ethical review or a general review (although the pre-question instructions referred to an ethical review, the actual question in the survey did not mention the word *ethical* for this question only). Although this did not vary between those studies funded by U.S. and those not funded by U.S. sources, nearly 40 percent of U.S.-funded studies were not reviewed at this level.

Two-thirds of the participants reported having an in-country *ethical* review, and again there was no significant difference between U.S. and non-U.S. funded projects. Local IRB reviews were most frequent, indicating that some form of an ethical review committee was either developed or already in place in these institutions for such a review. The high prevalence of this phenomenon is refreshing. Studies pertaining to the topics of infectious diseases and HIV/AIDS were more likely to be reviewed, while those dealing with health systems and health services were less likely to have had an in-country review. Along the same lines, studies in the fields of epidemiology, microbiology, and clinical care were more likely to have undergone review, while those under anthropology were less likely to have been reviewed.

One-fourth of the respondents indicated that the specific study they were thinking of had no ethics review in the country where the research was conducted. Similarly, nearly half the respondents indicated that their index study did not have a Ministry/Department of Health review in the host country. *Further analysis indicated that 15 percent of the studies did not undergo even one review in the host country*—either a Ministry/Department of Health review or an IRB review at any level—regardless of the source of funding. Of those funded by U.S. sources, one-fifth did not receive an ethical review within the country. The survey was limited in further analysis of this issue, because no alternatives were provided to explore the reasons why a review was not done. For these studies, where no ethical review was conducted in the countries, what happened? It is possible that:

- The respondents stringently looked at the three options in the question—"IRB, ethics board, or Ministry of Health"—and somehow decided that the ethical review entity did not fit in with these categories?
- The studies were reviewed and given "exemptions" and, therefore, the respondent did not report that review? Or were considered "exempt" by the researchers?
- The studies in question were only reviewed by the collaborating institution in the West?
- The studies were not reviewed at all?

It is clear that the last two options are very serious and need to be investigated further. A situation in which studies are not reviewed in either the host or the donor country would be unacceptable. Qualitative explorations also indicated that there are a number of studies that were reported to have escaped the attention of or need for ethics reviews in these countries. Focus group participants indicated that sometimes studies funded within the country by bilateral or international organizations, especially those related to the social sciences, did not undergo standard review processes. There may be a special need to further explore the ethical review processes of social science and anthropology studies.

The result of an IRB review process is affected by the guidelines that are followed, the procedures for review, and the composition of the IRB. Some of the most important representatives on an IRB are those who represent civil society, and it is here that the respondents expressed a weakness in local IRBs, with two-thirds reporting inadequate community representation on IRBs. Younger respondents and those not funded by U.S. sources were more likely to agree with this statement. Community participation has long been known as an essential component for the success of any health program; and, indeed, for any health research when considered in its entirety. The notion that health research should be responsive to the needs of the communities in which it is conducted and be respectful of their way of life was expressed by these respondents. As a result, one of the mechanisms to promote this is to empower communities to evaluate the research process. Thus, community members serving on IRBs are but one way to gain this input, while community dialogue, permission, and formal feedback mechanisms represent other ways.

It was interesting to note that there were significantly more respondents who were members of IRBs among those who reported that a study had to be abandoned as a result of lack of IRB approval in a developing country. This may be due to the fact that:

- These members were more likely to acknowledge the abandoned study (may or may not be as a consequence of recall);
- Their participation in an IRB may be related to their experience (over time) and desire to learn more about the ethical review process; or
- They may have interpreted this question in a more generic fashion to indicate that there are research studies that are rejected.

Further exploration of this issue with IRB members would constitute an interesting qualitative research project.

The process of ethical review, however faulty in both the United States and the developing world, did not prevent a large majority of the research work from moving forward. This is an important finding for proponents (often researchers themselves) who view ethical review processes as potential "barriers" to research. Only 6 percent of the responses indicated that a project had been abandoned due to the lack of an ethical approval from the U.S. IRB, while 19 percent indicated the same for the developing country IRB (this difference is not statistically significant). None of these was related to the sensitivity of the information gathered in the study. In all, 22 percent of those respondents who answered both questions (n = 93) indicated that they had to abandon their research projects because it was impossible to get an IRB approval from either the developing country or the United States or both.

These percentages may include some cases that were unfairly judged or the victims of overburdened bureaucracies and long time lags, but it is also likely that there were studies that should not have been permitted from an ethical viewpoint. Thus, the idea that all (100 percent) studies should be approved after modification, assumes that all scientific questions are worth asking. Under a different assumption, that good science is a prerequisite for good ethics, there will always be poorly asked questions or questions that cannot be answered within the acceptable realm of ethical trials. Therefore, there will always be a small percentage of research proposals that will not be able to obtain ethical clearances for these reasons. What this "small" percentage is, whether it varies by country, research topics, and the nature of IRBs, and other related questions would require a more detailed exploration than can be provided here.

U.S. Regulations: Application to the Developing World

In evoking their opinions about the applicability of U.S. ethical guidelines to developing country research, the survey asked respondents to review their entire working experience. In addition, the survey offered the category of "sometimes" as a response, which caused the majority of responses to be in this category. We could interpret the "sometimes" to mean that the respondent agrees upon an issue but that he or she wants to be less categorical than "always" and therefore marks "sometimes." On the other hand, it could also be that the respondent feels that, in some cases at least, these issues would be true and therefore marks "sometimes."

In relation to the U.S. ethical guidelines, the most positive opinion expressed was when half of the participants agreed that the current U.S. ethical guidelines *always* ensure high ethical standards. This was also the only case in this section (Section G) of the survey where the majority of responses were not in the "sometimes" category. Up to three-fourths commented on the insensitivity of U.S. guidelines to local cultures, while more than half of the respondents expressed the fact that political considerations were affecting the guidelines at least some of the time. The responses to these statements did not vary by source of funding, gender, age, professional qualifications, or affiliations of the respondent.

These opinions are important to construe that:

- The issue of cultural sensitivity, although it may be expressed in the guidelines, is being consistently reported as a weakness within the U.S. ethical guidelines as enforced in or viewed by the developing world; this is an easily modifiable issue within the guidelines, and a renewed stress within the guidelines on appropriate cultural sensitization in developing countries would make an impact on this opinion.
- Politics is viewed as playing a role in the functioning of the U.S. IRB; this is a serious perception, although it relies heavily on the interpretation of the word "politics." The work of U.S. IRBs should not be viewed by more than half of developing country respondents as even *sometimes* being influenced by any issues that are not ethical or scientific in nature, because this opens the door for differential application of guidelines based on other U.S. interests. NBAC will have to be creative in exploring the operational implications of this finding and how the guidelines can respond to this concern in creating a new "standard" for the working of U.S. IRBs, where this issue is explicitly addressed. The current survey offers little additional insight into this potentially important issue.

In relation to developing country ethical guidelines, as opposed to those of the U.S., only one-fifth expressed the opinion that they are "always" able to protect research subjects. This lower proportion reflects a mixture of their absolute opinion, as well as their relative comparison with the United States (since these questions were also placed together in the same section of the survey). It is important to note that the fact that ethical guidelines in developing countries exist and are able to offer some protection to research subjects is different from the generally held opinion that such guidelines are entirely worthless. However, the low percentage of support is of concern, especially when compared to the larger agreement for the effectiveness of U.S. guidelines. Respondents who were IRB members were more likely to support the working of the national guidelines than were non-IRB members, and this seemed consistent with their proximity to the development or application of such national guidelines. Similarly, the role of political considerations in the review process was also expressed and with surprisingly similar proportions as with U.S. IRBs.

Another hypothesis that was tested in this survey was the issue of costs associated with running IRBs. It was thought that the cost of such operations may be a limiting factor in developing countries. Therefore, the survey explored whether this issue had been raised with the researchers by their local IRBs. More than half reported that it was "never" the case. However, the presence of a significant proportion, although a minority, expressing that it had been raised indicates that it may well be an issue in some cases and needs to be explored in circumstances where it will prevent a fair and appropriate ethical review. This reflects the generally poor availability of infrastructure and support in developing countries.

Capacity Development

The notion of helping resource-poor countries develop their capacities in health research is integral to the practice of true collaborative research. The efforts at capacity development may take several forms:

- Intentional
  - Formal training (degrees, certifications)
  - Teaching for research (formal/informal)
  - Availability of resources (library/Internet/journals)
  - Provision of equipment (laboratory, computers)
  - Capital development (buildings, rooms, laboratories)
- Unintentional
  - Educational processes in the conduct of research
  - Scientific dialogue
  - Exposure to new methods and technologies
  - Availability of networks/contacts

Each of these is important for the developing world scientists; however, this survey only asked about the intentional elements of capacity development.

Building Up People

Survey respondents in general rated their own involvement in the process of research very highly. More than three-fourths of respondents indicated that they participated in tasks from planning of the study to writing of papers, and from field tasks to data analysis. In the great majority of cases, the research projects lead to training opportunities for local investigators. Although very refreshing to read, these results would be interesting to compare with the reports from U.S. investigators to explore any differences in reporting. The results could mean that:

- The developing country researchers are being involved comprehensively in the research process, such that they have the opportunity for capacity development.

- The researchers *perceive* themselves to be involved in such tasks and are made to feel involved, although their actual contribution may or may not be significant; this *paternalistic interpretation* needs to be verified by comparison between the U.S. and the international survey components of this project.
- The focus of the training may be on the investigators (perhaps as according to the need of the project) and limited to technical issues (again, as according to requirement).
- Formal training in research ethics was not commonly stated, suggesting that this could be an area where explicit attention needs to be given, such that it becomes equally important in developing local capacities.
- Noninvestigators, field, and other staff may have received less opportunity for training, and even informal dialogue on ethical issues was not very common; this could mean that unless specific training programs are built into research projects, staff members may have to rely on informal strategies for individual capacity development.

Qualitative work provided another feeling of unequal power relationships between countries of the "North" and those of the "South." In many cases, grants originate in the developed country and are then presented to developing country investigators. Respondents felt that investigators from developing countries should be involved in grant writing, to reduce the potential for coercion of governments to accept research opportunities that they find difficult to refuse, particularly when the project is already funded. These unequal power relationships create difficult situations for developing countries in which to negotiate the terms of research. Cultural, social, political, religious, and economic factors must be considered in designing studies in resource-poor countries. Additionally, for health research, investigators must have a clear understanding of the health care system in the host country.

Infrastructure

Nearly all the researchers indicated that there would be some infrastructure left behind at the conclusion of research in the developing country. Equipment and pharmaceutical supplies were the most frequently reported of these items. In addition, two-thirds reported that organizational plans and processes were also part of the package left behind after conclusion of research. It is important to note that:

- Although the primary intention of developing such infrastructure would have been to ensure success of the research project, it still contributes to an increase in available resources, since the materials are left behind.
- When done unintentionally as a consequence of convenience or to avoid cost of re-shipment, leaving behind such equipment, for example, may not ensure proper utility. The presence of trained personnel to use and service it and the need for supplies to maintain it are all important and may need to be planned as part of the project, if capacity development is important for the external team.
- The notion that a research project could leave an "organizational plan or structure" for health care or research is very interesting. This may be referring to a learning process within local institutions of how to conduct a research trial, or it may refer to a health systems study that provides insight into how health services should be organized. In either case, these are only suggestions, and potential plans would require intra-national discussions at high levels, including policy debates, prior to any consideration of being applied in the country. It is possible that some of these reported cases did reach that stage of development, but it is unlikely that the majority did so. Therefore, interpreting this statement conservatively would be more appropriate. It also provides a hint that a significant proportion of these studies could therefore relate to health systems and health services (30 percent or so were under this heading) even though they may be categorized under a different topical heading (so that a study on cholera could be categorized under the

discipline of microbiology, but if it yields tips on how the health system should respond to cholera, it would be subsumed within this statement).

Recommendations

The survey was able to return to the issue of collaborative international research in the recommendation section, yielding specific insights into the similar and often unified thinking of developing country researchers regardless of their geographic and disciplinary backgrounds.

Although the statement that local IRBs may have urgent cost issues did not strongly bear out, researchers nevertheless agreed that local IRBs need to be financially supported. This is in line with a sympathetic attitude towards their colleagues (or themselves) working on IRBs in a setting where the *opportunity cost* of voluntary work is very high. Disagreeing with such a positive statement is difficult, although more male respondents were likely to disagree than female respondents.

Respondents to the survey recommended that international guidelines, rather than U.S. guidelines, would serve them better. This is a very important statement that requires careful interpretation along with a consideration of the following:

- Earlier statements regarding the usefulness of U.S. ethical guidelines were supported by an overwhelming majority of these same respondents; therefore, this cannot mean that they are entirely unhappy with U.S. guidelines.
- It could relate to the fact that they are unhappy with some specific issues within the U.S. ethical guidelines (such as their insensitivity to local cultures) and that the international guidelines do better on those specific issues.
- The application of U.S. guidelines may be more cumbersome (or viewed as such) than the potential application of international guidelines; by intent, the former are for U.S. interests and the latter are based on a multicountry perspective.
- Although the U.S. guidelines serve as well, it would be more "politically correct" to have international rather than U.S.-based guidelines. Any guidelines deemed "international" would presumably have been developed by an international collaborative activity and could also be amenable to input from the international community.
- The wording of the statement made the respondent compare the U.S. ethical guidelines with the CIOMS guidelines, since that was the only example quoted within the question. Even if the expressed preference is for the CIOMS guidelines only, it still underscores the fact that a preference is being expressed for a more "international" guideline than a uni-national one.

A common thread in these potential interpretations is that despite the fact that respondents feel that U.S. guidelines work, they would prefer to use other guidelines.

The need for a local/national ethical review of every study in the developing world has been stated in earlier sections as well, and it received an overwhelming approval at various points in the survey. The minority who disagreed with this premise may be those researchers who have had negative experiences with local IRBs, those with research projects they feel do not require an ethics review, or those who feel that the capacity for such review does not exist in their countries. Nonphysicians were more likely to disagree with this statement than were physician respondents. Further qualitative exploration with these few researchers would be enlightening.

Similarly, the composition of the IRB board, which is also controlled by U.S. ethical guidelines, was found to be dictatorial. An overwhelming majority reported that the U.S. guidelines should not determine the composition, although U.S.-funded respondents were significantly less likely to agree with this statement. Physician

respondents also demonstrated a trend of being less likely to agree with this statement. Again, this may be seen as an expression of the preference that issues should not be controlled by one entity—U.S.-based ethical guidelines. Rather, a more international standard should be adopted. We can hypothesize that the issue is that a single source of guidelines is presented, in this case U.S. ethical guidelines, and that the response would have been similar had the survey presented a different single source for guidelines, for example, guidelines from the United Kingdom. The issue is the difference between guidelines from one country being applied elsewhere as opposed to guidelines that stem from a *collaborative standard*.

D.6.6 Commentary on the Entire Study's Recommendations

The survey ended with a general recommendation section, the components of which have already been analyzed within the main issues discussed above. Although each statement of recommendation was developed by the authors, each is open to interpretation by the respondents, and each varies from positive to negative in tone, the results provide important messages for the U.S. bioethics community. All but two of the recommendations were supported by at least a two-thirds majority, with most higher. This calls for serious consideration of these issues in further analysis of U.S. ethical guidelines as they are used and applied in internationally sponsored research.

One of the most critical appeals is expressed in the call for studies the benefits of which reach the study population after they end. The context of scarcity in the developing world, the abject poverty of all types of resources, and the righteous needs of the people make this call more poignant. Research is questionable under any circumstance and needs to be justified based on the scientific question at hand; under these circumstances, it becomes even more necessary to balance the risks and benefits and to make certain that the benefits are tangible and are received.

Moreover, this recommendation is very appropriately coupled with the call for exploring and developing mechanisms to ensure that populations actually receive benefits and represents recognition of the great challenge that such a demand poses upon all stakeholders in the research enterprise. And yet, it needs to be seen as an essential component of ethical research at some level. Therefore, it is now a challenge for U.S. ethical guidelines (as it is for other national and international guidelines) to devise more precise and innovative mechanisms to address this issue of providing benefit during and after research. The intent is not to develop loopholes where such responsibility is displaced or avoided. Rather, the intent is to develop creative solutions that allow for a predetermined process to occur and for the benefits to flow to the deprived communities. At the same time, the need to look at this issue collectively and fairly for all parties is central to the success of any potential solution.

E. Comparative Results of U.S. and International Components

This section of the report will explore the differences and similarities between the responses received from researchers in the United States and those from the developing world. The intent is to consider potential reasons for such observations and offer policy recommendations based upon them.

E.1 The Samples

A comparison of the respondents in the United States and international components of this study reveals that the two samples are comparable in terms of gender and age. (See Table E.1.1). International researchers are more likely to have been involved in at least five studies in a developing country over their careers, although this may be because all of their work, one would assume, was international according to our definition. That is, the two groups of researchers may have been involved in equal numbers of projects overall, but some of the studies conducted by the United States may not have been in developing countries.

Table D.6.1: Summary of Recommendations from Survey of Developing Country Researchers

Main Issue	Recommendations	Explanatory Notes
Informed consent	1. More flexibility in documenting informed consent	1. Going beyond written to other forms
	2. Informed consent may or may not be required in observational studies	2. *Split support* for this issue on a specific study design
	3. Community approval should be required	3. As appropriate
	4. Testing of participants understanding prior to joining research should be required	4. Important to note for guideline revision
Risks and benefits*	1. Standard of care should be decided on case-by-case basis	1. Care provided during research study
	2. No research unless benefits of research can be provided afterwards**	2. Strong support for this overall premise
Obligations to subjects and communities*	1. Study data should be provided to study population directly after study ends	1. Feedback to community from researchers
	2. Mechanism to continue delivery of medical care afterwards should be required**	2. Part of planning the study and its consequences
International collaborative research	1. Funding for developing country IRBs should be provided	1. Addressing donors and research investors
	2. International guidelines should be used instead of U.S. ethical guidelines	2. CIOMS stated in the question as an example
	3. Developing country ethical review should be required	3. Very high support for this process
	4. Composition of developing country IRBs should not depend on U.S. guidelines	4. As a requirement from the U.S., this is rejected
	5. The SPA requirement should or should not be eliminated	5. Few respondents and *split decision*
	6. Funds for pilot testing should be released prior to full/complete ethical approval	6. Currently not usually done

*Recommendations overlap for these issues.

**Important overall impressions supported by 80 percent of respondents.

Table E.1.1: Demographics

Gender	% U.S.	% International	P-Value
Female	35	32	.53
≥50 years old	31	31	.95
Working on index study currently	82	67	<.001
Worked on index study >2 years	73	53	<.001
Role on index study • Principal Investigator • Project Coordinator	 80 20	 73 27	.04
Have worked on ≥ 5 studies	55	81	<.001
Spends > 50% of time on research	67	27	<.001
Past or current member of IRB	23	44	<.001

U.S. researchers were more likely to be involved currently in an international research project (the index study), more likely to have worked on the index study for more than two years, and more likely to spend over 50 percent of their time on research. Some of these differences are an artifact of the differences in sampling strategies between the U.S. and international projects, but others may be true differences between U.S. and

international researchers. This U.S. project recruited participants heavily through the NIH-CRISP database, which includes researchers who currently or recently were funded for research by the NIH. Thus, one would expect more currently funded researchers in the sample. Moreover, additional recruitment was conducted through personal contacts who were asked to identify professionals who conduct research in developing countries. Thus, one might expect these contacts to have identified researchers conducting projects currently. The international sample, by contrast, was constructed based on membership lists of four international professional organizations. It is assumed that it will take some time and experience for a developing country researcher to become part of an international database and to have collaborative projects, lending support to the finding that these respondents are more experienced, while society membership does not necessarily imply that a member has research ongoing. Most of both sets of researchers were the principal investigators of their index studies, although this was somewhat more likely to be true for U.S. investigators.

In general, health professionals in the developing world are not dedicated solely to research. The same individuals likely have multiple roles—including clinical practice, teaching, and administration—and, therefore, the amount of time that they dedicate to research inevitably is less compared to their counterparts in the United States. The lack of trained professionals in developing countries often means that the few people who have the requisite skills to conduct major research projects typically perform several functions, as required by the needs of the country or institution.

It must be remembered when comparing characteristics of research projects and attitudes of investigators from the international and the U.S. surveys that our two samples of researchers were not literally one another's counterparts or colleagues, nor were they necessarily referring to the same studies, and, indeed, international respondents may not have been referring to research that was collaborative with the United States at all in many instances. Thus, where responses differ, both sets of responses may be accurate reflections of research experiences of two different groups of respondents. At the same time, it is also possible that there are significant differences in attitude, opinions, or values held by U.S. versus developing researchers as a whole, which deserve careful consideration.

It is also important to note that the U.S. researchers are likely to be more *homogenous* than the international respondents in many relevant respects. The former are from one country working within the general rules, guidelines, and cultural norms of a single nation. International researchers, on the other hand, represent researchers from three continents and dozens of countries following a wide variety of rules and guidelines within their nations and dealing with many other international or Western ethical guidelines. As a result, the within-sample diversity would be much higher in the international sample than in the U.S. sample. This qualification is critical as we discuss the comparative analysis, since this provision colors the statements we will make that refer to the international group as a unified entity. However, the diversity also is a strength in terms of documenting a more comprehensive range of relevant experiences and views.

As described in Sections B.1 and C.3, data from the UNDP Human Development Report (UNDP 1999) was incorporated into the survey database in order to facilitate analysis of selected survey variables in comparison with a UNDP development indicator. The indicator variable, HDI, also was used to compare international and U.S. survey data. Table E.1.2 shows the percentage of index studies in countries with different development levels, for the U.S. and international surveys. The U.S. survey more often reported index studies in countries with low HDI scores ("low" human development was defined by UNDP as <500), and more often intervention studies were carried out in those countries as well. Using two categories of HDI level, with a cutoff point of 682, these differences were statistically significant; the U.S. survey had a greater percentage of studies in lower HDI, compared to the international survey (50 percent versus 41 percent, $p = .05$) and the same was true for intervention studies (59 percent versus 41 percent, $p = .02$).

Table E.1.2: HDI Levels of Countries Where Index Studies Were Conducted

HDI Levels of Countries	<500	500-800	<800
U.S. survey, % of all index studies	23	73	4
International survey, % of all index studies	13	83	4
U.S. survey, % of intervention studies	30	68	3
International survey, % of intervention studies	17	77	5

E.2 Informed Consent

Respondents to both the U.S. and international surveys were asked to answer questions related to the process and outcomes of informed consent in their index studies.

Methods for Informing Participants and Documenting Consent. U.S. respondents were more likely to have used written informed consent in their studies than the international researchers and were more likely to use written consent than any other method (see Table E.2.1). These differences may reflect U.S. researchers following the requirements of U.S. ethical guidelines for documenting informed consent. While most international researchers used written consent (62 percent), even more (77 percent) reported using an explanation of the study to participants followed by a question/answer session. International focus group participants reported their own use of verbal consent in many cases. International researchers were more likely than U.S. respondents to use pictorial descriptions to inform research participants and were more likely to say they checked participants' understanding prior to their enrollment, something that both groups articulated should be done much more often; it was a minority of both groups, however, that actually used such a test.

Beliefs About the Consent Process. The overwhelming majority of both groups thought that the consent process is an important means of educating participants about the study, although international respondents were even more likely to agree with this (94 percent versus 82 percent, $p < .001$). International focus group members were particularly likely to raise the issue that the consent process served as a valuable opportunity to provide health education and counseling more broadly to patients. Furthermore, international researchers were significantly more likely to agree that the consent process is too focused on the individual (66 percent versus 23 percent, $p < .001$; see Table E.2.2) and that the religious/cultural beliefs of the study population are inconsistent with individual decisionmaking (47 percent versus 37 percent, $p = .04$; see Table E.3.1). Both groups were more likely to believe that religious and cultural beliefs are inconsistent with individual decisionmaking if their index study was carried out in a lower HDI country. International researchers obtained consent from a family member in 20 percent of studies, while U.S. researchers did so in 14 percent of studies; however, it is interesting to note that international respondents who used written consent or who were IRB members were significantly less likely to obtain consent from family members, suggesting that perhaps in some cases international researchers had adopted a more "Western" model of consent processes.

Overall, international researchers were significantly more likely than U.S. researchers to agree that, in addition to individual informed consent, U.S. IRBs should *require* community leaders' approval (63 percent versus 32 percent, $p < .001$). In focus groups, U.S. respondents seemed to feel that host country colleagues and IRBs understood when community approval should be obtained much better than they (the researchers) or the U.S. IRBs. One U.S. researcher said that no U.S. IRB would ask him to talk to the village chief before going into the village. U.S. researchers often admitted their "cultural ignorance" on this issue, or that "our culture doesn't understand a community the way [South American country] does." International researchers also raised in focus groups the discrepancy between the U.S. emphasis on individual rights and the community or family level decisionmaking processes of developing countries. Most international researchers in focus groups, however, thought that although community consent was important, individual consent should also occur.

Table E.2.1: Different Methods of Informing Participants and/or Documenting Consent Used for the Research Project

Option	U.S. Survey % Yes	International Survey % Yes	P-Value
Written informed consent, requiring a signature, thumbprint, or equivalent	76	62	.001
Pictorial description of study or study procedures	7	20	<.001
Oral consent with a witness signature	40	32	.1
Community meeting to describe the study	44	51	.1
Approval from a village or community leader	42	49	.2
In research with adults, approval or consent from another family member	14	20	.1
Explanation and question and answer session with participants (either individually or in groups)	74	77	.6
Video to explain study	2	4	.3
Test of participant understanding of research before enrollment	16	27	.01

Table E.2.2: Percent Agreeing or Strongly Agreeing with Various Statements Regarding Consent in an Index Study

Option	U.S. Survey % Yes	International Survey % Yes	P-Value
The informed consent process is focused too much on the individual rather than on the family and/or community.	23	66	<.001
Participants often do not understand the concept of placebo.	57	51	.6
Study participants are usually aware that they are in a research study.	87	84	.2
The consent process is an important means of educating participants about the study.	82	94	<.001
The consent process provides an opportunity to discuss ethics issues with field staff.	82	89	.03
After learning about the study, some potential participants declined enrollment.	72	58	.001
The formality of going through the informed consent process raises distrust in study participants.	29	27	.7
Local staff shortened or simplified the consent procedures compared to the original protocol.	37	35	.9
Legalistic language was required on consent forms that was not meaningful to study participants.	52	29	<.001

International researchers may have used written consent as much as they did because it was required of them in their collaborative projects, or they had grown accustomed to it through their experience with collaborative research, or because in certain settings they felt that it was appropriate. Both U.S. and international respondents were more likely to use written consent in higher HDI countries, and researchers from both groups who used written consent forms also used other methods to inform participants. For example, among researchers who used written consent in their index study, 75 percent of U.S. and 69 percent of international also used an explanation and question/answer session, and 41 percent of U.S. and 45 percent of international researchers also used a community meeting to describe the study. Our data clearly suggest that both groups believe that nonwritten methods may be more appropriate in certain contexts, or should be an integral accompaniment to written consent.

Although international researchers were significantly more likely to use a test of understanding with participants, international and U.S. researchers were equally likely to believe that many of their participants do not understand placebos (over 50 percent reported this in both surveys). The two groups were equally likely to believe that, in general, their participants were aware they were in a research project. About one-fourth of each group believed that the consent process raised distrust among participants, and both groups reported in focus groups that consent forms included too much technical information, which can induce anxiety among participants. U.S. researchers were significantly more likely to believe that the legal language in consent forms is meaningless for participants (52 percent versus 29 percent, $p < .001$), but it may well be that the international researchers actually put less of that legal language into their forms. Indeed, in focus groups, U.S. researchers devoted considerable attention to their frustration with consent forms having an increased focus on legal protection for investigators and institutions. International investigators mentioned in focus groups that the legal framework inherent to the U.S. consent process does not exist outside the United States and is inappropriate.

In terms of voluntariness, it is interesting that so many more U.S. researchers reported that some of their participants had refused to participate (72 percent versus 58 percent, $p = .001$). It could be that the consent processes used in U.S. research projects more clearly distinguished the research from clinical activity and/or emphasized the voluntariness of participation; it is also possible that developing country investigators had closer relationships with study communities that may have facilitated acceptance of the research.

E.3. Assessing Risks and Benefits

Only 12 percent of U.S. researchers and only 5 percent of international researchers ($p = .01$) classified their index studies as entailing greater than minimal risk. It is not clear from this finding whether the number of risky studies truly differed or whether researchers' perceptions of risk varied instead. Indeed, it is quite conceivable that risk was underestimated by both groups of researchers.

In terms of benefit, approximately 60 percent of both international and U.S. researchers agreed that the care provided to participants in studies generally is not available outside of the study (Table E.3.1). Those in the international survey were significantly more likely to believe that this made it difficult to establish appropriate interventions for control groups (67 percent versus 52 percent, $p = .01$), and that participants had unrealistic hopes about personal benefits from participation (55 percent versus 33 percent, $p < .001$). It is interesting to note that developing country scientists more often agreed with statements about ethical issues arising from the disparities in levels of medical care between sponsor and host countries. Since the samples of U.S. and international respondents are not literally each others' collaborators—that is, they were not referring to the same index studies, it is possible that international respondents more often worked in areas where the available medical care was inadequate, thus creating ethical challenges in study design. It also should be noted that the international survey had higher percentage of studies involved in clinical care (24 percent versus 14 percent for U.S., $p = .005$) and therefore possibly more likely to encounter difficulties in determining appropriate levels of treatment, although international researchers were less likely to work in the lower HDI countries. In addition, perhaps international researchers had a higher sensitivity to the needs of study participants for medical care or a greater sense of responsibility for providing care that was not locally available.

An exploration of the reasons for conducting U.S.-funded research in developing countries revealed a set of interesting differences between the U.S. and international respondents (Table E.5). As stated above, the index studies referred to by each group of respondents are different studies, and, therefore, differences observed in responses may reflect different characteristics of those studies; alternatively, the respondents may have different perceptions regarding similar research projects. It should also be noted that the response rate differed for each of the reasons listed for conducting the research in the host country; between 10 percent and 30 percent of the respondents did not answer a given question and were excluded from calculations. While both U.S. and international researchers frequently listed relevance of the intervention, global inequalities in health, and developing

country requests for collaboration as reasons for conducting the study in the host country, U.S. researchers were much more likely to state that disease prevalence in the host country was a relevant factor. International respondents who were funded by the United States were as likely as U.S. respondents to work on topics where one might expect disease prevalence to be relevant, such as infectious diseases other than HIV (about 38 percent of each group) or HIV/AIDS studies (approximately 25 percent of each group). International researchers, whom one can assume often conducted their research in their home countries, may not have focused on the difference in disease prevalence between the United States and their own country, since they were working, presumably, on health problems that affected their home nation.

Table E.3.1: Reasons for the Study Being Carried Out in the Host (Developing) Country as Opposed to in the United States ("% of yes" by the researchers in developing countries)

Question	U.S. Survey % Yes	International Survey % Yes	P-Value
Prevalence of disease in question is much greater in the host country than in the United States	83	66	.001
Interest in addressing global inequalities	73	73	.9
Host country researchers asked for U.S. collaboration	72	70	.7
Intervention being tested more relevant to host country than to the United States	69	76	.3
Recruitment of patients more rapid in host country than in the United States	47	53	.4
Less expensive to do study in host developing country than in the United States	36	63	<.001
Easier to identify a cohort of patients relevant to research	61	56	.4
Research question relevant to U.S. strategic interests in the region	32	49	.01
Marketing approval for drug or device will be sought in host country	12	25	.01

A more notable finding is that international researchers were much more likely than U.S. researchers to believe that the index study was located in the host country because of several pragmatic reasons: cheaper cost, relevance to U.S. strategic interests in the region, and the need to obtain marketing approval for drugs or devices. While it is a minority (25 percent) of international respondents who listed marketing approval as a reason for the index study to be carried out in a developing country, almost half checked U.S. strategic interests, and more than half (63 percent) checked cheaper cost as reasons for conducting the study in the host country. It may be that differences in the types of index studies reported by international researchers, compared to U.S. researchers, relate to these practical issues. For example, a greater percentage of studies in the international survey were funded by private companies (16 percent versus 10 percent of U.S.); some of these studies may have been carried out in developing countries for practical reasons, as mentioned by some U.S. focus group respondents. Also, international respondents' perceptions of the reasons for conducting research in developing countries may differ from those of U.S. respondents, even for similar studies. Although the practical reasons listed do not a priori exclude consideration of the health needs of the developing country, these health needs may not be addressed by research that is driven by financial or strategic motives.

It is important to note that three-quarters of both groups of respondents said they were conducting research in developing countries because they were interested in addressing global inequalities in health. This noble reason clearly motivates researchers around the world. The degree to which they feel they are able to provide the fruits of their research to local communities after studies are over, however, will be addressed in the next section.

E.4 Obligations to Communities and Participants

Our surveys addressed two aspects of obligations and collaborations: one related to what role international researchers had in collaborative research and how much capacity building U.S. researchers engaged in; the other was how studies addressed continuing to provide care or interventions to study participants or communities after the study was over.

In terms of responsibilities within research collaborations, as shown in Table E.4.1, both U.S. and international researchers reported that international researchers are likely to be involved in most aspects of the research. More than 90 percent of researchers in both samples agreed international researchers are involved in training of research personnel and are listed as authors on papers. More than 80 percent of both said international researchers are involved in the initial study design, changes in study design, recruitment of participants, consent discussion with participants, and drafting of manuscripts. There were significant differences, however. U.S. researchers were most likely to say that their international colleagues were involved in procedural tasks (such as recruitment, consent discussions, and staff training) and less likely to say they were involved in more substantive tasks like grant writing and data analysis. International researchers, while also less likely to mention grant writing as a task with which they were involved, still reported themselves significantly more involved in that task than did the U.S. researchers (72 percent versus 53 percent, $p < .001$). They also reported themselves more involved in data analysis than did the U.S. researchers (86 percent versus 69 percent, $p < .001$), and somewhat less likely to be involved in recruitment or consent discussions.

Table E.4.1: Developing Country Researcher Were/Are Included in the Following Research Tasks

Option	U.S. Survey % Yes	International Survey % Yes	P-Value
Initial study design	87	86	.8
Grant writing	53	72	<.001
Change in study design	94	88	.03
Recruitment of participants	98	86	<.001
Drafting consent form	82	84	.7
Consent discussions with participants	94	84	.001
Training of research personnel	94	92	.4
Drafting manuscripts	83	87	.4
Data analysis	69	86	<.001
Listed as authors on papers	97	95	.2

It is possible that the index studies described by the two groups differ, on average, in the level of developing country scientist involvement with specific tasks. On the other hand, it also could be true, at least in part, that U.S. researchers underestimate how involved their colleagues are in substantive matters, or developing country researchers overestimate their involvement. An important future study would be to recruit researchers who were paired in terms of actually serving as the U.S. and international counterparts for the *same* studies. This and many other study comparisons would be further clarified by such a design.

In terms of capacity building more broadly, researchers were asked whether resources or research infrastructure would remain after the study had ended. Over 90 percent of both groups answered "yes" to this question. The type of capacity or resources that were improved or remained after study completion differed little between the groups.

Thirty-nine percent of U.S. researchers and 44 percent of international researchers reported conducting an *intervention* study. They then were asked whether the intervention was provided to participants or communities after the study was over, if the intervention proved efficacious. International researchers were more likely to answer "yes" to this question (92 percent versus 67 percent, $p = .009$), although the majority of both groups answered positively. U.S. intervention studies were more likely to be ongoing (82 percent versus 64 percent, $p = .008$); the data from the U.S. survey indicated that U.S. researchers were less likely to say that they would provide the intervention if they did not yet know if it was efficacious, although they were no more or less likely to describe plans to provide it if the study was ongoing. Logically enough, more U.S. intervention studies were funded by the U.S. government (71 percent versus 19 percent, $p < .001$) and fewer were funded by the developing country government (18 percent versus 33 percent, $p = .02$). Funding levels were similar for bilateral and international organizations. Many more of the U.S. intervention studies were HIV studies (35 percent versus 15 percent of international intervention studies, $p = .002$), and fewer were chronic disease studies (9 percent versus 24 percent, $p = .004$); the most frequent topic for each group was infectious diseases, non-HIV (41 percent of U.S. and 34 percent of international intervention studies.) International intervention studies were much more likely to be health services research (31 percent versus 10 percent, $p < .001$). It is possible that many of the international studies that provided an intervention were in fact interventions already being implemented through the existing health system, where the health system itself was the focus of study. We lack further details to clarify this point. Also, the higher percentage of HIV studies in the U.S. group may be related to a diminished likelihood (compared to the international group) of providing the intervention after the study, although in the U.S. survey, HIV studies were more likely to provide interventions than studies on other topics. Both groups report a similar percentage of intervention studies classified as operational research/program evaluation (25 percent of U.S. and 28 percent of international). These program evaluation studies could be providing interventions as part of a health program, rather than as a post-study benefit.

It is also possible that international researchers are more likely to report providing successful interventions after study completion because they are more likely to work on problems that are relevant to the policy priorities of their home countries and governments; they may be better situated to influence local policy implementation since they are more likely to know and work with (or are themselves) government officials. Also it is possible that, by virtue of being more likely to live amidst the health problems in question, they are much more committed to advocacy to change local conditions. Consistent with this, international researchers were significantly more likely to believe that research to test an intervention should not be done in a developing country unless the intervention, if successful, will be made available to the country at the conclusion of the study (78 percent versus 53 percent, $p < .001$) and to believe that international policy regarding research should require researchers to establish mechanisms for continuing delivery of medical care after the completion of the study (79 percent versus 27 percent, $p < .001$). International researchers were more likely than U.S. researchers to believe that interventions would not be available to most citizens of the host country (48 percent versus 33 percent, $p = .01$); thus, perhaps they felt a greater need for policies to address this gap. U.S. researchers, while supporting the principle that benefits should accrue to those populations and countries where research was carried out, frequently expressed concern in survey comments about the difficulty in obtaining funding for providing ongoing interventions and medical care.

The strong commitment of many researchers to providing the benefits of research to developing country populations is very significant. This reflects an inherent desire on the part of these researchers to make health research a benefit to the populations within which it is conducted both during the study and after it is completed. Clearly, additional mechanisms need to be developed to support such intentions within collaborative health research.

Another important difference is that international researchers were significantly more likely than U.S. researchers to believe that the research priorities of outside funding agencies were not congruent with the

developing country's priorities (58 percent versus 39 percent, $p < .001$; Table E.4.2), although it is interesting to note that only 40 percent of the international researchers who received U.S. funding believed this to be true. The fact that international researchers questioned the priorities of the funding agencies is consistent with a commitment on their part to promote research that addresses the health needs of the developing country populations and consistent with a critical view of research driven by financial or strategic motives, which was frequently expressed in international focus groups.

Table E.4.2: Ethics Issues in International Research

Option	U.S. % True or Sometimes True	International % True or Sometimes True	P-Value
Medical care provided to participants in this study generally is not available to local population outside the study.	63	61	0.6
Study gathered potentially sensitive or stigmatizing information about participants.	49	58	0.08
Study participants have unrealistic hopes about personal benefit from study participation.	33	55	<0.001
The standard of medical care in the host country may be much lower than that of funding country, creating difficulties in establishing appropriate procedures for control group.	52	67	0.01
Participants join because of the desire for compensation, medical care, or other benefits.	68	64	0.3
Research priorities of the outside agency that is funding the study are not congruent with top priorities of developing country funding.	39	58	<0.001
Treatment or intervention being tested is unlikely to be available to most citizens of developing country in the foreseeable future.	33	48	0.01
There is inadequate true community representation on the local IRBs/ethics boards for this study.	50	62	0.04
Religious beliefs and/or cultural norms of study population are inconsistent with the practice of individual decision-making.	37	47	0.04
Ethics issues are rarely discussed with field staff on this research project.	24	39	<0.001

E.5 Review and Oversight

E.5.1 U.S. IRB Review

Both the U.S. and international surveys asked respondents about the U.S. and host country IRB review of their research. The percentages of studies that underwent different types of review are shown in Table E.5.1. International respondents whose index study received U.S. funding (n = 86) were asked if their study was reviewed in the U.S.; it is quite striking that only 55 percent reported U.S. IRB review, while 96 percent of U.S.-funded studies reported in the U.S. survey had such review. Nineteen respondents, or 22 percent of those who had U.S. funding, did not answer the question about U.S. IRB review and were not included in the calculations. It is not clear why essentially half of the U.S.-funded studies in the international survey were not reviewed in the United States. Of those 30 U.S.-funded studies that did not undergo U.S. IRB review, 7 percent had funding from the U.S. government, 67 percent from U.S. nonprofits, and 30 percent from U.S. private companies. There were 14 international studies that received U.S. private company funds, and 82 percent of them had no U.S. IRB review. As noted in section C.5, U.S. private companies conducting studies either inside or outside the United States are not necessarily required by U.S. law to undergo ethics review in the United

States, although if they submit clinical data to the FDA, they must undergo IRB review at each study site, including study sites in developing countries. Also, it is possible that the international respondents in the survey were not always aware that a U.S. IRB review had taken place, especially if such review occurred prior to developing country review or before their involvement with the study protocol. Even so, it is probable that a number of studies reported by international researchers truly did not receive any U.S. IRB review, which is cause for concern. Out of the studies that had reported U.S. IRB review, 32 percent reported no ethics review in the host country and thus were not reviewed by any board; this represents 6 percent of all the index studies in the international survey.

Table E.5.1: Percentage of Index Studies Undergoing IRB Reviews

IRB Reviews: All Studies, Regardless of Source of Funding			
Board	**U.S. Survey: Percent Reviewed**	**International Survey: Percent Reviewed**	**P-Value**
Ministry of Health (host country)	77	56	<0.001
Any ethics review (host country)	87	75	0.001
National IRB (host country)	51*	49*	0.7
State/provincial IRB	16*	27*	0.03
Collaborating institution IRB	84*	92*	0.03
Other board	7*	15*	0.03
U.S.-Funded Studies Only, in Both International and U.S. Surveys (U.S.-funded is defined as any study that reported at least one source of funds from the United States. Does not include bilateral organizations as a U.S. source.)			
Board	**U.S. Survey: Percent Reviewed**	**International Survey: Percent Reviewed**	**P-Value**
U.S. IRB	96	55	<0.001
Ministry of Health (host country)	76	58	0.002
Any ethics review (host country)	89	79	0.02
National IRB (host country)	51*	43*	0.3
State/provincial IRB	17*	25*	0.2
Collaborating institution IRB	84*	98*	0.004
Other board	6*	12*	0.2

*Percentages refer only to those who responded positively to the question about any ethics review; those who did not undergo ethics review were excluded from further calculations.

It was notable that for each IRB issue mentioned in the survey, international respondents were more likely than U.S. researchers to state that the U.S. IRB had raised the issue. (Table E.5.2). This difference was statistically significant ($p < .05$) for the relevance of research to host country, confidentiality issues, control group procedures, and availability of intervention after study. These findings suggest that the U.S. IRB review and role may be perceived differently by both groups of respondents. International respondents, for example, perceive that the U.S. IRB raised these issues more, or are more sensitive to multiple issues being raised about their

studies. Indeed, international researchers, presumably having less experience with U.S. IRBs, may have had different expectations, and may have remembered all of the concerns raised, whereas U.S. researchers may have forgotten some of the concerns that seemed to them routine. It also is possible, since our two samples, again, were referring to different studies, that the studies truly differed in their need to have issues raised, although we assume that such individual variation would be neutralized over the large samples for each group. On the other hand, U.S. IRBs may indeed give more scrutiny to developing country researchers than they do to U.S. researchers, or U.S. researchers may have been able to appear before their IRBs and address concerns before ever receiving the formal comments from the IRB.

E.5.2 Host Country IRB Review

Respondents in both the international and the U.S. survey were asked about review by the host country Ministry of Health and by ethics boards. In the international survey, those studies conducted in lower HDI countries were more likely to have Ministry of Health review (67 percent versus 47 percent, p = .009). For those whose index study was reviewed by one or more ethics board, respondents were asked to identify the type of board or boards that were involved, as shown in Table E.5.1. U.S. researchers significantly more often reported Ministry of Health review and ethics review in the host country than did international researchers. This was true overall and also true when U.S.-funded studies in each group were compared. For those who did undergo host country ethics review, both international and U.S. researchers were most likely to report that the host country IRB that reviewed their study was associated with the collaborating institution, and next most likely to report that a national IRB had conducted the review, although the international researchers had an even higher percentage of studies being reviewed by collaborating institutions compared to the U.S. researchers (98 percent versus 84 percent, p = .004). International researchers were also more likely to have studies reviewed by provincial boards, compared to U.S. researchers. International respondents who are working within the countries may prefer to seek approvals from provincial boards, even for collaborative projects, due to familiarity with people and processes and potentially fewer bureaucratic procedures.

It is interesting to note the discrepancy in host country IRB review between the U.S. and the international survey. International researchers report host country review significantly less often than U.S. researchers, even for U.S.-funded studies (79 percent in the international survey versus 89 percent for the U.S. survey, p = .02). In the case of U.S.-funded research, U.S. regulations would require a host country review to be conducted in most cases, and, in fact, when FDA regulations apply, the host country review is the only one that is required. Presumably all studies that received U.S. funds, reported either in the U.S. or in the international survey, would have been governed by some U.S. regulations, either the Common Rule or those of FDA. It is not clear if the studies that were not reviewed in either survey gained an exemption from review, and, if so, on what basis.

More than three-quarters of the respondents from both groups felt that developing country ethics review should be required for all studies, although international researchers felt so even more frequently (85 percent versus 77 percent, p = .03). At the same time, developing country researchers were more likely to feel that community representation was inadequate on local boards (62 percent versus 50 percent, p = .04).

In comparing the responses from both surveys on the outcomes of the review done in the host country, international respondents (as in the previous section) were more likely to suggest that all issues had been raised. This global trend was significant for issues related to the relevance of the study to the host country, cultural appropriateness, approvals, control procedures, confidentiality issues, voluntariness, and availability of intervention. The reasons for this difference probably are similar to the reasons suggested above for why international researchers reported a greater likelihood of issues being raised for them by the U.S. IRB.

If the U.S. IRB or the local IRB would tend to review collaborative projects more stringently, then both groups should reflect it in the responses. The fact that there is the same differential in response (international greater than U.S.) for both reviews is indicative of issues that pertain to the international respondents and their

Table E.5.2: Comparison of Responses to Issues Raised by U.S. IRB(s) vis-à-vis Issues Raised by Host Country Ethics Board

Options	Raised by U.S. IRB			Raised by Host Country Ethics Board		
	According to U.S. Researchers	According to International Researchers	P-Value	According to to U.S. Researchers	According to International Researchers	P-Value
	% Yes	% Yes		% Yes	% Yes	
Relevance of research question to country where research is conducted and/or rationale for doing study outside the United States	30	52	.02	23	55	<.001
Complexity of language on consent form	45	64	.05	29	59	<.001
Cultural appropriateness of study procedure	48	63	.1	38	45	.2
Need for local language consent form	66	84	.03	50	58	.2
Need for letters of approval from developing country representatives	65	79	.1	31	47	.005
Intervention was considered too risky	4	15	.01	4	10	.03
Appropriateness of procedures for control group	18	50	<.001	17	39	<.001
Confidentiality protections for participants were not adequate	14	42	<.001	8	18	.004
Participant voluntariness may be compromised because of benefits study provides	10	20	.09	7	24	<.001
Use of placebos	12	22	.2	12	26	.006
Availability of intervention (if successful) to host country after study is over	23	46	.01	25	54	<.001
Political considerations	7	17	.09	14	16	.6

characteristics. In general, there has been an historical tendency for the few trained researchers, especially physician-researchers, to do their work without much question in the developing world. At the same time, the processes of peer review, group critique of proposals and papers, and the expectation that people can question and challenge senior researchers is a relatively new phenomenon in many parts of the developing world. As a result, the IRB review processes may be a source of greater consternation and concern for developing country researchers, as compared to the U.S. respondents. In addition, the heightened sensitivities of the international researchers would affect their response to such critique and their recall of such processes as well. These findings would partly explain the result discussed in the previous section and this section.

International researchers were more likely to agree that funding agencies should provide funding to support the work of developing country IRBs (85 percent versus 70 percent, $p < .001$) and to report that developing country IRBs had raised concerns to them about the costs associated with IRB operations (44 percent versus 26 percent, $p < .001$, Table E.5.3). These are consistent with the notion that volunteering time for such activities is much more difficult and has a greater opportunity cost in the developing world than in developed countries; it is likely that developing country researchers would be more acutely aware of these issues than their U.S. colleagues.

In comparing countries with different development levels, using combined data from the U.S. and international surveys, it seems that ethics review capacity, at least on the surface, is not associated with HDI levels of the host country. Index studies in countries with lower HDI levels were not any less likely to have undergone host country ethics review (about 82 percent overall); this review was more often carried out by a national IRB in the lower HDI countries compared to higher HDI countries (63 percent versus 39 percent, $p < .001$), and less often by a provincial IRB (14 percent versus 23 percent, $p = .05$) or an IRB at a collaborating institution (79 percent versus 92 percent, $p < .001$). Also, respondents reported that IRBs were formed because of U.S. regulations with the same frequency for low and high HDI countries (about one-quarter of the cases overall). On the other hand, lower HDI countries took significantly longer to complete host country ethics review (53 percent of studies took greater than three months, compared to 37 percent of studies in higher HDI countries, $p = .003$), which may be a disincentive to conduct research in these countries. Also, 13 percent of respondents whose index study was in a lower HDI country reported they had ever abandoned a research project due to difficulty in obtaining developing country IRB approval, compared to 6 percent of those who worked in higher HDI countries ($p = .03$). Respondents more often reported that host country IRBs were more concerned with politics than with protecting research subjects in lower HDI countries (80 percent versus 66 percent, $p = .003$), and less often reported that host country collaborators relied on U.S. ethics regulations for guidance in lower HDI countries (87 percent versus 94 percent for higher HDI countries, $p = .01$), although the percentage of respondents who believed that national guidelines are sometimes or always effective in protecting research subjects was the same for those who conducted their index study in low or high HDI countries (about 94 percent of each group).

In terms of IRB review, lower and higher HDI countries showed similar percentages for most issues that could be raised by IRBs, with a few exceptions. Lower HDI countries' IRBs more often brought up the need for letters of approval (45 percent versus 28 percent, $p = .002$) and the potential for voluntariness to be compromised (17 percent versus 10 percent = .06). While the letters of approval are a procedural matter, the issue of voluntariness may indicate a real concern for the well-being of the potential research participants. In general, it is not clear if there are any differences of substance in terms of host country ethical review between poorer and richer nations, or if procedural difficulties may arise more often in some cases due to lack of resources to fund IRBs or other government bureaucracies. In addition, our survey data does not include information about national guidelines that might have been applied in different countries where research was conducted; this topic deserves further inquiry.

Generally, international researchers were more likely to agree that international guidelines should be used instead of U.S. rules and regulations to govern collaborative research in developing countries, although the majority of both sets of researchers agreed with this recommendation (77 percent versus 64 percent, $p = .001$), and some U.S. researchers commented in focus groups that international guidelines would be more appropriate. This is likely to be the result of a number of factors, including a resistance to the idea that other countries should be held accountable to rules emanating from a single nation, to real concerns about the lack of flexibility in application, to a preference for a more international approach to the ethics of research.

In comparing researchers' attitudes towards human subjects regulations (Table E.5.3), it can be seen that both international and U.S. researchers were critical of the current U.S. regulations and of IRBs, both in the United States and in the host countries. However, the vast majority of both groups also said that U.S. human subjects regulations sometimes or always ensure high ethical standards in research. This apparent paradox can be explained if we postulate that researchers in general find that the regulations do provide protection to research participants, but that the protection could better be achieved through more flexible and culturally appropriate mechanisms. It should be added that those researchers who said that the regulations "sometimes" ensure high ethical standards are also implying that "sometimes" the regulations do not provide this assurance.

In focus groups, U.S. researchers commented that some procedural requirements, for example, lengthy consent forms, actually impede the substantive part of research ethics, such as ensuring adequate participant understanding.

Table E.5.3: U.S. and International Human Subjects Regulations and Guidelines

Option	U.S. Researchers, % Sometimes or Always	International Researchers, % Sometimes or Always	P-Value
U.S. human subjects regulations are flexible where they need to be.	68	63	.4
Developing country collaborators rely on U.S. ethics regulations for guidance.	91	91	.9
U.S. IRBs are more concerned with politics than they are with protecting the interests of research subjects.	66	58	.2
The current U.S. rules and regulations governing human subjects ensure high ethical standards in research.	97	95	.6
U.S. IRB regulations are insensitive to local cultural norms and traditions outside the United States.	94	83	.001
Developing country IRBs are more concerned with politics than they are with protecting the interests of research subjects.	79	63	.001
Developing country IRBs have voiced concerns to me about the costs associated with the IRB carrying out its work.	26	44	<.001
National guidelines in developing countries are effective in protecting research subjects.	95	92	.1

E.6 Summary

There are broad areas of agreement, on the whole, between U.S. and international researchers, as well as significant differences. In general, both groups of researchers expressed strong commitment to ethics principles in their research, while at times expressing frustration with procedural requirements or difficulties of interpretation of ethics guidelines in different countries and cultures. Both U.S. and international respondents felt that U.S. guidelines could be significantly improved by becoming more flexible and more culturally appropriate. Both groups expressed strong commitment to the elements of informed consent, namely, participant understanding and voluntary participation in research. In focus groups, both groups said that IRBs in the United States and in developing countries need to be educated, the former about realities of life in the developing world, and the latter with regard to ethics and ethics review.

Researchers in both surveys were asked if they agreed or disagreed with a series of recommendations about the conduct of international collaborative research and the human subjects regulations that govern such research. A strong majority of both international and U.S. researchers recommended support for developing country review processes, including requiring developing country review for all studies, supporting developing country IRBs with funding, and not imposing on developing country ethics boards the U.S. requirements for IRB composition. International respondents were less likely than U.S. researchers to agree that the SPA requirement should be eliminated, which may indicate that fewer of them had experience with SPAs or that those who had dealt with SPAs had not experienced the considerable frustration with the process that U.S. researchers expressed in survey comments and in focus groups. A majority of both groups, and international respondents even more frequently than U.S. respondents, supported the use of international ethical guidelines such as CIOMS rather than U.S. rules and regulations for human subjects research.

Table E.6.1: Recommendations

Recommendations	U.S. % Strongly Agree or Agree	International % Strongly Agree or Agree	P-Value
U.S. regulations should allow more flexibility in ways of documenting informed consent.	85	72	.001
Formal individual consent should not be necessary for observational studies.	48	39	.05
Where appropriate, community leaders' approval should be required by U.S. IRBs, in addition to individual informed consent.	32	63	<0.001
A mechanism to measure participants' understanding should be built into any research study.	65	83	<0.001
Research funding agencies should provide funding to support the work of developing country IRBs.	70	85	<0.001
International guidelines (e.g., CIOMS) should be used instead of U.S. rules and regulations.	64	77	.003
A developing country ethical review should be required for all studies.	77	85	0.03
The composition of ERBs used in developing countries should not be dictated by U.S. regulations.	83	92	0.004
The SPA requirement should be eliminated.	49	29	<0.001
The issue of what standard of medical care to provide to study participants should be decided on a case-by-case basis.	78	77	.8
Some research funds for piloting consent forms should be released before final IRB approval is obtained.	61	70	.04
U.S. researchers *[international survey: 'researchers']* should be required to make data from research study directly available to study population after study is over.	62	80	*Not calculated*
Research to test an intervention should not be carried out in a developing country unless the intervention, if found to be successful, will be made available to that country at the conclusion of the study.	53	78	<0.001
International policy regarding research should require researchers to establish a mechanism for continuing delivery of medical care after completion of the study.	27	79	<0.001

Concerning informed consent, a strong majority of both groups supported increased flexibility in documenting consent, although international researchers were less likely to recommend this than U.S. researchers. A majority of both groups recommended the measurement of participant understanding of research projects and the release of funds before IRB review so that researchers can pilot consent forms with study populations.

Both international and U.S. respondents supported the idea that the level of medical care provided to study participants should be decided on a case-by-case basis. Expressions by members of both groups in focus group discussions indicated that this aspect of study design was ethically problematic and that there was no clear consensus about what should be required of researchers. Some researchers in both groups felt that the level of medical care that would be available locally should be considered reasonable for control groups, even when that care would be considered grossly insufficient in the country that sponsored the research.

More than half of U.S. researchers and more than three-quarters of international researchers believed that research to test an intervention should not be carried out in a developing country unless that intervention will be made available to the host country. International respondents, both in the survey and in focus groups, mentioned the need to provide benefits of research to host countries and were often adamant that this should be required. U.S. researchers, on the other hand, were more tepid in their approach to this issue, due to their concern about funding difficulties and their opinion that needed and useful research would not take place if requirements for providing research products became financially overwhelming and that such requirements should not be their sole responsibility. The survey data regarding interventions show that more than half of U.S. and almost all international researchers are providing successful interventions to some residents of study communities, and sometimes to larger groups, at the conclusion of their research projects, but it is not clear from the survey data what types of interventions are being provided, at what cost, and what the required infrastructure might be.

There was less agreement between U.S. and international researchers concerning the provision of medical care generally after a research protocol has ended; more than three-quarters of international respondents but only 29 percent of U.S. respondents felt that researchers should be responsible for establishing this ongoing care. In survey comments, many U.S. researchers remarked that although they supported the principle of providing ongoing benefits to developing countries, funding for continuation of medical care could be problematic.

In general, the majority of both international and U.S. researchers support significant changes to policies and ethics guidelines for international collaborative research, with international respondents being even more likely to advocate for change. The substantial agreement by the more than 500 researchers who participated in this project on the majority of these recommendations makes these findings particularly notable. The experiences of these researchers, from diverse countries and backgrounds, provide valuable insight into the current workings of ethics review processes in international collaborative research and point toward constructive changes in this area.

F. Conclusion

F.1 Limitations of the Study

F.1.1 Sample Issues

This study has two components—the U.S. project and the international project. While we use the general terms "U.S. researchers" and "international researchers" or "developing country researchers" throughout this report, it is important to acknowledge that some developing country scientists, of course, are employed by U.S. institutions and may have been included in the U.S. sample. Similarly, some U.S. or European nationals probably were among our international respondents. We are aware that this misclassification exists; however, we expect that it constitutes only a small minority of the respondents.

Sampling for both components of the survey was subject to selection bias. Comprehensive lists of researchers who conduct health-related research in developing countries, unfortunately, do not exist in any country. Hence, different methods to assemble a respondent pool were utilized for this study that varied in how systematic they were. For the U.S. survey, the CRISP database was assumed to be a reasonable source of investigators who were funded by the NIH. While probably a fair assumption, a number of researchers known to the investigators as NIH grant recipients did not appear on our lists. Also, much international research is conducted through funding sources other than the NIH. Therefore, we began assembling lists of potentially eligible researchers through U.S. university websites. While this additional strategy yielded many additional respondents, our response *rate* decreased considerably, perhaps because our new method was overly inclusive and surveys were sent to many

researchers who were not eligible but never returned a survey explaining their ineligibility. Further, given that no lists comparable to the CRISP database exist for the other sectors (U.S. government researchers, U.S. military, or private industry), we had to rely solely on a few personal contacts within each sector to help us identify relevant researchers. The likely result of such convenience sampling in our study is the creation of a pool of respondents that does not fully represent the universe of U.S.-based researchers who work in developing countries. However, it is hoped that the researchers selected through this wide number of sources, contacts, and sectors reduces the impact of this problem to some extent.

A major limitation of the U.S. survey is the limited number of responses from researchers within the pharmaceutical industry, despite repeated attempts to include larger numbers. Our sponsor for this project, NBAC, met several times with leaders from PhARMA, the pharmaceutical industry trade organization, who unfortunately declined participation in the study. We also made several attempts to contact international health researchers at various U.S.-based pharmaceutical companies to describe our study and evoke interest in participation. While several individual researchers sounded willing to participate, when we approached their public relations divisions, as was required, we generally were denied access to researchers. Thus, we relied on existing personal contacts at a handful of companies to help identify individual researchers willing to participate in the study. It is perhaps worth noting that this distinction between the researchers and the public relations or marketing division of pharmaceutical companies was a distinction made by researchers themselves in our focus groups. That is, pharmaceutical researchers in focus groups described confronting ethics issues that other researchers had raised—including how to achieve adequate participant understanding; how to determine appropriate standards of care; and what should be left behind after the study was over—but referred to pressure from their marketing divisions to conduct research more quickly and/or to engage in procedures that researchers found troubling.

For the international survey, there similarly were no comprehensive global lists of developing country health researchers. For the purposes of this survey, the objective was to construct a "reasonable" sample of developing country researchers. The absence of a sampling frame or defined universe made this issue more challenging. As a result, the list of respondents was generated *de novo* for this study from professional organizations, U.S. survey respondents, and attendees of an international research ethics workshop. Furthermore, only those researchers who had e-mail contacts were included initially, due to time, economy, and ease of contact. Later, additional surveys were sent by courier and the U.S. global mail system, and about one-third of the responses were received in hard copy.

Since we made our survey available on an Internet website, this decision to begin with e-mail contacts facilitated reaching potential international respondents who could complete the survey online. Indeed, more than two-thirds of the 210 surveys were completed via the website. The survey took approximately 30 to 45 minutes to complete. For many researchers in developing countries, it is expensive to stay online for long periods, and frequent disconnection is common. This may have discouraged some researchers from completing the survey, which is obvious from a large number of incomplete responses. Besides the cost of staying online (relative to the U.S. researchers), other possible impediments to completing the survey included inconvenience/difficulty in accessing the Internet, type of Web browser being used, low computer memory, or other computer/technical problems.

Ideally, this study would have been designed by identifying index international collaborative studies and then surveying both the U.S. and international researchers from the *same* study. This would have allowed us to make comparisons between the two samples more directly.

F.1.2 Survey Instrument Issues

The survey questionnaire consists of 169 closed-ended questions and 2 open-ended questions (see Appendices B and D). As such there were the generic issues that plague any survey instrument. For example, closed-ended questions limit the initial choice of answers for each question (although an "other" category is present), because the respondent is confined to checking off one answer when he/she may prefer to elaborate.

The survey was based on two major approaches to asking questions in order to elicit the attitudes and opinions of researchers on ethics guidelines: questions seeking their experiences and questions seeking their opinions. Responses based on an index study depend on the specific study that the researcher has selected, which may or may not be representative of the usual experience of the researcher. However, our premise is that the more than 200 (developing countries) or 300 (U.S.) responses will result in a wide spectrum of responses that together will mirror the experiences of researchers in the field.

As with many studies, we realized that the survey instrument failed to ask certain key questions. For example, we never asked what benefits researchers actually provided in their studies, despite asking them their opinions about how much benefit should be provided and whether IRBs questioned the degree of benefit they were providing. Further, although we asked researchers many questions concerning whether particular issues were raised by their IRB/ethics boards during study review, we cannot know from the questions we asked whether a board not raising a particular issue meant that the board did not think of it, or whether the issue had been adequately addressed by the investigator in the protocol submitted. Nonetheless, despite this limitation, the fact that certain issues were asked by IRBs more often than others is revealing.

Further, while our researchers' experiences spanned many countries, diverse research topics, and different study designs, every situation and country is unique. While we referred to all research in developing countries as eligible research, the level of development among countries varies widely and does so in ways integrally relevant to many of our outcomes of interest. As one of our participants said:

> I would certainly spend a little time defining what type of country. Because I know that Brazil and Argentina, to me are not third world countries. You go to Burkina Faso, you're going to see a third world country. So I think it is going to be difficult to lump them all into one bag as third world country or underdeveloped or whatever you want to use….So the conditions in these different places will be important to use existing structure to [categorize] one as nearly like in the United States, to something that is in the Middle Ages. And that is clearly difficult to make a policy when you deal with such a diversity of situations.

F.1.3 Qualitative Data Collection

Seven focus groups were held for the U.S. projects, while six were convened for the international project, of which two were held in the developing world. Eight additional in-depth interviews were conducted for the international project in Geneva and Pakistan. Additional groups undoubtedly would have enriched the qualitative data and enhanced our ability to draw conclusions from it more confidently.

As with all qualitative data, broad comparisons should be made with caution. The data collected here reflect the thoughts and experiences of those who were purposively sampled and do not a represent a probability-based sample of investigators.

The majority of investigators from developing countries were recruited and interviewed in the United States. These investigators likely vary in their experiences and training from those developing country investigators who were not accessible to the project. Investigators who have the opportunity to visit, work, or study in the United States could be inherently different than the investigators who do not share this background. Ideally, all data collection would have been conducted in developing countries; however, financial and logistical constraints made this impossible. The majority of in-depth interviews were conducted in one developing country alone. Findings could be influenced to some extent by the over-sampling of one country.

A total of four different Hopkins researchers facilitated the focus groups and conducted in-depth interviews of the developing country investigators. Each researcher brings his or her own individual perspective and interpretation of data, which potentially elicited varied responses. Greater reliability could have been obtained through consistency in data collection by using the same interviewer or facilitator.

The participants in the focus group discussions were less homogenous than that of the U.S. focus groups. Among developing country investigators, participants may have been entirely unknown to one another, perhaps restricting the level of comfort for some. Participants from developing countries were associated in varying capacities with a variety of research institutions and organizations throughout the world. This level of familiarity could have affected the depth and detail of discussion and the openness of individual participants' responses. Furthermore, the topic of discussion and questioning was possibly more pertinent to the U.S. investigators relative to the developing country investigators. This system of ethical review affects virtually every U.S. investigator whether through their academic institution, funding mechanisms, or employer. By contrast, a developing country researcher is required to work under the rules and regulations as put forth by his own government and is possibly not required on any level to be involved in U.S. regulations regarding research.

Further, if time had permitted, it would have been helpful to conduct qualitative work again after our quantitative data collection. There were several findings in the quantitative survey that could have been elucidated through qualitative interviews with researchers, and, indeed, researchers were asked in the survey to indicate their willingness to complete a follow-up interview, and many agreed. While such follow-up may be done in the future, it is not included in this report, because of time limitations.

F.2 Project Recommendations

This study is the first large-scale survey of U.S. and international researchers regarding ethics in international health research. As such, it can provide some data on researchers' experiences and opinions regarding informed consent, obligations during and after a study is conducted, and ethics review and oversight. It is our hope that this study can begin to fill the void of the lack of data that have been available to support or refute normative claims regarding how, ethically, international health research should be conducted. We hope this study will provide data useful to policymakers regarding whether and how current regulations should be modified, where the educational goals should be directed, and how IRBs and researchers can further their clearly shared goals of conducting sound scientific research that protects and furthers participants' welfare and respects them and their interests.

Based on our findings, we make the following series of recommendations:

1. *Informed consent is central to the research process and is supported by developed and developing country researchers as a leading principle.*

Quantitative and qualitative data from both projects suggest that researchers agreed overwhelmingly that informed consent is important and necessary in the conduct of research. Researchers described it as important in and of itself and also as a means to educate participants about the study and raise ethics issues with study staff.

2. *There should be greater flexibility in the means of informing participants about research and in the methods of documenting consent in international and collaborative research.*

While clearly valuing informed consent, many researchers were frustrated with how narrowly consent requirements have been interpreted by most U.S. IRBs. One researcher suggested as an alternative a "menu of choices" from which researchers could choose. Others suggested that multiple methods be used in the same study (a practice employed by many of our respondents) and that all methods should be explained to the IRB, not just

the written one. Clearly, for our researchers, the goal of informing participants is not negotiable, but the means for doing so should be flexible. Specifically, written consent should not be required universally, and IRBs should ask researchers what multiple methods they plan to use and why. Methods of documentation should range from participant signature (written consent) to researcher or witness signature for oral consent procedures, depending on relevant characteristics of the study population. Methods generally should be sensitive to cultural norms and levels of literacy in the local community, and researchers in their applications to IRBs/ethics boards should justify choice of methods.

3. *Tests of understanding should be incorporated into research studies.*

Respondents to our survey and focus group participants overwhelmingly thought that participant understanding was the appropriate goal for informed consent procedures. Ultimately, research only can go forward if participants understand what the research entails. While there was overwhelming support for trying to assess participants' understanding, most researchers admitted they had never conducted such a test themselves. One reason for this may be that doing so is difficult; another may be that it is not part of current regulations or guidelines. Incorporating assessments of participant understanding—whether through a formal quiz or through more informal questions about key concepts—into guidelines, codes, and IRB applications would increase the likelihood that this procedure would be followed more frequently. Ultimately, regardless of the methods used for consent, the test of understanding will reveal the success or failure of efforts to communicate the study's procedures, risks, and benefits to the study population.

4. *All research studies concerning any topic should be reviewed by an appropriate ethics board if they involve human subjects, although review should be streamlined based on a study's level of risk.*

There may be cases where reviews are hastened to meet a deadline or a waiver granted after preliminary review (for secondary data analysis or extremely low-risk studies), but all studies, regardless of topic and method, need to be reviewed. The notion that studies pertaining to social sciences, especially anthropological sciences, and those involving qualitative research methods need not be reviewed is inappropriate. Some of the most sensitive issues of human interactions are raised in such studies, and risks arising from breaches of confidentiality, particularly in certain countries, can literally be life threatening.

Rather than determine whether review should occur based on a study's discipline or method, IRBs should streamline their review based on the level of *risk*. Riskier studies should have more rigorous and detailed reviews, more justification from researchers, more thorough consent processes, and a higher threshold of participant understanding.

All studies need to be reviewed, regardless of the source of funding. Donor agencies—private, international, national, nongovernmental—all are within the purview of ethical reviews. Therefore, bilateral agencies working within countries fund research, and such studies need to be reviewed as well.

5. *Studies involving international collaborations need to be reviewed in both/all countries.*

All studies that involve collaborative research must be reviewed in both countries—the United States and the host country. The United States has certain cultural and legal standards that require certain research practices or approaches; at the same time, host country boards are expected to be more cognizant of appropriate methods culturally for informing participants, to be more aware of certain types of risks that would be overlooked by U.S. boards, and to be more aware of what level of benefit to provide is realistic.

6. *U.S. IRBs should gain greater expertise in the realities of life in a developing country.*

Many U.S. researchers expressed frustration with unrealistic requirements raised by their U.S. IRB that, to them, revealed their IRB's ignorance about field realities in a developing country. Examples included requiring

phone numbers, often of U.S. officials, to be included on consent forms, or requiring multiple revisions and new approvals of a study from host country ethics boards that might not have the resources to copy protocols for all members, not to mention bring them in from all over the country for another meeting. Having someone on the U.S. IRB with international experience is helpful, or having, instead, an outside consultant to provide guidance can begin to address this problem. Moreover, even a short "in-service" training for U.S. IRB members and staff on how local conditions (from rates of electricity or phone service to cultural or religious norms) and/or beliefs might affect issues of research review, consent, expectations, or host IRB working conditions would be helpful.

7. *Host country ethics boards should gain additional experience in ethics.*

Many U.S. researchers voiced concerns that host country boards had little familiarity with ethics. Thus, when ethics boards convened, they focused on other issues that felt more comfortable, such as the scientific design or the budget. Increasing ethics capacity of local boards is mentioned in the CIOMS guidelines as an appropriate task for researchers to undertake, although we are not suggesting here that this should be the responsibility solely of researchers. While researchers should consider providing mechanisms for ethics training to their colleagues along with other types of training, funding agencies similarly should devise mechanisms for increasing ethics capacity in local countries, such that countries are better equipped to determine for themselves how guidelines are best drafted and interpreted for their setting, or whether studies are providing appropriate levels of care.

8. *Collaborative research studies should be monitored at periodic intervals to ensure that procedures stated in the protocol are being carried out as planned.*

While IRBs and collaborating institutions can require certain ethical principles to be upheld in design and planning of a research project, if the plans are not carried out as promised, the safety and interests of the study participants can be compromised. A mechanism must be put in place to ensure that appropriate study procedures actually are followed.

9. *Capacity building should be integral to any study.*

Research collaborations occur between rich and poor countries, not only because poor countries cannot afford to finance the studies, but often because there are not enough people in the poorer country who are trained in study design and data collection and analysis. It should be the U.S. researcher's goal to encourage capacity building during every research collaboration, such that higher and higher proportions of study staff are local residents. Sometimes this will mean funding graduate training of collaborators; other times it will mean providing short-term, in-country training on specific topics such as laboratory techniques or consent procedures. Particular attention should be paid to increasing the developing country researchers' training and role in substantive tasks, such as data analysis and grant writing. Researchers should conceive of their role as facilitating host countries' capacity to eventually conduct most of their research independently and should aim for such capacity development as one of the most significant benefits a study can provide.

10. *The study population or community must benefit as a consequence of the study, and mechanisms to ensure this must be discussed and/or developed as part of the study proposal.*

Researchers, especially international researchers, overwhelmingly agreed that the study population must benefit as a consequence of research conducted within that community. They also encouraged the exploration of mechanisms to ensure that the benefits of research actually reach these people and promoted the inclusion of such understanding in the early stages of thinking about research. This recommendation emerges from both an overarching philosophical stance that can be gleaned from the respondents regarding the conduct of research in impoverished settings and also a very operational element in their opinions on research planning and implementation.

Researchers believed, however, that consideration of future benefit should not be their responsibility alone. Innovative mechanisms must be devised for encouraging researchers to engage donors, aid agencies, or service delivery organizations in discussions about realistic interventions before a study is initiated. Possible mechanisms might include requiring discussion in a grant proposal about prospects for future implementation; including a professional from a donor agency on study sections for international health research; encouraging IRBs to incorporate questions related to future access in their review; or offering continuation grants for implementation and infrastructure creation to support research interventions shown to be successful. This does not necessarily mean that studies cannot go forward without guarantees of future access; however, it does mean that studies cannot go forward where researchers have given no thought to how realistic future implementation is and how it could be actualized. While researchers do not need to shoulder this responsibility alone, it still is not appropriate for funders to support research where no one is taking responsibility for working on future access to effective health interventions.

Notes

1 According to UNDP, development levels are defined as follows: High human development is greater than .800 HDI, medium is .500 to .800 HDI, and low is less than .500 HDI. Source: UNDP website, www.undp.org.

2 Federal regulations regarding protection of human subjects in research, 45 CFR 46, are referred to as the Common Rule, and, in general, are applicable to all research with human subjects that receives U.S. federal government funding. Private companies that do not receive such funding would not be bound by these regulations, but in cases where clinical data is to be used for drug approval in the United States, regulations for clinical research set forth by the Food and Drug Administration must be followed.

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APPENDIX A

Focus Group Guide

I. Introductions: [Go around the room]

1. What do you do?
2. What countries have you worked in? For how long?
3. Generally, what types of studies?

II. U.S. Review of Studies

1. Generally, do your studies need to go through an ethics review (IRB or equivalent)?
2. If so, is that at your institution, or elsewhere (where)? Other layers of approval necessary?
3. How well did that process work? How meaningful an ethics review?
4. Substance of review: Were you asked mostly about administrative details or about issues you thought related to human subjects protections and ethics?

III. In-Country Review of Studies

1. Generally, do your studies need to go through an ethics review in the host country before you start a study?
2. If so, how many in-country IRBs or ethics boards did you need to go through? Is ethics review separate from or combined with scientific review?
3. Did boards exist or did they need to be established for your study? Because of U.S. requirement or not? Was composition or procedures of board influenced by U.S. regulations?
4. Generally, how well did process work? How meaningful an ethics review?
5. Substance of review: Were you asked mostly about administrative details or about issues you thought related to human subjects protections and ethics?

IV. Informed Consent Procedures

1. Did you get/seek informed consent from individual participants? From other individuals (relatives)? Communities? Others?
2. How was informed consent handled (written, oral, groups)?
3. How meaningful do you think the informed consent process was?
4. Were you faced with cultural differences in how consent procedures should be implemented?
   4.1 Did U.S. regulations require you to do anything you thought was culturally inappropriate?
5. How foreign is the concept of informed consent:
   5.1 How foreign a concept is research?
   5.2 Do doctors/providers usually DISCLOSE much about diagnoses, etc., to patients?
   5.3 Do patients usually have CHOICES or MAKE DECISIONS in their own medical care?

V. Ethics Issues That Arise

1. What kinds of ethics issues have arisen in your studies?
2. How did you try to resolve them?
3. (Examples:)
   3.1 Didn't think participants understood.
   3.2 What intervention to provide to comparison group.
   3.3 Providing additional benefits (e.g., more health care) to participants.

VI. After Study Ended

1. Dissemination of intervention after study ended?
2. Interventions you studied ever implemented in country?
3. Was implementation discussed before study was initiated?

VII. Overall Recommendations

1. How should U.S. ethics regulations be modified?
2. Should there be in-country IRBs?
3. How best to protect vulnerable, poor, uninformed participants?
4. What recommendations would you make?

APPENDIX B

Survey of U.S. Researchers' Experiences with and Attitudes Towards Human Subjects Regulations

OMB no. 0925-0472
Expiration date 9/30/2000
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Survey of U.S. Researchers' Experiences with and Attitudes towards Human Subjects Regulations

A survey conducted by the U.S. National Bioethics Advisory Commission

Please direct questions concerning this survey to:

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A Introduction

This survey is designed to collect information from researchers based in the U.S. (not necessarily of U.S. origin) who have carried out research involving human subjects in developing countries. *If you have not conducted research in a developing country, please do not complete this survey.*

Please Note: **In order to receive the $25 payment for completing the survey you must fill out every question with a black dot ●.**

A1 Are you currently involved in a study in the developing world that requires human subjects?

- Yes ***(Please skip to question A2)*** . . . . . 1 ❍
- No . . . . . 2 ❍

A1a If no, have you been involved in a study in the developing world that requires human subjects:

- Within the past five years . . . . . 2 ❍
- More than five years ago . . . . . 3 ❍
- Never ***(Please do not complete this survey)*** . 1 ❍

If your answer to question A1a. is "never" please do not complete this survey. Thank you for your time.

A2 How many years total have you been conducting human subjects research in developing countries?

_____ Years

A3 How many studies (total) in developing countries have you been involved in?

- 1 . . . . . 1 ❍
- 2 to 4 . . . . . 2 ❍
- 5 to 10 . . . . . 3 ❍
- Greater than 10 . . . . . 4 ❍

A4 In what regions of the developing world have you conducted research? *(Check all that apply)*

- Asia . . . . . 1 ❍
- Africa . . . . . 2 ❍
- Pacific Islands . . . . . 3 ❍
- South America . . . . . 4 ❍
- Central America/Mexico . . . . . 5 ❍
- Caribbean . . . . . 6 ❍
- Other (*Please specify)* . . . . . 7 ❍

_____

A5 During the last year, in what country have you lived most of the time?

- U.S.A. . . . . 1 ❍
- Country where research is conducted . . . . . 2 ❍
- Another country . . . . . 3 ❍

B Developing Country Research Project

Please think about the developing country study on which you have spent the most time in the last five years. We will refer to this study as the "index study". Please think of this "index study" in answering the following questions:

Please Note:
In order to receive the $25 payment for completing the survey you must fill out every question with a black dot ●.

B1 In what country was/is this study? _____

B2 To date, how long have you been working on this study?

Less than 1 year . . . . . 1 ❍
1 to 2 years . . . . . 2 ❍
2 to 5 years . . . . . 3 ❍
Greater than 5 years . . . . . 4 ❍

B3 Is the study still ongoing (data collection and/or analysis)?

Yes . . . . . 1 ❍
No . . . . . 2 ❍
Don't know . . . . . 8 ❍

B4 What topic(s) is/was this study investigating? *(Check all that apply)*

Infectious disease, non-HIV/AIDS . 1 ❍
HIV/AIDS . . . . . 2 ❍
Chronic disease . . . . . 3 ❍
Vaccine development/testing . . . . . 4 ❍
Nutrition . . . . . 5 ❍
Cultural practices/behavior . . . . . 6 ❍
Injury . . . . . 7 ❍
Genetics . . . . . 8 ❍
Environmental Health . . . . . 9 ❍
Health Systems/Health Services . . . 10 ❍
Reproductive Health . . . . . 11 ❍
Perinatal Health/Birth defects . . . . 12 ❍
Other *(Please specify)* . . . . . 13 ❍

_____

B5 Which discipline(s) best describes this study? *(Check all that apply)*

Behavioral science . . . . . 1 ❍
Epidemiology . . . . . 2 ❍
Microbiology . . . . . 3 ❍
Clinical care . . . . . 4 ❍
Health Services research . . . . . 5 ❍
Psychology/Mental Health . . . . . 6 ❍
Anthropology . . . . . 7 ❍
Ethics . . . . . 8 ❍
Other *(Please specify)* . . . . . 9 ❍

_____

B6 Which of the following methodological approaches are you using in this study? *(Please check all that apply)*

- Randomized controlled trial . . . . . 1 ❍
- Observational/descriptive study . . . . 2 ❍
- Prospective study . . . . . 3 ❍
- Case-Control . . . . . 4 ❍
- Community-based intervention . . . . 5 ❍
- Operational research/ program evaluation . . . . . 6 ❍
- Qualitative methods . . . . . 7 ❍
- Don't know . . . . . 8 ❍
- Other *(Please specify)* . . . . . 9 ❍

_____

B7 In your opinion, what level of risk does this study involve for participants?

- Minimal Risk . . . . . 1 ❍
- Greater than minimal risk . . . . . 2 ❍
- Don't know . . . . . 8 ❍

B8 What is (are) the source(s) of funding for this study? *(Please check all that apply)*

- U.S. government (non-military) . . . . 1 ❍
- U.S. military . . . . . 2 ❍
- U.S. private company . . . . . 3 ❍
- U.S. non-profit (foundation, NGO) . 4 ❍
- Developing country government . . . 5 ❍
- Developing country private company . . . . . 6 ❍
- Developing country non-profit (foundation, NGO) . . . . . 7 ❍
- European government (non-military) 8 ❍
- European military . . . . . 9 ❍
- European private company . . . . . .10 ❍
- European non-profit (foundation, NGO) . . . . . .11 ❍
- Bilateral organization (SIDA, USAID, etc.) . . . . . .12 ❍
- International organization (WHO, PAHO, UNICEF, etc.) .13 ❍
- Other *(Please specify)* . . . . . .14 ❍

_____

B9 Which of the following best describes your role in this study?

- Project Coordinator . . . . . 1 ❍
- Co-investigator . . . . . 2 ❍
- Principal investigator . . . . . 3 ❍
- Other *(Please specify)* . . . . . 4 ❍

_____

B10 Are you or any of your colleagues conversant in a language or dialect of the study participants?

Yes . . . . . 1 ❍
No . . . . . 2 ❍
Not applicable . . . . . 9 ❍

B11 Which of the following groups are included in the study? *(Please check all that apply)*

Non-pregnant women . . . . . 1 ❍
Pregnant women . . . . . 2 ❍
Men . . . . . 3 ❍
Children 1 to 15 . . . . . 4 ❍
Infants (younger than 1) . . . . . 5 ❍
Don't know . . . . . 8 ❍

B12 What is (are) the religious affiliation(s) of study participants? *(Please check all that apply)*

Local indigenous religion . . . . . 1 ❍
Buddhist . . . . . 2 ❍
Muslim . . . . . 3 ❍
Hindu . . . . . 4 ❍
Animist . . . . . 5 ❍
Jewish . . . . . 6 ❍
Christian . . . . . 7 ❍
None . . . . . .9 ❍
Don't know . . . . . .8 ❍
Other *(Please specify)* . . . . . 10 ❍

_____

B13 What level of education is predominant in the study population?

No formal education . . . . . 1 ❍
1 to 6 years of formal schooling . . . . 2 ❍
6 to 12 years of formal schooling . . . 3 ❍
University educated . . . . . .4 ❍
Don't know . . . . . 8 ❍
Other *(Please specify)* . . . . . 5 ❍

_____

B14 What percentage of the study population is literate?

Less than 20% . . . . . 1 ❍
20% to 60% . . . . . 2 ❍
60 to 90% . . . . . 3 ❍
Greater than 90%. . . . . 4 ❍
Don't know . . . . . 8 ❍

B15 On average, each year, how many weeks do you spend at the research site of this "index study"?

2 weeks or less . . . . . 1 ❍
2 to 8 weeks . . . . . 2 ❍
Greater than 8 weeks . . . . . 3 ❍

B16 In your opinion, what were the reasons this study was carried out in the host (developing) country as opposed to in the U.S.?

	Yes	No	Don't know	Not applicable
a Prevalence of disease in question is much greater in the host developing country than in the U.S.	1 ❍	2 ❍	8 ❍	9 ❍
b Intervention being tested more relevant to host country than to U.S.	1 ❍	2 ❍	8 ❍	9 ❍
c Easier to identify a cohort of patients relevant to research question (e.g., patients without prior treatment history)	1 ❍	2 ❍	8 ❍	9 ❍
d Recruitment of patients more rapid in host country than in U.S.	1 ❍	2 ❍	8 ❍	9 ❍
e Less expensive to do study in host developing country than in the U.S.	1 ❍	2 ❍	8 ❍	9 ❍
f Host country researchers asked for U.S. collaboration	1 ❍	2 ❍	8 ❍	9 ❍
g Research question relevant to U.S. strategic interests in the region	1 ❍	2 ❍	8 ❍	9 ❍
h Marketing approval for drug or device will be sought in host country	1 ❍	2 ❍	8 ❍	9 ❍
i Interest in addressing global inequalities in health	1 ❍	2 ❍	8 ❍	9 ❍
j Other *(Please specify)* _____ _____	1 ❍	2 ❍	8 ❍	9 ❍

The following questions relate to review by Institutional Review Boards (IRBs). Institutional Review Boards are formally constituted human subjects research ethics review boards.

B17 Did your study undergo IRB review in the U.S.?

Yes ***(Please continue)*** . . . . . 1 ❍
No ***(Please skip to question B20)*** . . . . . 2 ❍
Don't know ***(Please skip to question B20)*** . 8 ❍
Not applicable
(Please skip to question B20) . . . . . .9 ❍

B17a How many U.S. IRBs reviewed your study?

One	1 ❍
Two	2 ❍
Three	3 ❍
Four	4 ❍
Five	5 ❍
Six	6 ❍
Greater than 6	7 ❍
Don't know	8 ❍

B18 Please indicate if any of the following issues were raised by the U.S. IRB(s) in its review of this index study protocol.

	Yes	No	Don't know	Not applicable
ⓐ Relevance of research question to country where research is conducted and/or rationale for doing study outside the U.S.	1 ❍	2 ❍	8 ❍	9 ❍
ⓑ Complexity of language on consent form	1 ❍	2 ❍	8 ❍	9 ❍
ⓒ Cultural appropriateness of study procedures	1 ❍	2 ❍	8 ❍	9 ❍
ⓓ Need for local language consent form	1 ❍	2 ❍	8 ❍	9 ❍
ⓔ Need for letters of approval from developing country representatives	1 ❍	2 ❍	8 ❍	9 ❍
ⓕ Intervention was considered too risky	1 ❍	2 ❍	8 ❍	9 ❍
ⓖ Appropriateness of procedures for control group	1 ❍	2 ❍	8 ❍	9 ❍
ⓗ Confidentiality protections for participants were not adequate	1 ❍	2 ❍	8 ❍	9 ❍
ⓘ Participant voluntariness may be compromised because of benefits study provides	1 ❍	2 ❍	8 ❍	9 ❍
ⓙ Use of placebos	1 ❍	2 ❍	8 ❍	9 ❍
ⓚ Availability of intervention (if successful) to host country after study is over	1 ❍	2 ❍	8 ❍	9 ❍
ⓛ Political considerations *(Please specify)* _____ _____	1 ❍	2 ❍	8 ❍	9 ❍
ⓜ Other *(Please specify)* _____ _____	1 ❍	2 ❍	8 ❍	9 ❍

B19 How long did it take to obtain U.S. IRB approval for this research?

- Less than 1 month . . . . . 1 ❍
- 1 to 2 month . . . . . 2 ❍
- 3 to 6 months . . . . . 3 ❍
- More than 6 months . . . . . 4 ❍
- Don't know . . . . . 8 ❍

The following questions concern documents which are sometimes required by U.S. federal regulations. The term Single Project Assurance (SPA) refers to a written document signed by government officials in the country in which the research is conducted. This document is intended to assure that an institution collaborating with U.S. researchers agrees to follow specific ethical review procedures mandated by U.S. federal regulations.

Thinking of the same "index" research project, please answer the following questions.

B20 Did you obtain a Single Project Assurance (SPA) for this project?

- Yes . . . . . 1 ❍
- No ***(Please skip to question B25)*** . . . . . 2 ❍
- Don't know ***(Please skip to question B25)*** . . . . . 8 ❍
- Not Applicable ***(Please skip to question B25)*** . . . . . 9 ❍

If you did not obtain an SPA, please skip to question B25.

B21 How long did it take to obtain the SPA?

- Less than 1 month . . . . . 1 ❍
- 1 to 2 months. . . . . 2 ❍
- 3 to 6 months . . . . . 3 ❍
- Greater than 6 months . . . . . 4 ❍
- Don't know . . . . . 8 ❍

B22 Did you encounter resistance on the part of developing country officials to agreeing to an SPA?

- Yes . . . . . 1 ❍
- No . . . . . 2 ❍
- Don't know . . . . . 8 ❍
- Not Applicable . . . . . 9 ❍

B23 Did you encounter resistance on the part of developing country officials to U.S. requirements for IRB composition?

- Yes . . . . . 1 ❍
- No . . . . . 2 ❍
- Don't know . . . . . 8 ❍
- Not Applicable . . . . . 9 ❍

B24 Did you consider the SPA process valuable in ensuring that a developing country ethics review was carried out?

Yes . . . . . 1 ❍
No . . . . . 2 ❍
Don't know . . . . . 8 ❍
Not Applicable . . . . . 9 ❍

B25 Did this study have a Data Safety and Monitoring Board (DSMB)?

Yes . . . . . 1 ❍
No ***(Please skip to section C)*** . . . . . 2 ❍
Don't know ***(Please skip to section C)*** . . 8 ❍

If this study did not have a Data Safety and Monitoring Board, please skip to section C.

B26 Were you made aware of results of DSMB meetings?

Never . . . . . 1 ❍
Sometimes . . . . . 2 ❍
Always . . . . . 3 ❍
Don't know . . . . . 8 ❍
Not applicable . . . . . 9 ❍

B27 Did ethics issues arise in DSMB review of the study (e.g., medical care offered to participants)?

Yes . . . . . 1 ❍
No . . . . . 2 ❍
Don't know . . . . . 8 ❍
Not Applicable . . . . . 9 ❍

C Developing country IRBs and other ethical review

We would like to find out about your experiences with ethical review in developing countries. The term "developing country IRB" refers to ethics boards in the country where research is conducted.

Please Note:
In order to receive the $25 payment for completing the survey you must fill out every question with a black dot ●.

C1 Did your study undergo review by the Ministry or Department of Health in the country where the research is/was conducted?

Yes . . . . . 1 ❍
No . . . . . 2 ❍
Don't know . . . . . .8 ❍
Not applicable . . . . . .9 ❍

C2 Did this study undergo some type of ethics review by an IRB, ethics board or Ministry of Health in the country where the research is/was conducted?

Yes ***(Please continue)*** . . . . . 1 ❍
No ***(Please skip to section D)*** . . . . . 2 ❍
Don't know ***(Please skip to section D)*** . . .8 ❍
Not applicable ***(Please skip to section D)*** .9 ❍

C2a In the country where research was conducted, was your study reviewed by the following:

	Yes	No	Don't know	Not applicable
a. A national IRB/ethics review board	1 ❍	2 ❍	8 ❍	9 ❍
b. State/provincial IRB/ethics review board	1 ❍	2 ❍	8 ❍	9 ❍
c. Collaborating/local institution IRB/ethics review board	1 ❍	2 ❍	8 ❍	9 ❍
d. Other in-country ethics review board	1 ❍	2 ❍	8 ❍	9 ❍

(If yes, please specify) _____

_____

C3a Was any of this developing country ethics review required by U.S. institution/regulations?

Yes . . . . . 1 ❍
No . . . . . 2 ❍
Don't know . . . . . 8 ❍
Not applicable . . . . . .9 ❍

C3b Required by developing country institution/ regulations?

Yes . . . . . 1 ❍
No . . . . . 2 ❍
Don't know . . . . . 8 ❍
Not applicable . . . . . .9 ❍

C4 Please indicate if any of the following issues arose during any of the developing country IRB or ethics board reviews of this study

	Yes	No	Don't know	Not applicable
(a) Relevance of research question to country where research is conducted and/or questioned why research done outside U.S.	1 ❍	2 ❍	8 ❍	9 ❍
(b) Cultural appropriateness of study procedures	1 ❍	2 ❍	8 ❍	9 ❍
(c) Complexity of language on consent form	1 ❍	2 ❍	8 ❍	9 ❍
(d) Need for local language consent form	1 ❍	2 ❍	8 ❍	9 ❍
(e) Need for letters of approval from developing country representatives	1 ❍	2 ❍	8 ❍	9 ❍
(f) Intervention was considered too risky	1 ❍	2 ❍	8 ❍	9 ❍
(g) Appropriateness of procedures for control group	1 ❍	2 ❍	8 ❍	9 ❍
(h) Confidentiality protections for participants were not adequate	1 ❍	2 ❍	8 ❍	9 ❍
(i) Participant voluntariness may be compromised because of benefits provided through study	1 ❍	2 ❍	8 ❍	9 ❍
(j) Use of placebos	1 ❍	2 ❍	8 ❍	9 ❍
(k) Availability of intervention (if successful) to host country after study is over.	1 ❍	2 ❍	8 ❍	9 ❍
(l) Political considerations *(Please describe)* _____ _____	1 ❍	2 ❍	8 ❍	9 ❍
(m) Other *(Please describe)* _____ _____	1 ❍	2 ❍	8 ❍	9 ❍

C5 How long did it take to obtain all developing country ethics board or IRB approval for this research?

- Less than 1 month . . . . . 1 ❍
- 1 to 2 months . . . . . 2 ❍
- 3 to 6 months . . . . . 3 ❍
- More than 6 months . . . . . 4 ❍
- Don't know . . . . . 8 ❍

C6 For this index study, was one or more developing country IRB or ethics boards established because of the US requirements?

- Yes . . . . . 1 ❍
- No . . . . . 2 ❍
- Don't know . . . . . 8 ❍
- Not Applicable. . . . . 9 ❍

D Consent

Thinking of the same "index" research study, please answer the following questions about the informed consent process.

Please Note:
In order to receive the $25 payment for completing the survey you must fill out every question with a black dot ●.

D1 Which of the following methods of informing participants and/or documenting consent did you use for this research project? *(Please check all that apply)*

	Yes	No	Don't know	Not applicable
a Written informed consent, requiring a signature, thumbprint, or equivalent	1 ❍	2 ❍	8 ❍	9 ❍
b Pictorial descriptions of study or study procedures	1 ❍	2 ❍	8 ❍	9 ❍
c Oral consent with a witness signature	1 ❍	2 ❍	8 ❍	9 ❍
d Community meeting to describe the study	1 ❍	2 ❍	8 ❍	9 ❍
e Approval from a village or community leader	1 ❍	2 ❍	8 ❍	9 ❍
f In research with adults, approval or consent from another family member	1 ❍	2 ❍	8 ❍	9 ❍
g Explanation and question and answer session with participants (either individually or in groups)	1 ❍	2 ❍	8 ❍	9 ❍
h Video to explain study	1 ❍	2 ❍	8 ❍	9 ❍
i Test of participant understanding of research before enrollment	1 ❍	2 ❍	8 ❍	9 ❍
j Other methods *(Please describe)* _____	1 ❍	2 ❍	8 ❍	9 ❍

_____

_____

_____

_____

Thinking of the same "index" study, please indicate if the following statements apply. *(Please check one response for each statement)*

		Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Don't know	Not applicable
D2	The informed consent process is focused too much on the individual rather than on the family and/or community.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
D3	Participants often do not understand the concept of a placebo.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
D4	Study participants are usually aware that they are in a research study.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
D5	The consent process is an important means of educating participants about the study.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
D6	The consent process provides an opportunity to discuss ethics issues with field staff.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
D7	After learning about the study, some potential participants declined enrollment.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
D8	The formality of going through the informed consent process raises distrust in study participants.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
D9	Local staff shortened or simplified the consent procedures compared to the original protocol.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
D10	Legalistic language was required on consent forms which was not meaningful to study participants.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍

E Relationship with developing country

Thinking again about the "index" study, please respond to the following statements about developing country involvement in your project.

Please Note:
In order to receive the $25 payment for completing the survey you must fill out every question with a black dot ●.

E1 Developing country researchers were/are included in the following research tasks:
(Please check one response for each statement)

	Yes	No	Don't know	Not applicable
(a) initial study design	1 ❍	2 ❍	8 ❍	9 ❍
(b) grant writing	1 ❍	2 ❍	8 ❍	9 ❍
(c) changes in study design	1 ❍	2 ❍	8 ❍	9 ❍
(d) recruitment of participants	1 ❍	2 ❍	8 ❍	9 ❍
(e) drafting consent form	1 ❍	2 ❍	8 ❍	9 ❍
(f) consent discussions with participants	1 ❍	2 ❍	8 ❍	9 ❍
(g) training of research personnel	1 ❍	2 ❍	8 ❍	9 ❍
(h) drafting manuscripts	1 ❍	2 ❍	8 ❍	9 ❍
(i) data analysis	1 ❍	2 ❍	8 ❍	9 ❍
(j) listed as authors on papers	1 ❍	2 ❍	8 ❍	9 ❍

E2 Will some of the resources or research infrastructure established for this study remain in the developing country after study has ended?

Yes . . . . . 1 ❍
No ***(Skip to question E3)*** . . . . . 2 ❍
Don't know ***(Skip to question E3)*** . . . . . 8 ❍
Not Applicable ***(Skip to question E3)*** . . 9 ❍

E2a If E2 answer is "Yes", please check all that apply

	Yes	No	Don't know	Not applicable
a. Personnel who were trained or who acquired skills on this research project	1 ❍	2 ❍	8 ❍	9 ❍
b. Medical, laboratory, or office equipment	1 ❍	2 ❍	8 ❍	9 ❍

	Yes	No	Don't know	Not applicable
c. Medical, laboratory, office, or pharmaceutical supplies	1 ❍	2 ❍	8 ❍	9 ❍
d. Computers or data management system	1 ❍	2 ❍	8 ❍	9 ❍
e. Buildings, laboratory facilities or renovations	1 ❍	2 ❍	8 ❍	9 ❍
f. Power generating equipment, water system, or motor vehicles	1 ❍	2 ❍	8 ❍	9 ❍
g. Organizational structure for health care or research	1 ❍	2 ❍	8 ❍	9 ❍
h. Other *(Please specify)* _____	1 ❍	2 ❍	8 ❍	9 ❍

E3 Is this index study an intervention study?

Yes . . . . . 1 ❍
No ***(Skip to section F)*** . . . . . 2 ❍
Don't know ***(Skip to section F)*** . . . . . 8 ❍
Not Applicable ***(Skip to section F)*** . . . . 9 ❍

E4 Has the study shown the intervention to be efficacious?

Yes . . . . . 1 ❍
Don't know . . . . . 8 ❍
No ***(Skip to section F)*** . . . . . 2 ❍
Not Applicable ***(Skip to section F)*** . . . . 9 ❍

E5 Was the intervention provided, OR will it be provided, if successful, to study participants or to any other host country residents at the conclusion of the study?

Yes . . . . . 1 ❍
No ***(Skip to section F)*** . . . . . 2 ❍
Don't know ***(Skip to section F)*** . . . . . 8 ❍
Not Applicable ***(Skip to section F)*** . . . . 9 ❍

E6 To whom was (or will) the intervention be provided?

Placebo or control group of study . . . 1 ❍
Entire study population . . . . . 2 ❍
Community from which the study population comes . . . . . 3 ❍
Certain regions of host country . . . . . 4 ❍
Entire host country . . . . . 5 ❍
Other *(Please specify)* . . . . . 6 ❍

_____

Don't know . . . . . 8 ❍

E7 What parties were (or will be) part of the arrangement to provide the intervention? *(Please check all that apply)*

U.S. research team carrying out this study . . . . . 1 ❍
U.S. institution carrying out this study . . . .2 ❍
U.S. funding agency for this study . . .3 ❍
International agency (e.g. WHO, UNICEF) . . . . . .4 ❍
Host country research team . . . . . .5 ❍
Host country government, including Ministry of Health . . . . 6 ❍
Host country institution (e.g. university, NGO, clinical center) . . . . . 7 ❍
Private for-profit company . . . . . .9 ❍
Private foundation . . . . . .10 ❍
Other *(Please specify)* . . . . . 11 ❍

_____

Don't know . . . . . 8 ❍

E8 How long was (or will) the intervention be provided?

Less than one year . . . . . 1 ❍
Two to five years . . . . . 2 ❍
Greater than 5 years . . . . . 3 ❍
Other *(Please specify)* . . . . . 4 ❍

_____

Don't know . . . . . 8 ❍

E9 How was (or will) the intervention be paid for? *(Please check all that apply)*

By research grant for this study . . . . . 1 ❍
By U.S. institution carrying out this study . . . . . .2 ❍
By U.S. funding agency for this study . . . . . 3 ❍
By international agency . . . . . 4 ❍
By host country government . . . . . 5 ❍
By host country institution . . . . . 6 ❍
By private for-profit company . . . . . 7 ❍
By private foundation . . . . . 9 ❍
Other *(Please specify)* . . . . . 10 ❍

_____

Don't know . . . . . 8 ❍

F Ethical issues in international research

The following statements have been made by some researchers in discussing research in developing countries. Thinking of the "index" study, please indicate whether you think these statements are True, Sometimes True, or False.

Please Note:
In order to receive the $25 payment for completing the survey you must fill out every question with a black dot ●.

		True	Sometimes True	False	Don't know	Not applicable
F1	Medical care provided to participants in this study generally is not available to local population outside the study.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
F2	Study gathered potentially sensitive or stigmatizing information about participants (e.g., HIV+ status; domestic violence).	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
F3	Study participants have unrealistic hopes about personal benefit from study participation (e.g. think their disease will be cured).	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
F4	The standard of medical care in the host country may be much lower than that of funding country, creating difficulties in establishing appropriate procedures for the control group.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
F5	Participants join because of the desire for compensation, medical care or other benefits.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
F6	Research priorities of the outside agency that is funding the study are not congruent with top priorities of developing country.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
F7	Treatment or intervention being tested is unlikely to be available to most citizens of developing country in the foreseeable future.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍

	True	Sometimes True	False	Don't know	Not applicable
F8 There is inadequate true community representation on the local IRBs /ethics boards for this study.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
F9 Religious beliefs and/or cultural norms of study population are inconsistent with the practice of individual decision-making.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
F10 Ethics issues are rarely discussed with field staff on this research project.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍

G. U.S. and international human subjects regulations and guidelines

These are general statements about U.S. regulations and about ethical review in developing country research. Thinking of all the developing country projects you have worked on, not just the "index case," please answer the following questions about ethics regulations and guidelines.

Please Note:
In order to receive the $25 payment for completing the survey you must fill out every question with a black dot ●.

	Never	Some-times	Always	Don't know	Not applicable
G1 U.S. human subjects regulations are flexible where they need to be.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
G2 Developing country collaborators rely on U.S. ethics regulations for guidance.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
G3 U.S. IRBs are more concerned with politics than they are with protecting the interests of research subjects.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
G4 The current U.S. rules and regulations governing human subjects ensure high ethical standards in research.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
G5 U.S. IRB regulations are insensitive to local cultural norms and traditions outside the U.S.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
G6 Developing country IRBs are more concerned with politics than they are with protecting the interests of research subjects.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
G7 Developing country IRBs have voiced concerns to me about the costs associated with the IRB carrying out its work.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
G8 National guidelines in developing countries are effective in protecting research subjects.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍

	Yes	No	Don't know	Not applicable
GA1 Have you ever had to abandon a research project because it was impossible to get U.S. IRB approval despite modifications?	1 ❍	2 ❍	8 ❍	9 ❍
GA2 Have you ever had to abandon a research project because it was impossible to obtain an SPA?	1 ❍	2 ❍	8 ❍	9 ❍
GA3 Have you ever had to abandon a research project because it was impossible to get developing country IRB approval despite modifications?	1 ❍	2 ❍	8 ❍	9 ❍

H Recommendations

Please indicate if you agree with any of the following statements. Also, feel free to elaborate on these or any other questions in the final section of the survey.

Please Note:
In order to receive the $25 payment for completing the survey you must fill out every question with a black dot ●.

		Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Don't know	Not applicable
H1	U.S. regulations should allow more flexibility in ways of documenting informed consent (e.g. non-written methods).	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H2	Formal individual consent should not be necessary for observational studies.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H3	Where appropriate, community leaders' approval should be required by U.S. IRBs, in addition to individual informed consent.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H4	A mechanism to measure participants' understanding should be built into any research study.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H5	Research funding agencies should provide funding to support the work of developing country IRBs.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H6	International guidelines (e.g., CIOMS) should be used instead of U.S. rules and regulations.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H7	A developing country ethical review should be required for all studies.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H8	The composition of ethics review boards used in developing countries should not be dictated by U.S. regulations.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H9	The single project assurance (SPA) requirement should be eliminated.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Don't know	Not applicable
H10 The issue of what standard of medical care to provide to study participants should be decided on a case-by-case basis.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H11 Some research funds for piloting consent forms should be released before final IRB approval is obtained.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H12 U.S. researchers should be required to make data from research study directly available to study population after study is over.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H13 Research to test an intervention should not be carried out in a developing country unless the intervention, if found to be successful, will be made available to that country at the conclusion of the study.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H14 International policy regarding research should require researchers to establish a mechanism for continuing delivery of medical care after completion of the study.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍

J Finally, please give us more information about yourself

Please Note:
In order to receive the $25 payment for completing the survey you must fill out every question with a black dot ●.

J1 Gender:

Female . . . . . 1 ❍
Male . . . . . 2 ❍

J2 Age:

_____ Years

J3 Degree(s) *(Please check all that apply):*

MD, DDS, MBBS, MBChB . . . . . 1 ❍
Ph.D., ScD., DrPH, or PharmD . . . . 2 ❍
RN, CNP, CNM, LPN, NP . . . . . 3 ❍
MPH, MS, MA, MHS . . . . . 4 ❍
BS or BA . . . . . 5 ❍
Other *(Please specify)* . . . . . 6 ❍

_____

J4 What type of institution is your primary employer?

University . . . . . 1 ❍
Government agency (non-military) . 2 ❍
Military . . . . . 3 ❍
Private for-profit research institute/organization . . . . . 4 ❍
Private non-profit research institute/organization . . . . . 5 ❍
Pharmaceutical/biotech . . . . . 6 ❍
Independent consultant . . . . . 7 ❍
Other *(Please specify)* . . . . . 8 ❍

_____

J5 Where is your primary employer located (headquarters)?

U.S. . . . . 1 ❍
Other industrialized country. . . . . 2 ❍
Developing country . . . . . 3 ❍

J6 What percentage of your work is spent on research as compared with teaching, clinical care, administration, or other work?

_____ %

J7 Are you, or have you been in the past, a member of an Institutional Review Board?

Yes . . . . . 1 ❍
No . . . . . 2 ❍

J7a Have you ever resided in a developing nation for 6 months or more at a time?

Yes . . . . . 1 ❍
No . . . . . 2 ❍

J8 Please elaborate on any of the questions that you feel require more detailed responses.

J9 Please describe changes that you would make to the existing U.S. policy and regulations regarding human subjects research in developing countries.

J10 Would you be willing to participate in a half hour in-depth interview with one of our project team to discuss these issues? Transcripts of interviews will not contain your name or institution, and specific place names will be replaced with region names where necessary, to protect your confidentiality.

❍ Yes

❍ No

Please provide us with a mailing address on the last page of this booklet, where we may send you a $25 check for completing the survey. Any contact information you give us will be separated from the completed survey, so that your survey responses will remain confidential.

Thank you for your participation

K Contact Information

Please provide us with a mailing address where we may send you a $25 check for completing the survey. Any contact information you give us will be separated from the completed survey, so that your survey responses will remain confidential.

Name _____

Address _____

City _____ State _____

Zip/Country Code _____

Country_____

APPENDIX C

Demographically Developing Countries:

China
India

Other Asia and Islands (OAI):

American Samoa
Bangladesh
Bhutan
Brunei Darussalam
Cambodia
Cook Islands
Fiji
French Polynesia
Guam
Indonesia
Johnston Island
Kiribati
Korea, Democratic People's Republic of
Korea, Republic of
Lao, People's Democratic Republic
Macao
Malaysia
Maldives
Marshall Islands
Mauritius
Micronesia, Federated States of
Midway Island
Mongolia
Myanmar
Nauru
Nepal
New Caledonia
Niue
Northern Mariana Islands
Palau
Papua New Guinea
Philippines
Pitcairn Island
Reunion
Seychelles
Singapore
Solomon Islands
Sri Lanka
Taiwan, China
Thailand
Tokelau Island
Tonga
Tuvalu
Vanuatu
Viet Nam
Wake Island
Wallis and Futuna Islands
Western Samoa

Sub-Saharan Africa (SSA):

Angola
Ascension
Benin
Botswana
Burkina Faso
Burundi
Cameroon
Cape Verde
Central African Republic
Chad
Comoros
Congo
Côte d'Ivoire
Djibouti
Equatorial Guinea
Eritrea
Ethiopia
Gabon
Gambia, The
Ghana
Guinea
Guinea-Bissau
Kenya
Lesotho
Liberia
Madagascar
Malawi
Mali
Mauritania
Mayotte
Mozambique
Namibia
Niger
Nigeria
Rwanda
Saint Helena
Sao Tome and Principe
Senegal
Sierra Leone
Somalia
South Africa
Sudan
Swaziland
Tanzania, United Republic of
Togo
Tristan de Cunha
Uganda
Zaire
Zambia
Zimbabwe

Latin America and the Caribbean (LAC):

Anguila
Antigua and Barbuda
Argentina
Aruba
Bahamas, The
Barbados
Belize
Bolivia
Brazil
British Virgin Island
Cayman Islands
Chile
Colombia
Costa Rica

Cuba
Dominica
Dominican Republic
Ecuador
El Salvador
Falkland/Malvinas Islands
French Guiana
Grenada
Guadeloupe
Guatemala
Guyana
Haiti
Honduras
Jamaica
Martinique
Mexico
Montserrat
Netherlands Antilles
Nicaragua
Panama
Paraguay
Peru
Puerto Rico
Saint Kitts and Nevis
Saint Lucia
Saint Vincent and the Grenadines
Suriname
Trinidad and Tobago
Turks and Calcos Islands
Uruguay
U.S. Virgin Islands
Venezuela

Middle Eastern Crescent (MEC):

Afghanistan
Algeria
Armenia
Azerbaijan
Bahrain
Cyprus
Egypt
Former Spanish Sahara
Georgie
Iran, Islamic Republic of
Iraq
Israel
Jordan
Kazakhstan
Kuwait
Kyrgyzstan
Lebanon
Libyan Arab Jamahiriya
Malta
Morocco
Oman
Pakistan
Qatar
Saudi Arabia
Syrian Arab Republic
Tajikstan
Tunisia
Turkey
Turkmenistan
United Arab Emirates
Uzbekistan
West Bank and Gaza
Yemen

Source:

WHO Ad Hoc Committee on Health Research Relating to Future Intervention Options. *Investing in Health Research and Development.* World Health Organization, Geneva, Switzerland, September 1996.

APPENDIX D

Survey of Developing Country Researchers' Experiences with and Attitudes Towards Human Subjects Regulations

OMB no. 0925-0472
Expiration date 9/30/2002
ID Code No. _____

Survey of Developing Country Researchers' Experiences with and Attitudes towards Human Subjects Regulations

A survey conducted by the U.S. National Bioethics Advisory Commission

by

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Please direct questions concerning this survey to Dr. A Hyder

A Introduction

This survey is designed to collect information from researchers who have carried out research involving human subjects in developing countries. ***If you have not conducted research in a developing country, please do not complete this survey.***

A1 Are you currently involved in a study in the developing world that requires human subjects?

Yes ***(Please skip to question A2)*** . . . . . 1 ❍
No . . . . . 2 ❍

A1a If no, have you been involved in a study in the developing world that requires human subjects:

Within the past five years . . . . . 2 ❍
More than five years ago . . . . . 3 ❍
Never ***(Please do not complete this survey)*** . 1 ❍

If your answer to question A1a. is "never" please do not complete this survey. Thank you for your time.

A2 How many years total have you been conducting human subjects research in developing countries?

_____ Years

A3 How many studies (total) in developing countries have you been involved in?

1 . . . . . 1 ❍
2 to 4 . . . . . 2 ❍
5 to 10 . . . . . 3 ❍
Greater than 10 . . . . . 4 ❍

A4 In what regions of the developing world have you conducted research? *(Check all that apply)*

Asia . . . . . 1 ❍
Africa . . . . . 2 ❍
Pacific Islands . . . . . 3 ❍
South America . . . . . 4 ❍
Central America/Mexico . . . . . 5 ❍
Caribbean . . . . . 6 ❍
Other (*Please specify)* . . . . . 7 ❍

_____

A5 During the *last year,* in what country have you lived most of the time?

_____

B Developing Country Research Project

We would like to find out about your experience with a developing country research study on which are currently working or have worked in the last five years. If you conducted human subjects research more than five years ago, please proceed to Section G (skip Sections C, D, E & F)

B0 In the last five years, have you either collaborated with U.S. investigators on a research project, **OR** received U.S. funds directly for your research?

Yes . . . . . 1 ❍
If "Yes," thinking of a project which has involved either direct U.S. funding or U.S. collaboration, please answer the following questions about the study. We will refer to this study as the "index study."

No . . . . . 2 ❍
If "No," please consider the project on which you have spent the most time during the last five years, and respond to the following questions. We will refer to this study as the "index study."

B1 In what country was/is this study?

_____

B2 To date, how long have you been working on this study?

Less than 1 year . . . . . 1 ❍
1 to 2 years . . . . . 2 ❍
2 to 5 years . . . . . 3 ❍
Greater than 5 years . . . . . 4 ❍

B3 Is the study still ongoing (data collection and/or analysis)?

Yes . . . . . 1 ❍
No . . . . . 2 ❍
Don't know . . . . . 8 ❍

B4 What topic(s) is/was this study investigating? *(Check all that apply)*

Infectious disease, non-HIV/AIDS . 1 ❍
HIV/AIDS . . . . . 2 ❍
Chronic disease . . . . . 3 ❍
Vaccine development/testing . . . . . 4 ❍
Nutrition . . . . . 5 ❍
Cultural practices/behavior . . . . . 6 ❍
Injury . . . . . 7 ❍
Genetics . . . . . 8 ❍
Environmental Health . . . . . 9 ❍
Health Systems/Health Services . . . 10 ❍
Reproductive Health . . . . . 11 ❍
Perinatal Health/Birth defects . . . . 12 ❍
Other *(Please specify)* . . . . . 13 ❍

_____

B5 Which discipline(s) best describes this study? *(Check all that apply)*

- Behavioral science . . . . . 1 ❍
- Epidemiology . . . . . 2 ❍
- Microbiology . . . . . 3 ❍
- Clinical care . . . . . 4 ❍
- Health Services research . . . . . 5 ❍
- Psychology/Mental Health . . . . . 6 ❍
- Anthropology . . . . . 7 ❍
- Ethics . . . . . 8 ❍
- Other *(Please specify)* . . . . . .9 ❍

_____

B6 Which of the following methodological approaches are you using in this study? *(Please check all that apply)*

- Randomized controlled trial . . . . . 1 ❍
- Observational/descriptive study . . . . 2 ❍
- Prospective study . . . . . 3 ❍
- Case-Control . . . . . 4 ❍
- Community-based intervention . . . . 5 ❍
- Operational research/ program evaluation . . . . . 6 ❍
- Qualitative methods . . . . . 7 ❍
- Don't know . . . . . 8 ❍
- Other *(Please specify)* . . . . . 9 ❍

_____

B7 In your opinion, what level of risk does this study involve for participants?

- Minimal Risk . . . . . 1 ❍
- Greater than minimal risk . . . . . 2 ❍
- Don't know . . . . . 8 ❍

B8 What is (are) the source(s) of funding for this study? *(Please check all that apply)*

- U.S. government (non-military) . . . . 1 ❍
- U.S. military . . . . . 2 ❍
- U.S. private company . . . . . 3 ❍
- U.S. non-profit (foundation, NGO) . 4 ❍
- Developing country government . . . 5 ❍
- Developing country private company . . . . . 6 ❍
- Developing country non-profit (foundation, NGO) . . . . . 7 ❍
- European government (non-military) 8 ❍
- European military . . . . . 9 ❍
- European private company . . . . . .10 ❍
- European non-profit (foundation, NGO) . . . . . .11 ❍
- Bilateral organization (SIDA, USAID, etc.) . . . . . .12 ❍
- International organization (WHO, PAHO, UNICEF, etc.) .13 ❍
- Other *(Please specify)* . . . . . .14 ❍

_____

B9 Which of the following best describes your role in this study?

Project Coordinator . . . . . 1 ❍
Co-investigator . . . . . 2 ❍
Principal investigator . . . . . 3 ❍
Other *(Please specify)* . . . . . 4 ❍

_____

B10 Are you or any of your colleagues conversant in a language or dialect of the study participants?

Yes . . . . . 1 ❍
No . . . . . 2 ❍
Not applicable . . . . . 9 ❍

B11 Which of the following groups are included in the study? *(Please check all that apply)*

Non-pregnant women . . . . . 1 ❍
Pregnant women . . . . . 2 ❍
Men . . . . . 3 ❍
Children 1 to 15 . . . . . 4 ❍
Infants (younger than 1) . . . . . 5 ❍
Don't know . . . . . 8 ❍

B12 What is (are) the religious affiliation(s) of study participants? *(Please check all that apply)*

Local indigenous religion . . . . . 1 ❍
Buddhist . . . . . 2 ❍
Muslim . . . . . 3 ❍
Hindu . . . . . 4 ❍
Animist . . . . . 5 ❍
Jewish . . . . . 6 ❍
Christian . . . . . 7 ❍
Don't know . . . . . .8 ❍
None . . . . . .9 ❍
Other *(Please specify)* . . . . . 10 ❍

_____

B13 What level of education is predominant in the study population?

No formal education . . . . . 1 ❍
1 to 6 years of formal schooling . . . . 2 ❍
6 to 12 years of formal schooling . . . 3 ❍
University educated . . . . . .4 ❍
Don't know . . . . . 8 ❍
Other *(Please specify)* . . . . . 5 ❍

_____

B14 What percentage of the study population is literate?

Less than 20% . . . . . 1 ❍
20% to 60% . . . . . 2 ❍
60 to 90% . . . . . 3 ❍
Greater than 90%. . . . . 4 ❍
Don't know . . . . . 8 ❍

B15a On average, each year, how many weeks do you spend at the research site of this "index study"?

2 weeks or less . . . . . 1 ❍
2 to 8 weeks . . . . . 2 ❍
2 to 6 months . . . . . 3 ❍
More than 6 months . . . . . 4 ❍

If the study you are describing received U.S. funds, either directly or through collaboration, please **continue.** ***If not, please*** **skip to section C.**

B16 In your opinion, what were the reasons this study was carried out in the host (developing) country as opposed to in the U.S.?

	Yes	No	Don't know	Not applicable
(a) Prevalence of disease in question is much greater in the host developing country than in the U.S.	1 ❍	2 ❍	8 ❍	9 ❍
(b) Intervention being tested more relevant to host country than to U.S.	1 ❍	2 ❍	8 ❍	9 ❍
(c) Easier to identify a cohort of patients relevant to research question (e.g., patients without prior treatment history)	1 ❍	2 ❍	8 ❍	9 ❍
(d) Recruitment of patients more rapid in host country than in U.S.	1 ❍	2 ❍	8 ❍	9 ❍
(e) Less expensive to do study in host developing country than in the U.S.	1 ❍	2 ❍	8 ❍	9 ❍
(f) Host country researchers asked for U.S. collaboration	1 ❍	2 ❍	8 ❍	9 ❍
(g) Research question relevant to U.S. strategic interests in the region	1 ❍	2 ❍	8 ❍	9 ❍
(h) Marketing approval for drug or device will be sought in host country	1 ❍	2 ❍	8 ❍	9 ❍
(i) Interest in addressing global inequalities in health	1 ❍	2 ❍	8 ❍	9 ❍
(j) Other *(Please specify)* _____ _____	1 ❍	2 ❍	8 ❍	9 ❍

The following questions relate to review by Institutional Review Boards (IRBs). Institutional Review Boards are formally constituted human subjects research ethics review boards.

B17 Did your study undergo U.S. IRB review?

Yes *(Please continue)* . . . . . 1 ❍
No *(Please skip to question B20)* . . . . . 2 ❍
Don't know *(Please skip to question B20)* . 8 ❍
Not applicable *(Please skip to question B20)* . . . . . .9 ❍

B17b Are you familiar with or have knowledge of the U.S. review process for this study?

Yes . . . . . 1 ❍
No *(Please skip to section C)* . . . . . 2 ❍

***If you are familiar with the U.S. IRB review process for this study, please* continue. *If not, please* skip to section C.**

B18 Please indicate if any of the following issues were raised by the U.S. IRB in its review of *this* index study protocol.

	Yes	No	Don't know	Not applicable
(a) Relevance of research question to country where research is conducted and/or rationale for doing study outside the U.S.	1 ❍	2 ❍	8 ❍	9 ❍
(b) Cultural appropriateness of study procedures	1 ❍	2 ❍	8 ❍	9 ❍
(c) Complexity of language on consent form	1 ❍	2 ❍	8 ❍	9 ❍
(d) Need for local language consent form	1 ❍	2 ❍	8 ❍	9 ❍
(e) Need for letters of approval from developing country representatives	1 ❍	2 ❍	8 ❍	9 ❍
(f) Intervention was considered too risky	1 ❍	2 ❍	8 ❍	9 ❍
(g) Appropriateness of procedures for control group	1 ❍	2 ❍	8 ❍	9 ❍
(h) Confidentiality protections for participants were not adequate	1 ❍	2 ❍	8 ❍	9 ❍
(i) Participant voluntariness may be compromised because of benefits study provides	1 ❍	2 ❍	8 ❍	9 ❍

	Yes	No	Don't know	Not applicable
(j) Use of placebos	1 ❍	2 ❍	8 ❍	9 ❍
(k) Availability of intervention (if successful) to host country after study is over	1 ❍	2 ❍	8 ❍	9 ❍
(l) Political considerations *(Please describe)* _____ _____	1 ❍	2 ❍	8 ❍	9 ❍
(m) Other *(Please specify)* _____ _____	1 ❍	2 ❍	8 ❍	9 ❍

B19 How long did it take to obtain U.S. IRB approval for this research?

Less than 1 month . . . . . 1 ❍
1 to 2 month . . . . . 2 ❍
3 to 6 months . . . . . 3 ❍
More than 6 months . . . . . 4 ❍
Don't know . . . . . 8 ❍

B20–24. The following questions concern documents which are sometimes required by U.S. federal regulations. The term Single Project Assurance (SPA) refers to a written document signed by government officials in the country in which the research is conducted. This document is intended to assure that an institution collaborating with U.S. researchers agrees to follow specific ethical review procedures mandated by U.S. federal regulations.

Thinking of the same "index" research project, please answer the following questions.

B20 Did you obtain a Single Project Assurance (SPA) for this project?

Yes . . . . . 1 ❍
No ***(Please skip to question B25)*** . . . . . 2 ❍
Don't know
(Please skip to question B25) . . . . . 8 ❍
Not Applicable
(Please skip to question B25) . . . . . 9 ❍

If you did not obtain an SPA, please skip to question B25.

B21 How long did it take to obtain the SPA?

Less than 1 month . . . . . 1 ❍
1 to 2 months. . . . . 2 ❍
3 to 6 months . . . . . 3 ❍
Greater than 6 months . . . . . 4 ❍
Don't know . . . . . 8 ❍

B22 Did you encounter resistance on the part of developing country officials to agreeing to an SPA?

Yes . . . . . 1 ❍
No . . . . . 2 ❍
Don't know . . . . . 8 ❍
Not Applicable . . . . . 9 ❍

B23 Did you encounter resistance on the part of developing country officials to U.S. requirements for IRB composition?

Yes . . . . . 1 ❍
No . . . . . 2 ❍
Don't know . . . . . 8 ❍
Not Applicable . . . . . 9 ❍

B24 Did you consider the SPA process valuable in ensuring that a developing country ethics review was carried out?

Yes . . . . . 1 ❍
No . . . . . 2 ❍
Don't know . . . . . 8 ❍
Not Applicable . . . . . 9 ❍

B25 Did this study have a Data Safety and Monitoring Board (DSMB)?

Yes . . . . . 1 ❍
No ***(Please skip to section C)*** . . . . . 2 ❍
Don't know ***(Please skip to section C)*** . . 8 ❍

If this study did not have a Data Safety and Monitoring Board, please skip to section C.

B26 Were you made aware of results of DSMB meetings?

Never . . . . . 1 ❍
Sometimes . . . . . 2 ❍
Always . . . . . 3 ❍
Don't know . . . . . 8 ❍
Not applicable . . . . . 9 ❍

B27 Did ethics issues arise in DSMB review of the study (e.g., medical care offered to participants)?

Yes . . . . . 1 ❍
No . . . . . 2 ❍
Don't know . . . . . 8 ❍
Not Applicable . . . . . 9 ❍

C Developing country IRBs and other ethical review

We would like to find out about your experiences with ethical review in developing countries. The term "developing country IRB" refers to ethics boards in the country where research is conducted.

C1 Did your study undergo review by the Ministry or Department of Health in the country where the research is/was conducted?

Yes . . . . . 1 ❍
No . . . . . 2 ❍

C2 Did this study undergo some type of ethics review by an IRB, ethics board or Ministry of Health in the country where the research is/was conducted?

Yes ***(Please continue)*** . . . . . 1 ❍
No ***(Please skip to section D)*** . . . . . 2 ❍
Don't know ***(Please skip to section D)*** . . .8 ❍
Not applicable ***(Please skip to section D)*** .9 ❍

C2a In the country where research was conducted, was your study reviewed by the following:

	Yes	No	Don't know	Not applicable
a. A national IRB/ethics review board	1 ❍	2 ❍	8 ❍	9 ❍
b. State/provincial IRB/ethics review board	1 ❍	2 ❍	8 ❍	9 ❍
c. Collaborating/local institution IRB/ethics review board	1 ❍	2 ❍	8 ❍	9 ❍
d. Other in-country ethics review board	1 ❍	2 ❍	8 ❍	9 ❍

(If yes, please specify) _____

_____

C3-1 Was any of this developing country ethics review required by U.S. institutions/regulations?

Yes . . . . . 1 ❍
No . . . . . 2 ❍
Don't know . . . . . 8 ❍
Not applicable . . . . . .9 ❍

C3-2 Required by developing country institutions/ regulations?

Yes . . . . . 1 ❍
No . . . . . 2 ❍
Don't know . . . . . 8 ❍
Not applicable . . . . . .9 ❍

C4 Please indicate if any of the following issues arose during any of the developing country IRB or ethics board reviews of this study

	Yes	No	Don't know	Not applicable
(a) Relevance of research question to country where research is conducted and/or questioned why research done outside U.S.	1 ❍	2 ❍	8 ❍	9 ❍
(b) Cultural appropriateness of study procedures	1 ❍	2 ❍	8 ❍	9 ❍
(c) Complexity of language on consent form	1 ❍	2 ❍	8 ❍	9 ❍
(d) Need for local language consent form	1 ❍	2 ❍	8 ❍	9 ❍
(e) Need for letters of approval from developing country representatives	1 ❍	2 ❍	8 ❍	9 ❍
(f) Intervention was considered too risky	1 ❍	2 ❍	8 ❍	9 ❍
(g) Appropriateness of procedures for control group	1 ❍	2 ❍	8 ❍	9 ❍
(h) Confidentiality protections for participants were not adequate	1 ❍	2 ❍	8 ❍	9 ❍
(i) Participant voluntariness may be compromised because of benefits provided through study	1 ❍	2 ❍	8 ❍	9 ❍
(j) Use of placebos	1 ❍	2 ❍	8 ❍	9 ❍
(k) Availability of intervention (if successful) to host country after study is over.	1 ❍	2 ❍	8 ❍	9 ❍
(l) Political considerations *(Please describe)* _____ _____	1 ❍	2 ❍	8 ❍	9 ❍
(m) Other *(Please describe)* _____ _____	1 ❍	2 ❍	8 ❍	9 ❍

C5 How long did it take to obtain all developing country ethics board or IRB approval for this research?

- Less than 1 month . . . . . 1 ❍
- 1 to 2 months . . . . . 2 ❍
- 3 to 6 months . . . . . 3 ❍
- More than 6 months . . . . . 4 ❍
- Don't know . . . . . 8 ❍

C6 For this index study, was one or more developing country IRB or ethics boards established because of the US requirements?

- Yes . . . . . 1 ❍
- No . . . . . 2 ❍
- Don't know . . . . . 8 ❍
- Not Applicable. . . . . 9 ❍

D Consent

Thinking of the same "index" research study, please answer the following questions about the informed consent process.

D1 Which of the following methods of informing participants and/or documenting consent did you use for this research project? *(Please check one response for each statement.)*

	Yes	No	Don't know	Not applicable
a Written informed consent, requiring a signature, thumbprint, or equivalent	1 ❍	2 ❍	8 ❍	9 ❍
b Pictorial descriptions of study or study procedures	1 ❍	2 ❍	8 ❍	9 ❍
c Oral consent with a witness signature	1 ❍	2 ❍	8 ❍	9 ❍
d Community meeting to describe the study	1 ❍	2 ❍	8 ❍	9 ❍
e Approval from a village or community leader	1 ❍	2 ❍	8 ❍	9 ❍
f In research with adults, approval or consent from another family member	1 ❍	2 ❍	8 ❍	9 ❍
g Explanation and question and answer session with participants (either individually or in groups)	1 ❍	2 ❍	8 ❍	9 ❍
h Video to explain study	1 ❍	2 ❍	8 ❍	9 ❍
i Test of participant understanding of research before enrollment	1 ❍	2 ❍	8 ❍	9 ❍
j Other methods *(Please describe)* _____	1 ❍	2 ❍	8 ❍	9 ❍

Thinking of the same "index" study, please indicate if the following statements apply. *(Please check one response for each statement)*

		Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Don't know	Not applicable
D2	The informed consent process is focused too much on the individual rather than on the family and/or community.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
D3	Participants often do not understand the concept of a placebo.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
D4	Study participants are usually aware that they are in a research study.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
D5	The consent process is an important means of educating participants about the study.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
D6	The consent process provides an opportunity to discuss ethics issues with field staff.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
D7	After learning about the study, some potential participants declined enrollment.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
D8	The formality of going through the informed consent process raises distrust in study participants.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
D9	Local staff shortened or simplified the consent procedures compared to the original protocol.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
D10	Legalistic language was required on consent forms which was not meaningful to study participants.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍

E Relationship with Collaborators

If your "index case" involved collaboration with foreign researchers, please complete this section. *If not, please skip to E3.*

Thinking again about the "index" study, please respond to the following statements about developing country involvement in your project.

E1 Developing country researchers were/are included in the following research tasks:
(Please check one response for each statement)

	Yes	No	Don't know	Not applicable
(a) initial study design	1 ❍	2 ❍	8 ❍	9 ❍
(b) grant writing	1 ❍	2 ❍	8 ❍	9 ❍
(c) changes in study design	1 ❍	2 ❍	8 ❍	9 ❍
(d) recruitment of participants	1 ❍	2 ❍	8 ❍	9 ❍
(e) drafting consent form	1 ❍	2 ❍	8 ❍	9 ❍
(f) consent discussions with participants	1 ❍	2 ❍	8 ❍	9 ❍
(g) training of research personnel	1 ❍	2 ❍	8 ❍	9 ❍
(h) drafting manuscripts	1 ❍	2 ❍	8 ❍	9 ❍
(i) data analysis	1 ❍	2 ❍	8 ❍	9 ❍
(j) listed as authors on papers	1 ❍	2 ❍	8 ❍	9 ❍

E2 Will some of the resources or research infrastructure established for this study remain in the developing country after study has ended?

Yes . . . . . 1 ❍
No ***(Skip to question E3)*** . . . . . 2 ❍
Don't know ***(Skip to question E3)*** . . . . . 8 ❍
Not Applicable ***(Skip to question E3)*** . . 9 ❍

E2a If E2 answer is "Yes", please check all that apply

	Yes	No	Don't know	Not applicable
a. Personnel who were trained or who acquired skills on this research project	1 ❍	2 ❍	8 ❍	9 ❍
b. Medical, laboratory, or office equipment	1 ❍	2 ❍	8 ❍	9 ❍

	Yes	No	Don't know	Not applicable
c. Medical, laboratory, office, or pharmaceutical supplies	1 ❍	2 ❍	8 ❍	9 ❍
d. Computers or data management system	1 ❍	2 ❍	8 ❍	9 ❍
e. Buildings, laboratory facilities or renovations	1 ❍	2 ❍	8 ❍	9 ❍
f. Power generating equipment, water system, or motor vehicles	1 ❍	2 ❍	8 ❍	9 ❍
g. Organizational structure for health care or research	1 ❍	2 ❍	8 ❍	9 ❍
h. Other *(Please specify)* _____	1 ❍	2 ❍	8 ❍	9 ❍

E3 Is this index study an intervention study?

Yes . . . . . .1 ❍
No ***(Skip to section F)*** . . . . . 2 ❍
Don't know ***(Skip to section F)*** . . . . . 8 ❍
Not Applicable ***(Skip to section F)*** . . . . 9 ❍

E4 Has the study shown the intervention to be efficacious?

Yes . . . . . .1 ❍
No ***(Skip to section F)*** . . . . . 2 ❍
Don't know . . . . . 8 ❍❖
Not Applicable ***(Skip to section F)*** . . . . 9 ❍

E5 Was the intervention provided, OR will it be provided, if successful, to study participants or to any other host country residents at the conclusion of the study?

Yes . . . . . .1 ❍
No ***(Skip to section F)*** . . . . . 2 ❍
Don't know ***(Skip to section F)*** . . . . . 8 ❍
Not Applicable ***(Skip to section F)*** . . . . 9 ❍

E6 To whom was (or will) the intervention be provided? *(Please check all that apply)*

Placebo or control group of study . . . 1 ❍
Entire study population . . . . . .2 ❍
Community from which the study population comes . . . . .3 ❍
Certain regions of host country . . . . .4 ❍
Entire host country . . . . . .5 ❍
Other *(Please specify)* . . . . . .6 ❍

_____

Don't know . . . . . .8 ❍

E7a What parties were (or will be) part of the arrangement to provide the intervention? *(Please check all that apply)*

- Foreign research team carrying out this study . . . . . 1 ❍
- Foreign institution carrying out this study . . . . . 2 ❍
- Foreign funding agency for this study . 3 ❍
- International agency (e.g. WHO, UNICEF) . . . . . 4 ❍
- Host country research team . . . . . 5 ❍
- Host country government, including Ministry of Health . . . . 6 ❍
- Host country institution (e.g. university, NGO, clinical center) . . . . . 7 ❍
- Private for-profit company . . . . . 9 ❍
- Private foundation . . . . . 10 ❍
- Other *(Please specify)* . . . . . 11 ❍

_____

- Don't know . . . . . 8 ❍

E8 How long was (or will) the intervention be provided?

- Less than one year . . . . . 1 ❍
- Two to five years . . . . . 2 ❍
- Greater than 5 years . . . . . 3 ❍
- Other *(Please specify)* . . . . . 4 ❍

_____

- Don't know . . . . . 8 ❍

E9a How was (or will) the intervention be paid for? *(Please check all that apply)*

- By research grant for this study . . . . . 1 ❍
- By foreign institution carrying out this study . . . . . .2 ❍
- By foreign funding agency for this study . . . . . 3 ❍
- By international agency . . . . . 4 ❍
- By host country government . . . . . 5 ❍
- By host country institution . . . . . 6 ❍
- By private for-profit company . . . . . 7 ❍
- By private foundation . . . . . 9 ❍
- Other *(Please specify)* . . . . . 10 ❍

_____

- Don't know . . . . . 8 ❍

F Ethical issues in international research

The following statements have been made by some researchers in discussing research in developing countries. Thinking of the "index" study, please indicate whether you think these statements are True, Sometimes True, or False.

	True	Sometimes True	False	Don't know	Not applicable
F1 Medical care provided to participants in this study generally is not available to local population outside the study.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
F2 Study gathered potentially sensitive or stigmatizing information about participants (e.g., HIV+ status; domestic violence).	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
F3 Study participants have unrealistic hopes about personal benefit from study participation (e.g. think their disease will be cured).	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
F4 The standard of medical care in the host country may be much lower than that of funding country, creating difficulties in establishing appropriate procedures for the control group.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
F5 Participants join because of the desire for compensation, medical care or other benefits.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
F6 Research priorities of outside funding agencies that are funding the study are not congruent with top priorities of developing country.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
F7 Treatment or intervention being tested is unlikely to be available to most citizens of country where research is conducted in the foreseeable future.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍

	True	Sometimes True	False	Don't know	Not applicable
F8 There is inadequate true community representation on the local IRBs /ethics boards for this study.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
F9 Religious beliefs and/or cultural norms of study population are inconsistent with the practice of individual decision-making.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
F10 Ethics issues are rarely discussed with field staff on this research project.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍

G. Ethical guidelines and regulations in human subjects research

Thinking of all the developing country projects you have worked on, not just the "index case," please answer the following questions about ethics regulations and guidelines.

If you have NEVER received U.S. funds directly or collaborated on a research project with a U.S. institution, please skip to question G6.

General statements about U.S. regulations and about ethical review in developing country research. Please indicate how much you think the following general statements are accurate when describing the application of U.S. human subjects regulations to research in developing countries.

	Never	Some-times	Always	Don't know	Not applicable
G1 U.S. human subjects regulations are flexible where they need to be.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
G2 Developing country collaborators rely on U.S. ethics regulations for guidance.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
G3 U.S. IRBs are more concerned with politics than they are with protecting the interests of research subjects.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
G4 The current U.S. rules and regulations governing human subjects ensure high ethical standards in research.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
G5 U.S. IRB regulations are insensitive to local cultural norms and traditions outside the U.S.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍

The following questions concern ethics review in developing countries.

		Yes	No	Don't know	Not applicable
GA1	Have you ever had to abandon a research project because it was impossible to get U.S. IRB approval despite modifications?	1 ❍	2 ❍	8 ❍	9 ❍
GA2	Have you ever had to abandon a research project because it was impossible to obtain an SPA?	1 ❍	2 ❍	8 ❍	9 ❍

			Yes	No	Don't know	Not applicable
G6	Developing country IRBs are more concerned with politics than they are with protecting the interests of research subjects.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
G7	Developing country IRBs have voiced concerns to me about the costs associated with the IRB carrying out its work.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍
G8	National guidelines in developing countries are effective in protecting research subjects.	1 ❍	2 ❍	3 ❍	8 ❍	9 ❍

		Yes	No	Don't know	Not applicable
GA3	Have you ever had to abandon a research project because it was impossible to get developing country IRB approval despite modifications?	1 ❍	2 ❍	8 ❍	9 ❍

H Recommendations

Please indicate if you agree with any of the following statements. Also, feel free to elaborate on these or any other questions in the final section of the survey.

		Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Don't know	Not applicable
H1	Human subjects regulations should allow more flexibility in ways of documenting informed consent *(e.g. non-written methods)*.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H2	Formal individual consent should not be necessary for observational studies.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H3	Where appropriate, community leaders' approval should be required by IRBs, in addition to individual informed consent.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H4	A mechanism to measure participants' understanding should be built into any research study.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H5	Research funding agencies should provide funding to support the work of developing country IRBs.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H6	International guidelines (e.g., CIOMS) should be used instead of U.S. rules and regulations.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H7	A developing country ethical review should be required for all studies.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H8	The composition of ethics review boards used in developing countries should not be dictated by U.S. regulations.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H9	The single project assurance (SPA) requirement should be eliminated.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍

		Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Don't know	Not applicable
H10	The issue of what standard of medical care to provide to study participants should be decided on a case-by-case basis.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H11	Some research funds for piloting consent forms should be released before final IRB approval is obtained.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H12a	Researchers should be required to make data from research study directly available to study population after study is over.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H13	Research to test an intervention should not be carried out in a developing country unless the intervention, if found to be successful, will be made available to that country at the conclusion of the study.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍
H14	International policy regarding research should require researchers to establish a mechanism for continuing delivery of medical care after completion of the study.	1 ❍	2 ❍	3 ❍	4 ❍	5 ❍	8 ❍	9 ❍

J Finally, please give us more information about yourself

J1 Gender:

Female . . . . . 1 ❍
Male . . . . . 2 ❍

J2 Age:

_____ Years

J3 Degree(s) *(Please check all that apply):*

MD, DDS, MBBS, MBChB . . . . . 1 ❍
Ph.D., ScD., DrPH, or PharmD . . . . 2 ❍
RN, CNP, CNM, LPN, NP . . . . . 3 ❍
MPH, MS, MA, MHS . . . . . 4 ❍
BS or BA . . . . . 5 ❍
Other *(Please specify)* . . . . . 6 ❍

_____

J4 What type of institution is your primary employer?

University . . . . . 1 ❍
Government agency (non-military) . 2 ❍
Military . . . . . 3 ❍
Private for-profit research institute/organization . . . . . 4 ❍
Private non-profit research institute/organization . . . . . 5 ❍
Pharmaceutical/biotech . . . . . 6 ❍
Independent consultant/ self employed . . . . . 7 ❍
Other *(Please specify)* . . . . . 8 ❍

_____

J5 Where is your primary employer located (headquarters)?

U.S. . . . . 1 ❍
Other industrialized country. . . . . 2 ❍
Developing country . . . . . 3 ❍

J6 What percentage of your work is spent on research as compared with teaching, clinical care, administration, or other work?

_____ %

J7 Are you, or have you been in the past, a member of an Institutional Review Board?

Yes . . . . . 1 ❍
No . . . . . 2 ❍

J8 Please elaborate on any of the questions that you feel require more detailed responses. *(Please identify the question number specifically)*

J9 Please describe changes that you would make to the existing U.S. policy and regulations regarding human subjects research in developing countries.

J10 Would you be willing to participate in a half hour in-depth interview with one of our project team to discuss these issues? Transcripts of interviews will not contain your name or institution, and specific place names will be replaced with region names where necessary, to protect your confidentiality.

❍ Yes

❍ No

Telephone Number _____

K Contact Information

Please provide us with a mailing address where we may send you a US $25 payment for completing the survey. Any contact information you give us will be separated from the completed survey, so that your survey responses will remain confidential.

Name _____

Address _____

_____

City _____ Country_____

Thank you for your participation

APPENDIX E

Focus Group Guide

I. Introductions

1. What do you do?
2. What countries have you worked in? For how long?
3. Generally, what types of studies?
4. *Were your studies done in collaboration with American researchers? Researchers from other countries?*

II. In-Country Review of Studies

1. Generally, do your studies need to go through an ethics review in your country before you start a study?
2. If so, how many in-country IRBs or ethics boards did you need to go through? Is ethics review separate from or combined with scientific review?
3. Did boards exist or did they need to be established for your study? Because of U.S. requirements or not? Was composition or procedures of the board influenced by U.S. regulations?
4. Generally, how well did the process work? How meaningful was the ethics review?
5. Substance of review: were you asked mostly about administrative details, or about issues you thought related to human subjects' protections and ethics?

III. U.S. (or other countries') Review

1. Generally, do your studies need to go through an ethics review (IRB or equivalent) *by your collaborator's country, such as the United States?*
2. If so, is that at your *collaborator's* institution, or elsewhere (where)? Other layers of approval necessary?
3. How well did that process work? How meaningful an ethics review?
4. Substance of review: were you asked mostly about administrative details, or about issues you thought related to human subjects protections and ethics?

IV. Informed Consent Procedures

1. Did you get/seek informed consent from individual participants? From other individuals (relatives)? Communities? Others?
2. How was informed consent handled (written, oral, groups)?
3. How meaningful do you think the informed consent process was?
4. Were you faced with cultural differences in how consent procedures should be implemented?
   - 4.1 Did U.S. regulations (or other regulations) require you to do anything you thought was culturally inappropriate?
5. How foreign is the concept of informed consent?
   - 5.1 How foreign a concept is research?
   - 5.2 Do doctors/providers *in your country* usually DISCLOSE much about diagnoses, *treatments*, etc., to patients?
   - 5.3 Do patients usually have CHOICES or MAKE DECISIONS in their own medical care?

V. Ethics Issues That Arise

1. What kinds of ethics issues have arisen in your studies?
2. How did you try to resolve them?
3. (Examples:)
   - 3.1 Didn't think participants understood.
   - 3.2 What intervention to provide to comparison group.
   - 3.3 Providing additional benefits (e.g., more health care) to participants.

VI. After Study Ended

1. Dissemination of intervention after study ended?
2. Interventions you studied ever implemented in your country?
3. Was implementation discussed before study was initiated?

VII. Overall Recommendations

1. How should U.S. ethics regulations be modified?
2. Should there be in-country IRBs?
3. How best to protect vulnerable, poor, uninformed participants?
4. What recommendations would you make?

APPENDIX F

Experiences and Attitudes of Developing Country Investigators Regarding U.S. Human Subjects Regulations: Interview Outline

I. Description of research

- How long have you been conducting research in your country?
- What kinds of research topics do you investigate in your country?
- How many research projects do you have ongoing at the moment?
- What is the source of funding for these studies?
- How many of these projects involve collaboration between U.S. and non-U.S. institutions?

II. Experiences with human subjects review committees

- If you have collaborated with American researchers, do all of those projects undergo U.S. IRB review?
- What kinds of issues have been raised in U.S. IRB reviews?
- Do you find U.S. IRB review helpful in addressing your research issues, or not?
- Does/did U.S. IRB require your country's ethics review?
- Was there (or is there) an ethics review in your country?
- In your country, was an ethics review board or IRB set up specifically for your study?
- What kinds of issues have been raised in your country's ethics review?
- Please comment on your experiences with human subjects review committees from other countries (e.g., the United Kingdom, Sweden) in comparison with your experience of U.S. IRBs.

III. Approval and consent issues

- Do you have to seek approval for your research from your Ministry of Health or other government officials?
- Do you seek approval from community or village leaders for the study? And if so, can you elaborate?
- Can you describe how the consent process was developed?
- What methods of informing participants do you use?
- Do you have any assessment of the effectiveness of these methods? Please describe.
- Are there difficulties in communicating biomedical research concepts to potential participants?
- Regarding decisionmaking, in your perception, are there cultural differences between your country's communities and American communities?
- Regarding the signing of documents, in your perception, are there cultural differences between your country's communities and American communities?
- Are the study participants literate, for the most part?

IV. Ethics issues

- How would you describe the background economic conditions in the study community?
- How would you describe the medical care available to the community?
- Did your study provide participants with medical care or benefits not generally available to others in the community?
- How did you decide which benefits or care, if any, would be provided through your study?
- When the study is over, is there medical care or research infrastructure left in the country?
- Why do people join the study?
- Are there sensitive issues (e.g., HIV status) raised by study participation?
- What was your role as the research collaborator in the project?
- Who will have access to the data from the study?
- If the intervention is successful, do you think it will be implemented in your country?
- What do you consider to be important ethics issues in your research?

V. Recommendations

- What kind of changes would you recommend to U.S. human subjects regulations?
- What kind of policies would be helpful generally?
- Do you think researchers in the United States or in developing countries need training in ethics?
- In your opinion, what are some key issues that members of U.S. human subjects review committees need to be made aware of regarding the conduct of research in your country?
- What do you think is an effective way to address ethics issues that currently are not addressed by regulations?
- Do you think international guidelines can be helpful for ethical issues in conducting research in your country?

The Relevance of Culture for Informed Consent in U.S.-Funded International Health Research

Commissioned Paper
Patricia A. Marshall
Loyola University-Chicago

I. Introduction

The current research agenda of the President's National Bioethics Advisory Commission (NBAC) includes analyzing and developing recommendations on the federal oversight system of U.S.-funded national and international research on human subjects and on the complex ethical and legal issues in U.S. federally and privately funded international research. The overall goal of this research agenda is to examine the adequacy and appropriateness of U.S. human subjects protections as they apply to research in other countries. Findings from this research will assist the Commission in determining the necessity of changes in federal regulations and policies and the development of recommendations for changes, if they are warranted.

One component of this broad initiative concerns the relevance of cultural context for processes involved in the application of informed consent to research in U.S.-funded international health investigations. The purpose of this specific project is to examine cultural beliefs and values regarding the meaning and expression of informed consent in U.S. biomedical and behavioral international health research. Particular attention will be given to the articulation of individual and social agency in the process of obtaining informed consent from individuals participating in research.

Project Summary

This project was initiated in January 1999. Initially, three specific objectives were outlined:

1. Review literature relevant to definitions of personhood and the expression of autonomy in cross-cultural context, with attention to their implications for the application of informed consent to research.
2. Conduct key informant interviews with scholars in the field and investigators who have been or are currently participating in biomedical and behavioral international research.
3. Conduct a case study of ethical issues involved in obtaining approval for the implementation of an ongoing investigation of hypertension in Nigeria, with special focus on the application of informed consent from human subjects.

Two changes were made in the proposed objectives during the development and implementation of the project goals. First, key informant interviews with scholars and investigators who are involved in international research (objective number 2) were not implemented. Drs. Nancy Kass and Adnan Hyder, as consultants to NBAC's initiative on international research ethics, have conducted focus groups with investigators to explore their concerns about ethical issues related to health research in international settings. The data gathered in these focus groups include information on informed consent and institutional review of protocols by ethics committees. Moreover, Dr. Kass and her colleagues will be conducting a large-scale survey with U.S. investigators on challenges related to ethical issues in the implementation of international research; in-depth interviews will be conducted with a small number of the individuals surveyed. Adnan Hyder is implementing a similar project with investigators from other countries. It is unlikely that the key informant interviews with scholars and investigators that I originally proposed would contribute substantially to the information gathered in these projects.

Second, the case study was designed initially to examine ethical issues associated with the implementation of a population-based genetic epidemiological study of hypertension in Nigeria. However, the case study was broadened to include genetic epidemiological studies on breast cancer and diabetes mellitus. This decision was made because the U.S. researchers with whom I worked on the case study are involved in ongoing large-scale collaborative investigations of these three diseases in Nigeria. The researchers, here in the United States and in Nigeria, work as a team on these three projects. Interviews were conducted with six investigators, five physicians and one psychologist, ten research assistants, and three research participants involved in the three studies. During interviews, it was common for individuals to discuss ethical challenges related to more than one of the projects.

Work Completed

1. A review of the literature on informed consent with attention to cultural factors that influence its interpretation and application in international research.
2. A case study of ethical issues involved in obtaining approval for the implementation of research examining the genetic and environmental determinants of hypertension, breast cancer, and diabetes mellitus in Nigeria, with special focus on the application of informed consent with human subjects. The case study was implemented during April 1999.

The literature review and the findings from the case study are reported in the following two sections.

II. Informed Consent in International Health Research

A. Historical Background: Research Ethics and Informed Consent

Societal concerns with ethical issues surrounding human experimentation were heightened following World War II during the Nuremberg Trials (Annas and Grodin 1992). These proceedings, which judged medical experiments conducted by Nazis on concentration camp prisoners, resulted in the Nuremberg Code for ethical conduct in scientific research. An important aspect of the Nuremberg Code was its commitment to informed consent in research involving human subjects (Katz 1972). The World Medical Association's Declaration of Helsinki in 1964 reiterated concerns for voluntary and informed consent to research, as have subsequent guidelines such as those prepared by the World Health Organization (WHO) and the Council of International Organizations of Medical Sciences (CIOMS) (ICH 1996; WHO/CIOMS 1993).

In the United States, in 1972, public reports of governmental research on untreated syphilis among low-income African American men in Alabama emphasized the absence of voluntary participation and the unwillingness of researchers to disclose the availability of a treatment (Jones 1981). Public outrage concerning the Tuskegee experiment prompted the appointment of a panel by the Department of Health, Education, and Welfare to review the study, and, in 1974, the National Research Act was passed. This act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report*, published in 1978 by the National Commission, described basic ethical principles regarding research with human subjects; this document recognized that informed and voluntary consent for research subjects is a vital dimension of the principle of respect for persons (U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1978).

Currently, throughout the world, institutional ethics committees have been established to provide oversight and approval for proposals to conduct studies involving human subjects (Brody 1998). In the United States, in 1966, the Public Health Service required the establishment of ethics committees at research institutions. Final regulations concerning policies governing research on human subjects were issued in 1981 by the Department of Health and Human Service (DHHS) (U.S DHHS 1981) and reissued a decade later (U.S. DHHS 1991). The federal mandates were clear: Any research involving human subjects that is funded by a Department agency, with certain exemptions, must be evaluated by an Institutional Review Board (IRB). Initially, eight criteria for IRB approval were outlined, including 1) a sound research design; 2) protection of privacy and confidentiality; 3) equality in treatment of subjects; 4) consideration of risks/benefits; 5) monitoring of data collection; 6) informed consent; 7) documentation of informed consent; and 8) a statement indicating that participation in the research is voluntary and that withdrawing from the study will not result in harm or penalty. Six additional criteria must now be addressed for particular projects.

IRBs have had a profound impact on the regulation of research with human subjects (Faden and Beauchamp 1986; Levine 1986; Veatch 1987). While there is consensus about the general purpose of IRBs, significant problems remain in the application of the review process. One issue concerns the selection of committee members (Veatch 1987). Committees are required to include representatives from nonscientific fields and from the community, but most are dominated by scientists who are responsible for reviewing the research protocols of colleagues and friends. Two issues become apparent. First, questions regarding professional competence arise in determining who is qualified to judge the professional merit of protocols. Second, professional bias may be an obstacle to objectivity regarding determination of harm to research subjects. The strong value placed on promoting scientific research among most IRB representatives may outweigh the concerns of a community representative. Moreover, lay members may experience psychological pressure to reach consensus and therefore they may be inclined to accept the arguments of a "professional." Additional problems center around which studies fall under the guidelines set by IRBs. Research that is perceived to involve minimal risk to subjects is exempt from review. The problem, of course, is one of interpretation regarding the judgment of "minimal risk."

Similar issues arise in the implementation of research ethics committees in international settings and may be particularly challenging where there are no clear institutional directives concerning membership criteria or committee responsibilities. In non-Western and developing countries, investigators (Christakis 1988, 1992; Christakis and Panner 1991; Goodgame 1990; Lane 1993; Levine 1991, 1993, 1996, 1998, 1999; Loue, Okello, and Kawuma 1996; Marshall, Koenig, Grifhorst, and Van Ewijk 1998) have called attention to the problematic development of appropriate standards for ethical conduct in scientific research. Lane (1993), for example, describes the development of a code of research ethics in Egypt; she argues that the social and cultural context of biomedical research in Egypt will influence the interpretation and application of generally accepted principles of research. Similarly, Loue, Okello, and Kawuma (1996), in their discussion of strategies for developing a Ugandan code of research ethics, suggest that, while ethical principles governing research are relevant to investigations in Uganda, their adoption and implementation must reflect the circumstances and cultural context that are unique to the Ugandan setting.

Despite overwhelming agreement regarding the duty to obtain informed consent and the importance of ethical review boards, practices associated with the consent process and review of scientific protocols remain problematic (Moreno, Caplan, Wolpe, et al. 1998). For example, in their recommendations for updating IRB protection for human subjects, Moreno and his associates argue that existing IRB guidelines do not take into account the significant changes in recent years associated with multisite and multinational trials; they suggest that IRBs should monitor the entire research process and outcome and that IRB members should have more training. Some investigators (Katz 1984) argue that neither patients nor communities involved in research understand adequately the risks associated with their participation or whose interests are served by research agendas. Indeed, recent public controversies, such as the trials conducted in developing countries testing the efficacy of less expensive alternatives to standard antiretroviral therapy for reducing perinatal transmission of HIV, call attention to inconsistent interpretations and applications of national and international ethical guidelines governing research (Angell 1997; Levine 1999; Lurie and Wolfe 1997; Varmus and Satcher 1997).

B. Factors Influencing Informed Consent to Scientific Research

Requirements for informed consent to research appeal to and are justified by the principle of respect for persons. National and international guidelines for ethical conduct in scientific research identify specific requirements for informed consent including the following three key elements: the provision of information, comprehension of information, and voluntariness in regard to participation (Brody 1998; Weisstub 1998). Adequate information for potential subjects must include a description of research purposes and a clear delineation of risks and benefits. Voluntary participation in research depends upon the respondent's ability to understand not just the

meaning of the research, but the impact it may have on his or her life. The offer of excessive financial compensation, bribes, or unrealistic promises may constitute coercion, especially if the subject is vulnerable because of social factors such as poverty or ethnic background. Moreover, the voluntary nature of participation in research is influenced significantly by the implicit or explicit power of investigators and the institutions they represent. Voluntariness in informed consent may be inhibited when there are social status and social class differences between investigators and potential subjects—differences based on gender, age, education, income level, religious affiliation, and ethnic identity.

A number of factors influence approaches to implementing informed consent—the nature of the research, the cultural context of the research project, communication issues that influence comprehension of information, and discrepancies in social power between subject and researcher. In international health research, the challenges associated with implementing informed consent are heightened because of language barriers that may inhibit effective communication, particularly regarding the translation of scientific or medical concepts and differences in beliefs about who may provide consent to participate in research.

The following discussion of factors influencing the process of informed consent is organized around three issues: 1) comprehension of information; 2) language barriers; and 3) location of decisional authority to provide consent to research.

Comprehension of Information. An individual's decision to accept treatment or to participate in scientific research is influenced by his or her comprehension of information and the meaning attached to the information communicated. In clinical settings, a summary of studies conducted in the United States over a 20-year period (1965–1985) on patient-clinician interaction found that patient satisfaction was associated with "partnership-building"—behavior such as facilitating conversations with patients and positive nonverbal behaviors; patient recall also was associated with the clinician's communication of information and more positive talk during the interaction (Roter, Hall, and Katz 1988; Hall, Roter, and Katz 1988). It is likely these same skills are found to promote effective communication in investigational consent discussions because they are the types of behavior that encourage trust—an essential aspect of decisionmaking in consent to research (Kass, Sugarman, Faden, and Schoch-Spana 1996). Tests of behavioral decision theory in experimental and natural settings demonstrate that individuals rarely conform to scientific rational models in making decisions (Elstein and Holzman, et al. 1987; Kahneman and Tversky 1981). Rather, choices often are made based on incomplete or inconsistent information, the strength of someone's ability to persuade, and past experiences that are relevant to the decision.

In medical research, particularly complex trials involving randomization or the use of placebos, investigators must explain sophisticated scientific concepts (Davis, Holcombe, Berkel, Pramanik, and Divers 1998; Geller, Strauss, Bernhardt, and Holtzman 1997; Olver, Buchanan, Laidlaw, and Poulton 1995). Studies have shown repeatedly that information included in informed consent documents is difficult for patients or potential research subjects to understand (Goldstein, Frasier, Curtis, Reid, and Kreher 1996; Grossman, Piantadosi, and Covabey 1994; Jubelirer 1991; Taylor, Bezjak, Hunter, and Fraser 1998). Most consent forms are written on a college or graduate school level, yet the average reading ability in the United States is significantly lower than that (Meade and Howser 1992; Miles and Davis 1995; Ogloff and Otto 1991), and in many resource-poor nations, illiteracy rates are high. In a study designed to test patients' comprehension of a standard versus a simplified consent form (seventh-grade reading ability) for a "hypothetical" randomized clinical trial, Davis and associates (Davis, Holcombe, Berkel, Pramanik, and Divers 1998) found that low levels of literacy were associated with a preference for the simplified consent. However, comprehension was low with both forms. Thus, Davis et al. suggest that simply lowering readability level does not result in increased comprehension. Despite low levels of comprehension due to ineffective disclosure practices (Andrews 1997) or a patient's inability to understand, most individuals view participation in scientific research favorably (Cassileth, Lusk, Miller, and Hurwitz 1982; Kemp, Skinner, and Toms 1984).

Application of informed consent with culturally diverse populations or in international settings is often problematic (Barnes, Davis, Moran, Portillo, and Koenig 1998; Christakis 1988; Ekunwe and Kessel 1984; El-Sadre and Capps 1992; Ijsselmuiden and Faden 1992; Kaufert and O'Neil 1990; Levine 1991; Marshall, Koenig, Grifhorst, and VanEwjik 1998). For example, in a study of informed consent in clinical practice in Bangalore, India, investigators found that doctors believed it was difficult to obtain consent from illiterate patients, and nearly a third of the 148 patients and 60 doctors interviewed believed that provision of information could sometimes be harmful (Sriram, Kishore Kumar, Jayaprakash, Sriram, and Shanmugham 1991). In a study of informed consent for an influenza vaccine for children in The Gambia, 90 percent of the 189 consenting parents knew the purpose of the vaccine was to prevent disease, but only 10 percent understood the placebo control design; the primary motivation for consenting was to receive the vaccine (Leach, Hilton, Greenwood, Manneh, Dibba, Wilkins, and Mulholland 1999). Freeman (1994) describes the work of the Indian Health Service in developing models of consent forms that are informative and understandable to American Indian and Alaskan Natives considering participation in research; these models emphasize brevity, clarity, and comprehensible formatting.

Language Barriers. Communication between health researchers and potential subjects may be difficult to achieve when the relationship extends across cultural boundaries. Misunderstandings and miscommunication about scientific research are more likely to occur when patients and practitioners speak different languages. The translation of informed consent documents from English to another language may be especially difficult if there are no equivalent expressions for particular concepts. In Nigeria, for example, investigators involved in genetic epidemiological research with Yoruba-speaking patients report that there are no Yoruba words for "genotyping" or "candidate gene."

Linguistical barriers may be reduced through the use of an interpreter, but potential problems remain (Barnes, Davis, Moran, Portillo, and Koenig 1998; Kaufert and O'Neil 1990; Marshall 1992a; Marshall, Koenig, Grifhorst, and VanEwjik 1998). An investigation requiring a translator creates a dual problem for health researchers (Marshall 1991). First, the investigator depends on the translator to communicate the research objectives correctly and effectively; second, the investigator depends on the translator to actually follow through with the consent, which means relaying the information and requesting participation in the study. In situations where a translator is used, consent can only be assumed if the respondent agrees to participate.

Translators are often thought to act as straightforward interpreters of information exchanged between health providers or researchers and patients. This perspective minimizes the complexities of the process of interpretation, where the translator must negotiate not only language, but also cultural and contextual factors (Carrillo, Green, and Betancourt 1999; Kaufert and O'Neil 1990; Koenig and Gates-Williams 1995; Marshall 1992b; Marshall and Koenig 1996). Moreover, if family members or friends are used for translation, there may be a tendency for them to camouflage, exaggerate, or minimize information (Putsch 1985). Some of the problems associated with medical interpretation include the inability to easily translate equivalent expressions across languages; paraphrasing that results in omissions or erroneous substitutions of terms; varying levels of comprehension among participants in the interaction; and the influence of conflicting cultural beliefs and values among participants. Drawing on their research with Native Canadian medical interpreters in Winnipeg hospitals, Kaufert and O'Neil (1990) argue that interpreters have a significant impact on medical interactions and their outcomes. They suggest that, in addition to mediating the explanatory models of illness held by clinicians and patients, Native interpreters often introduce their own beliefs and personal agendas into the interaction. Kaufert and O'Neil (1990) emphasize the dynamic nature of the interaction. They describe the triad that exists between the patient, interpreter, and clinician, in which the process of feeding information back and forth results in a restructuring of both the patient's and the provider's understanding of the medical problem.

It is inevitable that interpreters exercise some degree of control over the communication between researchers and potential study participants. Their influence on communication is articulated through the role of gatekeeping; interpreters make crucial decisions about the selection of information to communicate, the terminology used to express concerns, and the simplification of information to suit particular interactions (Barnes, Davis, Moran, Portillo, and Koenig 1998). The modification of the message that researchers wish to give to potential subjects, and conversely, the response of individuals to questions, have serious implications for the informed consent process.

Wasongarz, Carter, Barnes, and Koenig (1995), as part of an ongoing ethnographic study of end-of-life decisionmaking among culturally diverse patients terminally ill with cancer, explored the way in which medical interpreters influenced decisions such as resuscitation, the limitation of treatments, and the completion of a Durable Power of Attorney for Health Care. Although this study does not address informed consent to research, the findings are applicable to an investigational context. These investigators challenge the assumption that interpreters are simply conduits of information between patients and providers. Results of their analysis suggest that interpreters modified language in order to make patients feel more comfortable about their diagnosis and prognosis. Translators were also found to influence the communication process by acting as cultural brokers, patient advocates, and counselors. For example, referring to her practice of modifying the words of the provider, one interpreter stated, "When I translated 'death,' I usually would avoid using the word 'death.' For Chinese patients, I would use 'letting go,' 'sleeping,' 'stop eating rice,' and other words to substitute the word 'death'" (Wasongarz, Carter, Barnes, and Koenig 1995:13). The investigators suggest that perhaps the interpreter changes the word "death" not only to ease the emotional burden of the patient, but also to ease the discomfort the interpreter feels when telling the patient that he or she is dying. Wasongarz and associates (1995) call attention to another process of modification in which translators expand upon what the physician says in order to communicate a technical medical procedure in culturally appropriate terms. They report that a Cantonese interpreter spent 15 minutes explaining a lumbar puncture to a patient; the oncologist had communicated this in one sentence.

Language barriers represent only one dimension of effective communication in international investigations. Cultural norms governing the structure and content of discourse in medical encounters are also vitally important (Barnes, Davis, Moran, Portillo, and Koenig 1998; Kaufert, and O'Neil 1990; Koenig and Gates-Williams 1995; Marshall and Koenig 1996). Beliefs and expectations concerning "appropriate" discourse in medical interactions—what is discussed, the timing of the conversation, who is present at the conversation, and who participates in the discussion—influence deliberation over ethical issues such as disclosure of information and confidentiality.

Autonomy and Locus of Decisional Authority. Who has the authority to provide consent for participation in research? Beliefs about personhood, individual autonomy, and decisional capacity are embedded within the social and cultural patterns of family ties and community obligations. In the United States, where personal autonomy is emphasized, patients are expected to make decisions for themselves or through designated surrogates. However, in many non-Western settings, religious or tribal leaders or a patient's extended family may play a significant role in decisions concerning health care and health research (Barry 1988; Barry and Molyneux 1992; DeCraemer 1983; Hall 1989; Levine 1991; Marshall, Thomasma, Bergsma 1994; Marshall, and Koenig 1996; Marshall, Koenig, Grifhorst, and VanEwjik 1998). Cultural differences in beliefs about the nature of personhood and the location of decisional authority for consent have been problematic for investigators conducting international health research.

In her discussion of AIDS research in Africa, for example, Barry (1988) describes the challenge of translating the concept of autonomy in areas where personhood is defined by one's tribe, village, or social group. In these situations, tribal elders, community leaders, religious authorities, or family members of the research subject

may need to be approached before obtaining consent from individuals. In an early report on consent for smallpox vaccination research in five areas of West Africa, investigators (Henderson et al. 1973) found that compliance with the decisions of tribal leaders in particular areas was the strongest factor influencing a community's receptivity to the program. In 1980, Ajayi identified numerous social obstacles to achieving informed consent to research in Nigeria according to the criteria mandated by the Helsinki Declaration; his discussion called attention to the importance of cultural beliefs concerning respect for community and family elders. In Uganda, more recently, Loue, Okello, and Kawuma (1996) note that, according to Ugandan civil law, an 18-year-old male living at home has the legal right to make his own decisions; it is customary, however, for the son to obtain his father's consent prior to entering into any obligation or contract, including participation in research. Additionally, without the consent of their partner, Ugandan women often refuse to make a decision regarding their own or their child's participation in research.

In their examination of informed consent practices associated with an influenza vaccine trial in The Gambia, Leach and his colleagues (1999) report that parental consent for a child's participation conformed generally to Western notions of autonomous decisionmaking. Parents sought the advice of health workers, families, and friends, but only 1 percent of the 189 parents involved traditional or religious leaders in their decision. However, 10 percent of the urban parents compared to 25 percent of the rural parents agreed that the village chief should have some input in making the decision to participate in the influenza vaccine trial. Moreover, all of the mothers from one entire village refused to participate in the research. None of these women agreed to be interviewed, but an elderly woman who was respected in the community made the following statement: "The mothers of this village don't want MRC [the United Kingdom Medical Research Council] affairs. MRC is fond of taking blood samples from babies who will then eventually die or continuously suffer….All the mothers and fathers, including the village chief, do not want MRC and we have agreed that nobody should accept your interview" (Leach, Hilton, Greenwood, Manneh, Dibba, Wilkins, and Mulholland 1999). The investigators argue that, in this case, the women may have been too frightened to refuse individually. The results of this study suggest that international codes of informed consent, emphasizing individual choice, are appropriate, but in particular settings, input from community leaders may be necessary.

Negotiating informed consent with the designated authorities in health research with non-Western populations requires investigators to move beyond narrow definitions of personhood, autonomy, and "self" determination. A number of scholars (Angell 1988; Newton 1990) have suggested that the application of Western ethical standards to scientific research conducted in developing countries with divergent cultural norms may be construed as a form of *ethical imperialism*. Nevertheless, as Angell (1988) and others (see e.g., Barry 1988; Christakis 1992; Christakis and Panner 1991; Ekunwe and Kessel 1984; Ijsselmuiden and Faden 1992; Levine 1991, 1993, 1996; Macklin 1998, 1999; Marshall 1992b; Marshall, Koenig, Grifhorst, and VanEwjik 1998) point out, while ethical relativism demands cultural sensitivity to local customs, investigators are never authorized to conduct research without regard to potential harm and without attempts to be informative throughout a project's implementation. In particular, scholars (see e.g., Angell 1997; Lurie and Wolfe 1997; Macklin 1998, 1999) have cautioned against an ethical relativism that would permit the exploitation of populations in non-Western settings in research that would not be allowed in the investigator's home country. In his development of a model for the negotiation of value differences relevant to science and health in a multicultural world, Baker (1998a, 1998b, 1998c) levels a strong critique against those who embrace moral fundamentalism—the idea that certain ethical principles are applicable cross-culturally (Beauchamp 1998; Macklin 1998, 1999). The struggle to respect the unique identity of culturally diverse communities and simultaneously to develop internationally applicable policies that respect the rights of individuals who may be vulnerable in scientific research remains problematic.

Overall, official international policies governing human subjects research promote cultural sensitivity in obtaining informed consent without losing sight of the importance of individual autonomy and freedom of choice (see e.g., ICH 1996; WHO 1998; WHO/CIOMS 1993). Brody (1998) contends that guidelines such as those espoused by WHO/CIOMS (1993) strengthen a commitment to transcending cross-cultural differences by mandating that research subjects from developing countries be told everything that would be told to research subjects in an industrialized country and that they be advised of their right of refusal. Thus, a tribal chief, village elder, or community leader may express approval of a research agenda, but sensitivity to cultural customs is secondary to honoring individual choice (Macklin 1999). Paradoxically, community "consent" to research may work either for or against the welfare of community members. In situations where research may benefit individuals or the broader community, approval from local authorities would not be problematic. However, in cases where the research is of questionable value or where the health and welfare of individuals is at risk, approval from local authorities could actually threaten community well-being.

III. Case Study: Ethical Review of Research Protocols and Informed Consent in Genetic Epidemiological Studies of Hypertension, Breast Cancer, and Diabetes Mellitus in Nigeria

A. Description of Case Study

The purpose of this case study is to document issues and challenges surrounding the process of institutional ethical review and the application of informed consent in studies funded by the United States (National Institutes of Health [NIH]) being conducted in Lagos, Ibadan, and Igbo-Ora, Nigeria, on the genetic and environmental determinants of hypertension, Type II diabetes, and breast cancer. These studies are part of the NIH-funded collaborative research of the *Chronic Disease Network*. Genetic epidemiologists and physicians at Loyola University of Chicago and physicians at the University Teaching Hospital in Lagos and the University College Hospital in Ibadan have been actively engaged in these studies for more than ten years.

The case study was implemented April 4–15, 1999. Interviews were conducted with 19 individuals in Nigeria: 5 physician/researchers, 1 psychologist/researcher, 10 research assistants, and 3 research participants. These in-depth interviews took place in individual and group settings. A team meeting of researchers involved in the Type II diabetes study in Lagos was also observed. Information obtained during interviews was recorded by hand and transcribed; when possible, interviews were audio-taped and transcribed. Ethnographic field notes were also recorded.

In-depth interviews were conducted using a modified version of the Interview Guideline for Researchers developed by Dr. Jeremy Sugarman and members of Family Health International. This interview guide was designed for Dr. Sugarman's project involving site visits to eight countries to talk with investigators about their experience with ethical issues related to the conduct of internationally funded health research (see, also in this volume, Sugarman, Popkin, Fortney, and Rivera, *International Perspectives on Protecting Human Research Subjects*). Data gathered during informal discussions with individuals were recorded in field notes.

Topics addressed in the interviews and informal discussions included the following: 1) formal structures for ethical review of research protocols; 2) experience with the ethical review process; 3) challenges associated with obtaining approval for implementation of the study; 4) issues surrounding the application of informed consent; 5) ethical issues involved in the process of data collection; and 6) the experience of informed consent from the perspective of the research subjects. Interviews lasted approximately 60 to 90 minutes.

IRB approval for this study was obtained from Duke University. The Nigerian case study was included as an amendment to the NBAC consultation project being implemented by Dr. Sugarman at Duke University.

Results of this case study cannot be generalized because of the small sample size, the unique circumstances of the study protocol, and the individual experiences of those involved in the implementation of the process of ethical review and informed consent. However, the purpose of the case study is not to produce generalizable results, but to generate questions and problems for further consideration and research.

B. Description of Research Projects

Hypertension Studies. In 1991, investigators received an NIH grant for the International Collaborative Study of Hypertension in Blacks to examine the social and environmental determinants of the gradient of hypertension risk in West Africa, the Caribbean, and the United States. By 1994, this study had enrolled and examined over 10,000 men and women ages 25 to 74 years from West Africa—Nigeria (with urban and rural sites—Ibadan, Idere, and Igbo-Ora); Cameroon (with urban and rural sites); the Caribbean—Barbados, Jamaica, and St. Lucia; the United Kingdom—Manchester (primarily migrants from the Caribbean); and the United States—Maywood, Illinois. Participants in this study had blood draws and physical examinations as well as interviews on family history of hypertension, medical history, and environmental risk factors for hypertension.

Collectively, the investigators have three additional NIH-funded research projects to study the genetic and environmental determinants of blood pressure and hypertension in populations of the African Diaspora with study sites in Nigeria, Jamaica, and the Chicago area. These ongoing genetic epidemiology studies so far have enrolled and examined over 400 families in Nigeria (Ibadan and Igbo-Ora), 200 families in Jamaica (Spanish Town), and over 300 African American families from the Chicago metropolitan area. These families have been extensively characterized both at the molecular level (using candidate gene and genome wide scan approaches) and at the phenotypic levels with special emphases to the renin-angiotensin system in relation to hypertension and blood pressure regulation. Participants undergo blood draws and physical examinations and interviews on family history of hypertension, medical history, and environmental risk factors for hypertension. Findings from these family studies have formed the basis for several publications regarding the genetic epidemiology of common complex diseases in multiple African origin populations.

Breast Cancer Studies. This project is an ongoing international collaboration between Nigerian and U.S. investigators to study breast cancer genetics in blacks of African descent. The main objective of this research is to identify high-risk alleles on two continents (Africa and North America). In Nigeria, over 200 breast cancer patients have been enrolled in the study. Although this study is being implemented at the University College Hospital in Ibadan, many patients come from other villages and cities because resources for cancer treatment are not available in their home towns. The University College Hospital is a referral center for breast cancer patients in this area. The study has provided useful information regarding the genetic epidemiology of breast cancer in Nigerian women. For example, in Nigeria, the peak age of incidence of breast cancer is 43 years, at least a decade earlier than in Anglo Americans. Fewer than 0.5 percent of U.S. breast cancer cases are younger than 30, compared to 12 percent in Nigeria.

The Diabetes Mellitus Study. This international collaborative study, initiated in 1997, examines genetic and environmental determinants of Type II diabetes in Nigeria (three sites: Enugu, Ibadan, Lagos) and Ghana (two sites: Accra and Kumasi). The investigators are using an affected-sib pairs study design. One spouse of either affected sibling is enrolled as the control. Participants undergo blood draws and a complete physical examination. In addition, they are interviewed once during the study. To date, 250 affected pairs of siblings and 200 case controls have been enrolled.

C. Institutional Ethical Review at Nigerian Study Sites

Nigerian investigators collaborating with foreign researchers must seek approval from local research ethics committees established at the institution sponsoring the research (e.g., universities, hospitals, and clinics).

There is considerable variation in the implementation of the process for ethical review between institutions. In Lagos, the diabetes mellitus study was reviewed by the research ethics committee at the University Teaching Hospital. There are approximately nine members on this committee. The hypertension and breast cancer studies were reviewed by the research ethics committee at the University of Ibadan through the University College Hospital. Approximately ten members are included on this committee. Committee members at the University Teaching Hospital in Lagos and the University College Hospital in Ibadan include faculty from various clinical and basic science departments, one faculty member from a nonscience department, and community members.

D. Results of Interviews

Data were analyzed using standard techniques for qualitative research (Bernard 1994; Denzin and Lincoln 1994). In order to facilitate the integration of the final NBAC report, the major categories and themes are outlined following the scheme devised by Drs. Kass and Hyder in their analysis of focus group data: informed consent; other issues relating to respect for persons; host country IRBs; and moral responsibility and justice issues. Four of the Kass/Hyder study categories are not included, because information on these topics was not systematically obtained (standard of care; U.S. IRBs; Office for Protection from Research Risks; defining research). However, a thematic category addressing cultural beliefs about disease etiology and western biomedical treatments was added. These issues are discussed briefly, with examples from the interviews to illustrate concerns that were raised. Recommendations from the respondents on strategies to resolve dilemmas in the application of the ethical review process and informed consent follow the report of findings for each thematic category.

Hereafter, the terms "investigator" and "researcher" refer to the physicians and psychologist interviewed, and the term "research assistant" refers to the research assistants working on the three different studies.

1. Informed Consent

Ethical challenges associated with obtaining and documenting informed consent were primary concerns for all of the investigators and research assistants interviewed. Although this concern is not unique to research being conducted in international settings, investigators involved in collaborative international research may encounter significant challenges in their efforts to obtain informed consent because of cultural traditions, language barriers, and structural factors surrounding the implementation of research. Five issues associated with the consent process are addressed below: 1) informing participants and participant understanding; 2) disclosure of risk; 3) autonomy and locus of decisional authority; 4) documentation; and 5) voluntariness

Informing Participants and Participant Understanding. A common concern expressed by the investigators and research assistants was the difficulty associated with language barriers. Translating an English consent form into Yoruba is often problematic because particular words may have no Yoruba equivalent. Moreover, Nigerian investigators and research assistants interviewed suggested that the U.S. consent forms tend to be lengthy and include information that may be confusing or alarming to patients. Additionally, the complexity of consent forms produced for patients in the United States may hinder the translation from English to Yoruba.

When investigators were asked about the process of translating an English document to Yoruba, they often discussed problems associated with back translation (translating a document from one language to another and then having an independent native speaker back translate the document into the original language). One physician noted the following:

> Concepts are very important...we may not have the equivalent words…[and it's hard] to communicate concepts...the second [problem] is when you read the direct translation [from English to Yoruba] it sounds funny...it's grammatically correct, but it sounds funny.

In this same group interview, another physician added that the direct translation may not be "culturally appropriate." Several physicians reported an incident that occurred in which an English consent form was translated into Yoruba, and then back translated by language experts at the university in Ibadan. When the final document was used with potential subjects in the field, individuals had difficulty understanding it. It was necessary to revise the consent once more, so that it could be used effectively with subjects.

Investigators and research assistants also expressed concern about the difficulties associated with translating genetic concepts into Yoruba. A physician involved in the diabetes mellitis study in Lagos reported the following:

> We have to translate the informed consent to the local language. You tend to lose some quality because some words don't have counterparts in Yoruba...like 'genotyping'...[or other words that have to do with] biotechnology…like 'candidate genes.' It's difficult to get that across….You have to go through this elaborate explanation process on how inheritance is governed...what factors are responsible for inheritance and how those factors can mediate the transmission [of certain diseases].

Another physician reported a similar frustration: "There's no point saying 'genotyping' when he doesn't speak English! It's rubbish! There's no word in Yoruba for it!" A third physician reported that "...the issue of interpretation [and] translation...is so difficult...there is no Yoruba word for 'gene.'"

One of the obstacles that investigators and research assistants identified is the relative lack of information and public education on issues such as informed consent in medical research, and more specifically, on medical issues such as genetic testing and screening. A physician involved in the breast cancer study noted that:

> In the United States, [people] may pick up information [on breast cancer, on genetic risks, on the genome project]…from the media...but here...[people are not that familiar with these things].

A physician involved in the diabetes study reported that the amount of time it takes to go through the consent process is directly related to an individual's educational background and his or her level of understanding regarding some of the difficult medical concepts. However, when asked if research participants understand the concept of inheritability, a physician replied, "To a large extent, yes...I think because of the prevalence of sickle cell anemia they have some familiarity with inheritability."

In a discussion with a physician involved in the diabetes research and one of his patients who is participating in the study, I asked the patient directly how the concept of "genes" was explained to him. He did not understand my question. The following interaction occurred between me and the physician when the patient could not respond:

Physician: "...it was explained [genotyping]...he blocked it out [because it is not meaningful to him]."

Marshall: "How do you explain it?"

Physician: "I say genes are what you inherit from your mother and your father. They understand that—[that genes refer to] what comes from your mother and father...to make you who you are. If you ask him that way then he'll understand what you're talking about."

Marshall: "Does anyone ask what a gene is?"

Physician: "Yes, and I tell them it's what comes from their parents when they are born...."

Despite the patient's inability or reluctance to describe what he was told about "genes" or the concept of "inheritence," when the physician asked the patient to tell me what he was told about the study, the patient gave a very concise and detailed response indicating that he understood the basic purpose of the research and what procedures would be done:

> You told me my brother also has diabetes [my brother was seen for a number of years for diabetes]...[You said] we are making a study on family diabetes. [If]...you have a brother or three brothers [with diabetes...then we want to talk with you about a study]....Then he examined me...[he said]...some people in America are suffering from diabetes too, and they are trying [to understand how it works in families]. I said I would go to great lengths to be a participant in the study...to help fellow Nigerians and beyond, to enable [the doctors to know more]...he said he would take care of me medically by supplying drugs and he sends me to the eye specialist to take care of my eyes….He said that [he would] be testing my fasting blood...[and that there would be] urine tests, weight checks [and checks on my] electrolytes.…

The importance of educating individuals and the community about the study and its specific purpose and procedures was mentioned by all those interviewed. Investigators and research assistants noted that education should begin at the community level, as indicated by the following interaction with several researchers who discussed the process involved in community entry and community education:

Researcher 1: "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."

Researcher 2: "They are clear headed, they will sift it [sort it through]…."

Researcher 3: "They educate [help educate the others]."

Researcher 1: "If anything bad happens they lose face, and when you lose face you lose it, not only you, your children and your generation...people have the memory of an elephant."

In regard to educating individuals about the study, the investigators and research assistants described the importance of allowing potential participants time to discuss the study with family members or others in the community. Many also mentioned that it is very helpful to have something written such as an information sheet or a brochure for people to take home with them. The following interaction with breast cancer researchers illustrates this point:

Researcher 1: "The [consent] process is not so bad….There is a need for continual evaluation of the consent process...[it's] important to allow patients time to think about the study and discuss it with their family."

Researcher 2: "So if they had information that they could take home [maybe that] would improve [their understanding]."

Marshall: "You mean something like a brochure?"

Researcher 1: "Our consent says [asks them] do they want to have it read to them.….They might be able to read [themselves]...[or they can] get their children [to read it]."

Researcher 3: "[It would be good to have] something that explains what is cancer [the brochure] and what are the advantages and disadvantages of having the gene test."

A research assistant working on the hypertension study reiterated the importance of discussing the study with family members for some individuals:

> Usually [what we focus our education on] depends upon what part [of the consent] they don't understand. Like they might say what [are the] benefits for me….We explain that they might not personally benefit, but others may say, 'what's in it for me?'…Others say, 'I need to talk to the head of the family.'

In summary, the investigators and research assistants interviewed expressed serious concerns about difficulties associated with the translation of the consent forms from English to Yoruba. Specifically, they noted difficulties with the translation of words for which there are no Yoruba equivalents and with communicating difficult scientific concepts in the field of genetics. They also stressed the importance of educating both the community and individual participants. They noted that education at the community level may begin long before the project is initiated through extensive interaction with community leaders in which local people are invited to participate in discussions of the study goals and strategies for implementation.

Disclosure of Risks in Informed Consent. Investigators and research assistants commented specifically on the informed consent documents for the genetic research and what they perceived to be the inclusion of extraneous, irrelevant, or culturally inappropriate information. They called attention to the emphasis placed on explaining the potential risks to study participants, noting that in the United States there is much greater concern about communicating the possibility of harm to research subjects. One physician said that patients may be alarmed by addressing all possible risks associated with the research:

> Look, [say] you've been my patient for 30 years. [A patient might say] 'You're telling me I'm going to faint when you take my blood? Why are you telling me I'm going to die?'...I look at what are the essential parts [of informed consent]. You introduce the subject...make sure you know what we are trying to achieve, what will be done to the patient, what participation in the study will require of him, the risks and benefits to him...you have to talk about both... [but] if I make a mountain out of a molehill [then it's not going to work]. There are not many risks [in this study]...so I'd scare them if [I talked a lot about risks].

Another physician made a similar point:

> I said it [the informed consent document] was fine for America, but it could be counterproductive here...it needs to be adapted to us. You don't say 'I'm going to give you a ride in the car'...you could have an accident or a stroke...you need to say 'I'm going to get you there.' Maybe, 'I'm going to get you there safely' and then maybe, 'God forbid we will not have an accident.' Think positive! I had to think of my environment [when adapting the informed consent document].

When asked about differences between the United States and Nigeria concerning beliefs about what potential subjects might want to know regarding risks, a physician described the experience of a resident obtaining consent for surgical procedures:

> [In the United States, we say things like]...'You may die...this may not benefit you.' I had a resident who was keen on informed consent. She would tell patients that they could die. [She would tell them this] pre-op [before they went into surgery]...and they would say, 'Why are you telling me I could die!?' They [the patients] thoroughly abused her. We [Nigerians] don't like to talk about it. It makes it more important...it distorts the importance [of the risk of dying].

Physicians working on the breast cancer study held a focus group with breast cancer patients not involved in the study to learn more about what kinds of concerns they would have about participating in the research. A research assistant on this project stated the following:

> Most had a common perspective…[they would participate] even if the research did not benefit them, they were willing to participate as long [as] we could give them reassurances [that they would not be harmed]...[then] they had no concerns.

The physician and research assistants involved in the breast cancer project also reported that focus group members expressed some anxiety about the use of blood:

> They want to know the importance of taking blood, and [we say] that it is to look at the mutations in the blood.

Many of the investigators and research assistants interviewed indicated that patients might be fearful about risks associated with blood draws. As the following interaction with an investigator suggests, one of the concerns that patients have relates to how the loss of blood will affect their ability to function:

Marshall: "How do you communicate the risks involved in the study?"

Researcher: "...[we] tell them about the procedures...[that we will be] drawing blood. They know that by taking blood...[it might] involve some discomfort."

Marshall: "Do the patients ask questions?"

Researcher: "Yes, [they want to know] if the amount of blood will affect how they function afterwards."

More information on concerns related to blood draws is reported in the section on cultural beliefs that impact the informed consent process.

A number of investigators mentioned challenges associated with communicating the concept of risk to potential subjects, noting that in Nigeria many people are not exposed to the extensive media attention given to health risks in the United States. The following interaction with a physician (Researcher 1) and two research assistants (Researchers 2, 3) illustrates this point:

Researcher 1: "In the United States, the community is pretty literate. [They know whether] something is a risk...I think what people [here] don't understand is what risk is...like...here is an example...a woman says 'What are my chances [of surviving cancer]?' I might say that 85 percent are alive five years later and she'll say, 'So I have a risk of dying of 15 percent?' and I say no...[and explain]….They are illiterate [about risk]….We [in Nigeria] are not yet at the stage where [concepts of risk] are more common knowledge."

Researcher 2: "[It's difficult] to communicate what is a gene test...why we're doing it—genetic testing."

Researcher 1: "The advantage [in the United States] is the amount of [media] information is more….Some patients here deny the risk of cancer...maybe their religious group says [to them] 'God says I can't have cancer.' At that level, it's difficult to get through [the idea] of genetic risk. We need to develop [a] literature [for patients]. It's easy to say, 'We'll send [you] the results of the clinical trials [for example, something from the drug company]. [But] it's very sophisticated [information]. We need to develop appropriate educational brochures [to provide] information for patients."

Researcher 3: "[It is hard] to come down to their level. You have to explain it right."

Many investigators and research assistants emphasized the importance of the patient's trust in his or her physician and the impact this has on the patient's willingness to participate in a proposed research project. The investigators called attention to the power they have because of their professional status and authority. One physician, describing his influence over patients, said pointedly, "Look, I am in a commanding position [because I am their doctor]." This physician noted that one of his patients was eager to participate and not concerned about risks associated with the study because of their relationship and because of the patient's experience working in the radiology department of the hospital for 36 years:

> Now, he has experience [with the hospital, with health care issues] so he will play down the risks.

The patient supported his physician's claims, saying:

> I have known him [the doctor] for a few years. I agree to follow him. He said he is going to make me well...and that he will give me drugs [for my diabetes]….Nothing will happen to me [in the study]….There is nothing to fear [about the blood draw].

Community trust in the research team was emphasized by many of the investigators and research assistants. When asked during an interview if patients were concerned about risks associated with the study, one research assistant noted the following:

> Yes...but if you assure them [that risks are minimal]...[then it's usually okay]...and since they know us in the community then they trust us.

In summary, information included in informed consent documents about risks associated with study procedures was a major concern for investigators and research assistants. They believe that in the United States there is a much greater emphasis on reporting risks. Additionally, they highlighted the importance of trust between the physician and patient and the powerful effect this has on an individual's willingness to participate in a study, regardless of the risks involved.

Autonomy and Locus of Decisional Authority. An important area of concern for the investigators and research assistants was the issue of individual consent, as it is generally expressed in the West, and the notion of community consent, as it is understood in settings like Nigeria, particularly in the more rural areas. One physician noted that, "Life here is still very communal. The basic unit is not the nuclear family, but the extended family."

The investigators, research assistants, and two of the rural study participants interviewed provided a description of what is meant by obtaining consent to conduct a study from community leaders, specifically, local tribal Chiefs. In the following transcript, a physician from the city of Lagos describes this process:

Researcher: "To enter [a] community you need to carry that community along with you. There are imperatives….[You must communicate] with the Chief and his council and some others from the community [community leaders]....The individualism that exists in the West does not exist here. I cannot go to a village and start doing something. I need to go to the local leader...the Chief [I might go to him] with kola nuts or whiskey…they [Chiefs] appreciate it, they expect it."

Marshall: "Do you go to the Chief by yourself, or with others?"

Researcher: "[You] go with local people and they do the introduction and sometimes you might not even speak the local language...[and they explain the study, what it is about, what is needed] and then he says 'Fine, you can do this.' Then he goes to the local people and says Dr. X is here to do this, give him cooperation."

Marshall: "Can you tell me more about community consent? How that works?"

Researcher: "There are really two levels. One is community and the other is individual. [The community consent is somewhat like getting approval from the IRB...you can't do the research without approval.] 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."

Marshall: "If the Chief approves, then how will the community respond?"

Researcher: "Most of the time they agree [to participate], when you have the conversation with the Chief and [he communicates to] household heads. You are likely to get approval."

A similar description of community consent and the importance of obtaining approval from local tribal leaders was given by investigators, research assistants, and research participants at the rural sites. For example, according to a member of the research team in Ibadan, "Community consent is very important in Igbo-Ora and Idere." In a group discussion with team members in Igbo-Ora, investigators and research assistants were asked how the chief communicates his approval or disapproval of the research project to the local population. A research assistant explained, "You know, we have sub-Chiefs. These [senior Chiefs] will take it to their household heads and from there [the household heads] will take it to each family. The other way is with a town crier." When asked how the information is communicated through a town crier, this individual replied as follows:

> That person [the town crier] goes to the street [to the neighborhoods or maybe the town center] and he has a big bell, a gong, and he bangs on it and people in the neighborhood will come and he'll announce [the message] and then go to a different neighborhood.

In some cases, the town crier might go to 20 or 30 locations to make his announcement. Members of the research team were asked what the town crier actually says in these announcements. A research assistant said, "It goes in the form of an instruction from the Chief [like...he'll explain the study] and say 'We want people to cooperate with them' [the researchers]."

When asked if a Chief will usually approve of studies, a research assistant involved with the rural study sites reported, "It could go either way, but [in the hypertension study] the case was well presented and in general these people are well educated and especially when there [is evidence of concern for] the good of the community, there is usually approval." Another research assistant agreed, adding, "Especially when they know [you], when they are associated with medical management." This theme was also addressed by a third research assistant who commented on the fact that the Chief and the local community are likely to be receptive to a study, "When they are familiar [with us]." Nevertheless, as the following statement made by one of the physicians indicates, respect for individual autonomy is still considered to be very important:

> Don't get it wrong, even if a [big leader] says [yes]...an individual can still say no.

A similar statement was made by another research assistant:

> You have your own self opinion, so you can think on your own. Some people like it, some don't.

However, when asked specifically if anyone goes against the Chief's decision, one research assistant replied, "Usually not many, but [sometimes]." Acknowledging the power of the Chief's permission to conduct a study, another research assistant reported:

> Some people couldn't be bothered [with the study]...but it [the study] would not be successful at all without his [the Chief's] approval.

When the issue of obtaining permission from a household head to participate in a study was explored with one research assistant, she reported that:

> [They] might need permission, but some are buying time. Some don't know for sure if they want to join the study [and they want to talk to the household head about it]. If they ask you to come back the next day and then you go back and they say the head of the house is gone for a week or something then you know they are not interested.

Several investigators discussed the practice of gift exchange between the local Chief and the researchers proposing a study. The following interaction addresses this issue:

Researcher 1: "Usually, if the Chief thinks that it [the study] is beneficial they will give you a gift."

Marshall: "What kind of gifts?"

Researcher 2: "A goat, a chicken….The tradition is that when you go to see the ruler, you bring a whiskey or a brandy, or kola nuts, but not because it's research, but because it's what you do anytime you visit at all [visit the Chief]. In the southwest you don't have to give but [here] it would be considered [appropriate to give a gift]."

All of the investigators and research assistants interviewed commented on differences between the rural and urban areas regarding the importance of obtaining permission from local community leaders such as tribal chiefs. When asked if the process of obtaining consent in urban settings was different from the consent process in rural settings, one of the physicians stated the following:

> Yes, because people [in urban areas] immigrated from various parts of Nigeria, so they, to a large extent, they can decide what to participate [in] and what not to. But in particular households, if the head of the household does not agree then they might not be able [to participate].

Another physician agreed with this assessment:

> In the rural area, community consent is stronger than the urban area. In Ibadan, some neighborhoods have traditional [leadership], some modern, some have a traditional Chief and the community structure still holds.

Many of the investigators and research assistants interviewed called attention to the need for foreign researchers to understand cultural traditions concerning the importance of the community and extended family relationships when implementing a study in Nigeria. A physician noted pointedly, "You need to respect local ethics." A physician involved in the breast cancer study noted that cancer patients often need the approval of the husband to participate. He emphasized that, in these cases, the woman's individual consent was essential, but that their research team supported a patient's wish to discuss the study with her husband and other family members. Indeed, most investigators and research assistants reported strategies that accommodated and encouraged discussion regarding study participation with family members. In the hypertension study, for example, the study is described to patients and they are given information to take home. An appointment is set for a later date to meet with the patient and obtain his or her consent.

Commenting on Western and non-Western views about ethics in relation to research, another physician stated:

> There are concepts that are universal, but you need to address the local context....There is an inherent assumption that foreign ethical standards are superior.

One physician remarked that:

> I think there is a third alternative [to using local standards or foreign standards of ethics]. When foreign researchers work in my country then there should be a hybridization of both local standards and international standards. What is most important from my perspective would be the rights of the individual even if the client is not aware of these issues.

In summary, in Nigeria, in addition to obtaining informed consent from individual study participants, investigators working in some areas, particularly the more rural areas, must negotiate permission to conduct the study from local community leaders, including tribal Chiefs. Findings from this case study indicate the need for developing a strategy for informed consent that provides the opportunity to respect individual autonomy while simultaneously showing deference for local traditions that demand particular attention to community elders. In

the United States and elsewhere, researchers often pursue the support of community representatives in areas where studies are being implemented. In some cases, interactions with these community leaders might involve obtaining permission to conduct the study. However, the notion of community "consent" as it is expressed in Nigeria, differs significantly from practices associated with community involvement in the United States. In Nigeria, especially in rural areas and urban communities where traditional relationships are strong, there exist well-defined protocols for obtaining permission from a tribal Chief to conduct a study. While the investigators and research assistants interviewed in this case study emphasized that individuals have the right to refuse to participate in a study even if a local leader has approved it, they suggest that most people will participate once the study is endorsed. Thus, upholding the internationally agreed-upon standard for individual voluntary consent may be challenging for persons who are vulnerable because of their gender or their status in their extended household or local community.

Documentation. Many of the investigators and research assistants commented on problems related to requirements for documentation of informed consent by U.S. funding agencies. They were particularly concerned about two issues: first, the length and complexity of informed consent documents; and second, the need for written consent. These issues were perceived as obstacles for those attempting to obtain consent from potential study participants. They were also viewed as possible impediments to participant understanding. For example, one physician called attention to the problem of overwhelming individuals with too much information for them realistically to be able to understand:

> Apart from the sheer amount [of information], the content of the information...[it's] too much...[and it's] not meaningful to have so much information presented to the patient. We go for the principles. It's confidential, it's voluntary, and [we talk about] risks and benefits. The difference [between what we would do and what we have to do to meet the U.S. requirements] lies in the amount of background and scientific information you put in there [the informed consent document].

In his discussion of the ineffectiveness of lengthy documents and the barriers to effective communication they create, another investigator stated:

> At the end of the day, you can't read a five-page document, so you need to make it smaller... [you use] bullets [you highlight the important parts].

Expressing similar concerns about the complexity of long documents that attempt to describe concepts that may be hard for some people to comprehend, a physician reported:

> It's not so much that it's not necessary [the information]. It's just that they can't take all the information] when their level of education is low.

In addition to concerns about the length and complexity of consent forms, many investigators and research assistants described some of the difficulties surrounding requirements for written consent, particularly among people who cannot read or write. One researcher noted the confusion that is sometimes expressed by individuals who do not comprehend the need for their written signature in order to participate in a study:

> Some [patients] don't understand why we have informed consent. Sometimes [they ask] 'Why are you asking me to sign?' They accept [the study] without needing to sign in writing.

When asked if he thought patients are less likely to participate if written consent is required, one physician replied:

> They won't refuse to participate but [they] may refuse to sign [a written consent]....They will [sign] after [we] explain it, that it [signing] is important, that it shows they understand [the study and what they are consenting to].

In a group interview, a research assistant noted that, "When people cannot read and write, then you get verbal consent [or get thumbprint]." Investigators and research assistants agreed that sometimes individuals may have some anxiety about writing their signature or placing their thumbprint on a formal document because of uncertainties about how the document may be used against them. As one of the research assistants indicated, "They can get very suspicious." An investigator concurred:

> 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.'

A perception that individuals may be concerned about signing a document was also expressed by a physician who noted that formality of the process might be intimidating for some people:

> That formal process they consider unnecessary and sometimes they might [feel] threatened if they have to sign [a written consent form]. [They might feel] there's more to it than [simply the study].

The challenges of meeting U.S. requirements for documentation of informed consent in international studies is particularly problematic when study participants are illiterate and if they are reluctant to formalize a document with their signature or thumbprint because of previous experiences that resulted in their victimization (e.g., loss of personal property or land) when "legal" documents were used against them.

Voluntariness. All of the investigators and research assistants interviewed recognized the importance of obtaining individual voluntary consent to participate in scientific research. Several issues were raised concerning challenges to voluntary consent, including a person's ability to comprehend the goals of the study and the risks involved and the vulnerability of patients to incentives such as the provision of money, drugs, or medical treatment. Investigators and research assistants also expressed concern about the power and authority of researchers because of their professional background and social status and the affect this power has on obtaining voluntary consent in research. A final challenge to voluntary consent noted by investigators and research assistants was the impact of community pressure to participate in a study if it has been sanctioned by community elders such as tribal Chiefs.

When asked what he thought the strongest challenges were in obtaining informed consent from prospective study participants, a physician noted:

> The strongest challenge is philosophical...that I'm [actually] getting informed consent, that participation is voluntary and that you've informed them to the point they can give informed consent.

Another physician stated:

> [You need to make sure to say] you are free to say no. I believe that anyone can understand those [basic] elements in the consent.

The issue of professional power and patient vulnerability in relation to voluntary consent in medical research was mentioned by many of the investigators and research assistants interviewed. For example, in his discussion of patients' understanding of the consent process, a physician suggested that it might be beneficial to have a focus group to learn more about what would increase their level of comprehension. He highlighted the power that investigators have in influencing voluntary participation because of their status and authority:

> What I would really like to do is administer an informed consent [document] to different people and then bring them together and ask what they felt about it and how they could be better informed about it, and how we could be more involved in insuring that the point where we got their signature they actually understand what you have explained without the 'White Coat' syndrome, without the power [issue].

The following observation made by a physician speaks directly to the vulnerability of patients and their reluctance to question or challenge physicians when the possibility of becoming involved in a clinical research project is raised:

> By the time a patient comes into the clinic or hospital he is a changed person. He is vulnerable, just hoping [he will be okay]. The thing that we have to establish is that the human rights perspective is very different in Nigeria and the United States and that modulates your response. If you haven't been brought up to question or challenge...[but to] accept circumstances, then I think there is [less willingness to challenge].

Several investigators called attention to the need for patients to understand that they could withdraw from the study, even after they agreed to participate. Despite the inclusion of this information in the consent discussion, researchers indicated that it was rare for individuals to withdraw from clinical studies, as noted by one of the physicians:

> Once they agree, they don't drop out...except if they feel you have not met your own obligations, for example, then you may find that people are 'turned off.'

Another investigator agreed, noting that as long as an individual receives medical treatment, it is unlikely they will drop out of the study:

> [One of the most important aspects of informed consent is to tell the person] that he doesn't have to participate, that he can pull out at any stage. [But] when a person is followed up and given free treatment, they do not want to pull out of they study. [For example, this patient's brother was also in the study but he has not been back for follow up.] Some patients, if they are only on a diet, they don't come around again. But if they are on drugs, then they usually don't back out of the study. The early patients, in Phase I [of the research], I don't see them so much [because the study part is over, the free treatment is over].

Many of the investigators and research assistants interviewed discussed the issue of providing inducements such as money, free drugs, medical care, or supplemental vitamins and medical supplies and the impact this may have on voluntary participation in scientific research. One physician indicated that because patients are informed fully of the study goals and what they receive if they agree to join a study, then there should not be a problem:

> Right now, the present state is adequate...[there is] no hiding of facts from them, [and there is] not anything that would be an inducement [to participate].

The following interaction between two physicians calls attention to the issue of trust and incentives to participate in the research:

Researcher 1: "The need to recognize their privacy [is important]...patients need to trust you. We need to give them a choice [and] there [are not] going to be any inducements."

Researcher 2: "The issue of inducements can be very subtle. [Sometimes] a patient [may] think that what she is doing is [trying] to please me, so sometimes you have got to be very professional. They are not used to it. Then you may come across as cold. If you come across as friendly [then it's easier for them]."

When asked about modifications of the consent form to accommodate the local context, a physician commented on the issue of incentives:

Physician: "Occasionally we do [need to modify it]. There are several cultural things, for example, we don't as a rule offer incentives. We offer incentives, but we don't include it in the informed consent."

Marshall: "Why is that?"

Physician: "Because the needs are different [in different communities]. We tailor the document to fit the needs of the community. For example, [when] we do studies in Ibadan, we say you will come [to the clinic] and we'll take some samples [e.g., tests], and we say we'll provide transportation fees and refreshments and vitamin supplements. In the rural area, we say we're doing this study so we can understand health care [whatever the problem is]. We offer explanations and we might give them vitamin supplements [but they may not need transportation, etc.]."

Several physicians noted that offering money as an incentive to participate in studies could be considered coercive under certain conditions:

Researcher 1: "Someone who offers $5.00 a week [to participate in their study], it could be coercive."

Researcher 2: "In the hypertension study in Maywood [U.S.], they offer money. But here we can't do that because it would be coercive because people would be so poor [they would participate no matter what]. We do offer incentives [for example, vitamins, drugs, transportation], but we don't tell them [they are incentives]….The real issue is this, if people participate, then it's as if it's only those people who need the money. They may feel obliged to do something, even if they are not. [They might think] 'I'll have a desire to please you because I feel obligated' [because of the money]."

Researcher 1: "So you don't drop me from the study or from the source of my money...instead of offering money we offer tablets or public health, or referrals [to other doctors]."

When asked about the impact of a study being sanctioned by community leaders such as tribal Chiefs on individual voluntary participation, a physician replied:

> It's important, but it's difficult to measure what is voluntary. The scenario I just described, when you have a central command system [the Chief...and council], and when you come with what is perceived as an improvement to their life, it would be difficult [to know if consent is voluntary] if the central command [Chief] says it [is good].

The importance of comprehension for voluntary consent was recognized by many of the investigators and research assistants. One research assistant working on the hypertension study emphasized how potential study participants are encouraged to take the consent form home to study it if they can read or to find someone who can read it for them if they cannot:

> We tell them [to find] someone to read [the consent if they don't read]...if they read [then they can do it themselves]...so we [tell them] we didn't force you. So they can take it to someone even if they don't read and then talk it over and then sign [with us later]. Most of the time this is what they do.

In summary, the investigators and research assistants agreed that an individual's voluntary participation was essential in conducting medical research. They emphasized the importance of personal trust in a physician or investigator and the powerful influence this has on a patient's willingness to participate. They also highlighted the potential for coercion through the offer of monetary inducements and the provision of drugs, medical treatments, or other supplies. Finally, comprehension was considered key to an individual's ability to voluntarily consent to a study. Investigators and research assistants mentioned strategies developed to reinforce voluntary consent such as explaining the study to a patient and encouraging him or her to review the consent form and discuss the project with family members.

2. Other Issues Related to Respect for Persons

Disclosure of Medical Information to Participants. The issue of disclosing or withholding medical information was discussed by several of the investigators and research assistants. They acknowledged that this is an important issue for physicians providing medical care when family members feel strongly about protecting loved ones from what they perceive as emotionally distressing information. For example, a physician and research assistants involved in the breast cancer study reported that often family members are reluctant to tell a patient that he or she has cancer because it is such a serious condition. One physician described an incident in which a woman from a "high positioned family" did not know that she was being treated for breast cancer because she was not told. However, most of the investigators indicated that they did not encounter problems associated with medical disclosure in the genetic epidemiological studies they were conducting. They emphasized that it would be impossible to obtain voluntary consent from an individual without fully informing them of the relevant medical information.

Confidentiality. The promise to respect privacy and confidentiality was perceived as an essential ingredient of the informed consent discussion among the investigators and research assistants interviewed. Many researchers commented on the tight-knit communities, neighborhoods, and families in Nigeria and the impact this can have on an individual if information about participation in a study is inadvertently disclosed. In the following interaction, for example, research assistants suggest that patients may be concerned about others learning their medical status or test results:

Researcher 1: "Before we get informed consent, [we explain the study] and they may have concerns about [how] it will affect other family members. Sometimes [they want to know tests results], and we don't have the results yet. They might be concerned about [whether] we are going to leak the information about the tests outside the family."

Researcher 2: "[They are concerned about] privacy."

Marshall: "Are they concerned about privacy in the family?"

Researcher 2: "Sometimes they want to keep it from the [village]."

Researcher 1: "I think it's the community...they don't want the community to know."

In another group discussion, research assistants stated similar concerns about respecting patient confidentiality:

Researcher 1: "Yes [confidentiality is important]. They don't want anyone to know in the neighborhood [that they are sick...or maybe that they are involved in the study]."

Researcher 2: "If they want to say something private they call you outside."

Several investigators and research assistants noted that the importance of confidentiality varies depending upon the nature of the specific study. One physician observed that in research on more controversial issues such as HIV/AIDS, maintaining confidentiality was absolutely critical:

> [The importance of confidentiality] depends on the study. If I was doing a study on sexuality, then if you want to get quality information, you need confidentiality all the time. For example, if it was a study on HIV [confidentiality is essential]. But [with something like the diabetes family study] then confidentiality is not so important. It depends on [medical] conditions that have bearing on one's integrity. For example, in this society, we like to think there are no homosexuals or lesbians...[in these cases] you have to be careful!

Another investigator described the importance of confidentiality in relation to stigma that might be attached to the disease being studied:

> [With] sickle cell anemia, it's serious. The thing is, even if you said you discovered a possible cure, everyone would try it [no matter what] because it [the disease] is so stressful. Most affected families are dislocated. Because [it's so hard]...they have some terrible social and psychological problems. Some families break up because you have to have a healthy child [sometimes you might need another wife to produce another child—hopefully without sickle cell]. So a lot depends on the condition and how it is viewed. Hypertension doesn't carry that kind of stigma.

One of the patients involved in the diabetes study recognized that some people might be concerned about privacy in relation to their medical condition or participation in a research project, but he claimed that he was not worried about this issue:

> I have nothing to hide….I fill out the questionnaire....I want to speak for diabetes [I want to do everything possible to make people feel more free to come forward when they are sick with diabetes].

A physician commented on the need to explain confidentiality to potential research subjects in a way that communicates clearly what is meant:

> The word 'confidentiality' [may be] too much for some patients to understand. So it's important to use language that they understand, like 'Information about you will not be spread around.'

3. Host Country IRBs

Nigerian investigators discussed administrative issues regarding the process of obtaining approval from ethical review committees. Several investigators commented on the difficulties of responding to the requirements of funding agencies in the United States and at local Nigerian institutions. They said it was particularly frustrating to try to respond to what they perceived as inconsistent requirements for ethical review. A physician in Lagos reported difficulties at many levels: dealing with the informed consent document itself, having to "fight with Washington" to change the consent form, and then going through the process of making the form useful and appropriate for his patients in Nigeria. In addition to adapting the consent document, this investigator was frustrated with the administrative aspects of the process including the amount of paperwork and committee negotiations:

> I had to produce *all* the documents for [our] IRB. They said it cannot be summarized. [I had to make nine copies] for our IRB. I photocopied the entire document and sent it to the Chair [of the IRB]. I told them in Washington I'm going to have problems [with the consent document]. [I revised it, then sent to our IRB.] I put it in the best language I could.

He noted that his office had to bear the burden of the expense of making the copies for the IRB and assembling the documents. This was difficult given the few resources available for copying and the lack of administrative assistance.

When asked whether they had encountered substantive problems in the review process with their local IRBs, the investigators reported that the most serious challenges were making accommodations in the informed consent. One physician observed:

> No [we did not have difficulties]. We met the informed consent [requirements] and they approved it. The protocol was no problem. We had to modify the informed consent, based on our experience with patients.

Another physician indicated that dealing with the local IRB was not difficult, but that addressing the concerns of Washington was more problematic:

> With the IRB here [in Nigeria] there were no problems. But we did have administrative issues with Washington, requests for modification of the informed consent [documents].

Several physicians expressed concerns about the possibility of overlooking some of the suggested modifications for consent forms because of the routing back and forth between U.S. and host researchers and their IRBs, in addition to the U.S. funding agency. One physician described a situation in which they received IRB approval for conducting a study from their institutional IRB. He went on to explain, "We sent it to [our colleagues in the United States] who sent it to NIH. They looked at the original consent [not ours] and they wanted modifications on the original." The U.S. investigators modified the consent form and sent it back to their Nigerian colleagues who, according to the investigator, "gave it to the [local] IRB who approved it and sent it back to NIH." In situations like this, the physician questioned whether all of the modifications would finally make it into the consent form actually used with patients because it would have gone through so many iterations and levels of review.

Investigators reported that IRB requirements in the United States called for a more precise and formal way of communicating information about a study. One physician said pointedly:

> In the West...the language is too exact and legalistic.

Other investigator respondents suggested that regulatory agencies in the United States should make a greater investment in the IRBs of host countries through training and the provision of materials and resources in order to facilitate the smooth and effective review and implementation of research projects. Some researchers believed that governmental funding agencies in the United States were often more interested in protecting themselves from litigation, rather than in promoting high standards of ethical conduct. The following interaction between several physicians illustrates some of the frustration with attempting to respond to requirements that appear to be too "legalistic:"

Researcher 1: "They should deal more with the local IRB [more attention should be given to the local IRB]."

Researcher 2: "Especially in a collaborative study because this is when it gets really crazy with NIH. Researchers from Ibadan send in a consent, and the NIH looks at it [and says] 'see page 3, line 5' and they are not in Ibadan. [The communication] is almost in a legalistic language."

Researcher 1: "They [the NIH] are more interested in avoiding litigation."

4. Moral Responsibility and Justice Issues

Many of the investigators interviewed expressed concern about issues related to human rights and the implementation of research in nations such as Nigeria that are resource poor. Investigators identified social and structural impediments that may hinder the effective application of what are considered to be international ethical standards. One physician described the profound influence of poverty on an individual's capacity to choose freely and autonomously to participate in research:

> Because of the scarcity of everything [in Nigeria], to be talking about a choice [is questionable]…in the United States, you can ask questions, you can ask for a second opinion, but that doesn't happen here. We are challenged by [our] culture, by poverty, by lack of literacy, by education of what basic rights a person has...[the] power [of these factors] is too awesome.

A physician commented specifically on the unequal access to resources between host country and U.S. collaborators that encourages a posture of acceptance to comply with what might be perceived as unnecessary or culturally inappropriate requirements in order to conduct a research project. He was particularly troubled about the rigorous standards of conduct applied to countries such as Nigeria when they were associated with an unwillingness to follow through with study evaluation or support at the completion of a project:

> There is the American system which requires us to do 'xyz' and that happens because they don't want to be responsible for things beyond the study. We are happy to do it because of the resources we get, apart from what's being asked. Also, there is the power issue in the donor-recipient relationship. If someone says here is $50,000 to do what you really want to do but before I give it to you have to [fulfill these requirements], fine….[But] there may not be follow-up or monetary [investment beyond the study] or evaluation. And no one really knows how we are applying [the regulations].

During individual and group interviews, investigators raised questions about the moral responsibility that researchers have to study participants and the communities in which the research is conducted. They also considered the implications of their research agendas for national priorities. The investigators recognized the stronger emphasis placed on individual rights in Western than in non-Western nations. In commenting on this issue, one of the respondents emphasized that it was not necessary to polarize respect for the individual and respect for the community, noting instead that both are essential and that in certain places in Nigeria it would be virtually impossible to conduct ethical research without acknowledging the importance of individual autonomy within the context of community. In his discussion of the application of foreign and local ethical standards, a physician suggested that both are significant, but that individual rights are paramount:

> I think there is a third alternative [to using local standards or foreign standards of ethics]. When foreign researchers work in my country, then there should be a hybridization of both local standards and international standards. What is most important from my perspective would be the rights of the individual even if the client is not aware of these issues.

5. Cultural Beliefs About Disease Etiology and Biomedical Procedures

Cultural beliefs about disease etiology and the use of body tissue such as blood for harmful purposes were thought to influence the informed consent process. The investigators and research assistants interviewed emphasized the importance of understanding, respecting, and accommodating cultural traditions concerning perceptions about the nature and cause of disease, beliefs about sorcery, and social relationships within the extended families that may affect recruitment practices and informed consent. In his reflections on the need for foreign investigators to respect the culture of the Yoruba people, a physician noted the following:

> The way the informed consent is presented must be sensitive to the culture of the people. The Yoruba, despite different religious views, tend to view life and death as a continuum, so death doesn't have that sense of finality that it has in the West. When [you are] talking about chronic disease and terminal illness, so much is influenced by cultural elements...expressions

> of religious [beliefs] and so on. Those influences are very strong, even though they don't find everyday expression.

Another physician commented on patients' beliefs about chronic illness and its affect on an individual's willingness to participate in the genetic epidemiological studies:

> In this study, no one refused [to participate], because we're dealing with a small number of people [so far]. It's not our patients who tend to [refuse]...but their siblings [who might] refuse. They are reticent. Most people don't know how to deal with chronic disease. Most people feel...[it can] be cured, so in the face of overwhelming disease they go into denial. They believe it shouldn't be happening...[They are] using traditional methods for a cure before they come to you. They believe that the diabetes will go away, so accepting to participate in a chronic disease study is like accepting defeat.

In some cases, cultural beliefs concerning the cause and treatment of disease may differ radically from Western views about underlying disease etiology. When asked if he thought patients understood the nature of the research, for example, a physician said:

> To a large extent, yes, but communication within the power structure of the conversation [is important]. It's difficult for one to say if what you are saying is acceptable to the other, or understood so they can make a decision. Indeed, 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.

When asked to give an example, this physician replied:

> If [a relative] dies suddenly they might believe the person was killed by sorcery. That's a very widely pervasive belief system. When you come from that background, when you talk about...meningitis or malaria...which is common…you spend a lot of time educating them...or you can use other people to educate them, to persuade them [so they understand the study].

Many of the investigators and research assistants described patients' concerns related to beliefs about the use of sorcery to inflict illness and disease on individuals. In describing beliefs about the cause of hypertension, for example, a physician noted that some of his patients think that it might be due to sorcery:

> Some people ask us what causes hypertension...whether it's inherited or whether it's caused by someone thinking something [as in sorcery].

Similar views were expressed by research assistants in their description of patients' understanding of the etiology of hypertension:

Researcher 1: "Some people think it's a new problem [hypertension] and we explain it's not. [They think it's new] because people would suddenly [get sick] and people did not know [that it was finally symptomatic]."

Researcher 2: "People did not know and would think it was caused by black medicine and they would drink alcohol [and do other things that might not be good for them]."

Many of the investigators and research assistants described patients' fears that blood drawn for laboratory tests could be used to practice sorcery against them, as indicated in this observation made by a physician:

> When you collect biological specimens [such as blood], people believe you can bewitch people. If you need 10 ml [of blood], you can't say that. You need to say [we will collect a] tablespoon or teaspoon. [But] people don't want to hear that.

A research assistant agreed, saying:

> There are concerns about drawing too much blood. People are worried about the affect on their health, and also what you are going to do with it [some might think it could be used for sorcery].

The power associated with blood and the implications for study procedures involving blood draws was mentioned repeatedly by many investigators and research assistants. The importance of cultural beliefs and values surrounding blood are revealed in the following interaction with three investigators:

Researcher 1: "When blood spills on the hand, or floor, or anywhere, patients get upset and [say] 'That much [blood]!?' because [the blood] spreads."

Researcher 2: "We think about blood in Yoruba in terms of sacrificial [rituals] or slaughter, but human blood is much different to deal with in a neutral fashion."

Researcher 3: "In fact, it can never be neutral because it's alive."

Investigators and research assistants highlighted beliefs concerning the negative impact of taking what is believed to be large amounts of blood for testing. Researchers attempt to minimize the amount of blood necessary for study tests, as one of the physicians suggests:

> [Patients say] 'You are taking so much blood from me and how will it affect me?' And I say, 'You shouldn't worry, you have so much and we are only taking just a little from you.' We try to explain in simple language what we do with the blood and that we will not use it in any other way outside of the tests.

Several investigators and research assistants reported that patients are concerned about replacing the blood that is taken for laboratory tests, as indicated in the following interaction between research assistants:

Researcher 1: "[They are] concerned...about how to replace the blood."

Researcher 2: "[They] ask for a drug to [help] replace it [the blood], or [they ask] for money for food."

Researcher 1: "But they will not ask for it directly...only indirectly."

Researcher 3: "[They will say], 'How are you going to replace [the blood]?"

Although investigators and research assistants reported that only a small number of patients refused to participate in the genetic studies because of questions concerning the use of their blood, they all agreed that beliefs about the potential harm associated with the misuse of blood specimens could be a consideration in the decisionmaking process. The following interaction between two physicians illustrates the profound impact these beliefs may have on informed consent and the successful implementation of a research project:

Researcher 1: "[Some] concepts are completely alien to people. For example, if you tell someone you are going to take some blood, or you say they are going to die in the process [of doing the study], no one can accept that. When you take someone's body fluid, some people think you are taking a person's goodness and that can [bring them] harm, even without you having done anything."

Researcher 2: "This is especially true with blood."

Researcher 1: "Psychologically, people may begin to feel strange. We went to a do a village study on anemia and we took [a very small amount] of blood from each child. After [we obtained] consent from everyone, a mother came [to us] after a few days and said her children could not participate in the study. [It happened in 1992], and this is a village where we'd been for years."

Researcher 2: "[News spreads] and the study had to stop because other mothers pulled out [after they heard that the one mother pulled her children out]."

Many of the investigators and research assistants commented on the importance of educating and reassuring potential participants about the purpose for drawing blood and how it might be used. A physician noted:

> [There is a problem] with blood drawing...[people may be] hesitant because of the amount of blood. Most people believe that blood is so precious that any amount could be wasted. You have to allay their fears and explain that the amount is insignificant.

An individual's experience with blood draws and his or her educational background are believed to influence response to the need for blood tests associated with the genetic studies. Indeed, one of the patients was asked during the interview if he had any questions about the study for the researchers when they obtained informed consent from him. He replied:

> I don't ask any questions about the blood because I work here and I am familiar with what they do with the blood. I am satisfied [with the study...with what happens to me...to my blood].

Other cultural factors that influence recruitment strategies and informed consent are normative social practices associated with marriages involving multiple wives. In genetic epidemiological studies, investigators may want to enroll family members who are genetically related to each other. When a man has more than one wife, but researchers only want to recruit the wife who is genetically important to the study, they must navigate the potentially disruptive social consequences for extended family households. The following interaction in a group discussion illustrates this point:

Researcher 1: "[Speaking of recruiting individuals for the control sample] The wife of one of the patients, she came willingly, but she's motivated."

Researcher 2: "This type of control is easier [to recruit] because they have experience [with diabetes...they are more familiar with the problems]."

Researcher 1: "We need one control per family."

Researcher 2: "[You might] go to a family and a man has three wives and you go to the youngest. She doesn't have kids yet, so theoretically she is not genetically related. So according to the requirements [it's not necessary to recruit her]. But you create a social problem...so we do it as a service [test her for diabetes]. So if [there is a perception] that [it will be a problem in the family if the youngest one is left out—the one with no children yet] go ahead and include her."

Researcher 3: "But the senior wife may refuse [because of her age, or her husband may be concerned about her age, her health and not want her tested]."

Researcher 2: "Try to explain why she's a better control than the younger wife...she may understand why it's better to have the 60 year old rather than the [younger wife]...but no arm twisting!"

In summary, investigators and research assistants reported a number of cultural beliefs that may impact the informed consent process and someone's willingness to participate in scientific research. Specifically, beliefs about the cause and expression of diseases such as hypertension and diabetes and beliefs about the practice of

sorcery and the power of body fluids and tissues were identified as factors that influence a potential subject's comprehension of the study goals and their decision concerning participation. Moreover, social traditions such as marriage customs in which men have more than one wife were also recognized as factors in recruiting participants for genetic epidemiological studies.

IV. Recommendations

Investigators and research assistants were asked about recommendations for changes in regulations for the ethical review of research protocols, including requirements for informed consent and documentation. The following recommendations include strategies used to overcome some of the obstacles they have encountered in their research along with suggestions for future modifications in the implementation of policy governing ethical review of research.

A. Informed Consent

Informing Participants and Participant Understanding. Investigators and research assistants expressed serious concerns about difficulties associated with communication and comprehension in obtaining consent from participants. Specifically, they noted difficulties with the translation of English words for which there are no equivalents and with communicating difficult scientific concepts. Additionally, they suggested that in the United States, consent forms tend to be lengthy and complex and often include information that may be confusing to patients.

In their recommendations, investigators and research assistants stressed the importance of educating both the community and individual participants about the study and its specific purpose and procedures. They noted that education at the community level may begin long before the project is initiated through extensive interaction with community leaders in which local people are invited to participate in discussions of the study goals and strategies for implementation. Community education should not be seen as a single event, but rather as an ongoing process in which the community is kept aware of research activities and findings. Maintaining an open and interactive dialogue at the community level could take a variety of forms including, for example, holding regularly scheduled meetings with local community leaders or tribal elders or distributing a newsletter that provides information about the research project and its study team.

In regard to educating individuals about the study, the investigators and research assistants recommended instituting strategies that allow participants time to discuss the study with family members or others in the community. They noted that it is very helpful to have something written, such as an information sheet or a brochure for people to take home with them. If patients do not read themselves, this gives them an opportunity to find someone to read the information to them. Another recommendation is to establish a process for informed consent that takes place over several encounters, not one. In the hypertension study, for example, the study is first explained to individuals at the clinic. They are provided with the consent form, and an appointment is made to visit them at home at a later date. Consent for the study is obtained at the second meeting.

Another option for ensuring that potential subjects understand the nature and purpose of the study is to assess their comprehension through a process of requesting feedback from them concerning the study goals and risks. This could be accomplished by simply asking individuals to tell the person obtaining informed consent what is understood to be the purpose of the study and the risks involved. Investigators and research assistants also emphasized that it would be important to get feedback on the crucial dimensions of voluntariness, confidentiality, and the possibility of withdrawing from the study at any time.

Disclosure of Risks in Informed Consent. Information included in informed consent documents about risks associated with study procedures was a major concern for investigators and research assistants. They recognize that in the United States there is much greater emphasis on communicating every possible harm to research subjects. They noted that the language regarding risks is often extraneous, irrelevant, or culturally inappropriate. They recommended that host country investigators should be allowed greater freedom to determine how to report risks in a way that is culturally sensitive and appropriate without diminishing the significance of the potential harms. They also emphasized the importance of providing strong reassurances about the procedures in place to minimize risks to individuals.

Autonomy and Locus of Decisional Authority. Researchers working in some areas must negotiate permission to conduct a study from local community leaders, including tribal Chiefs, in addition to obtaining informed consent from individual study participants. Investigators and research assistants interviewed emphasized the need for developing strategies for informed consent that respect individual autonomy while simultaneously showing deference for local traditions that demand particular attention to community elders. Well-defined protocols for obtaining permission from community elders to conduct a study exist in Nigeria and other countries where community approval is required. Foreign investigators should accommodate these traditional community protocols. However, upholding the internationally agreed-upon standard for individual voluntary consent may be challenging for persons who are vulnerable because of their gender or their status in their extended household or local community. Investigators and research assistants recommended that patients should be given considerable reassurances about their ability to refuse to participate and to withdraw if they choose. Educating patients about study objectives and the informed consent process was considered to be an essential aspect of reinforcing respect for individual autonomy in the context of community sanctions that may encourage participation.

Documentation. Investigators and research assistants were concerned about two issues regarding requirements for documentation of informed consent by U.S. funding agencies: first, the length and complexity of informed consent documents; and second, the need for written consent. They called attention to the problem of overwhelming individuals with too much information for them to realistically comprehend. The challenges of meeting U.S. requirements for documentation of informed consent in international studies is particularly problematic when study participants are illiterate and if they are reluctant to formalize a document with their signature or thumbprint because of previous experiences that resulted in their victimization such as losing personal property or land when "legal" documents were used against them. Investigators recommended that regulatory agencies should allow greater freedom in developing consent forms that address the essential aspects of the study and ethical standards for voluntary consent.

Voluntariness. Four issues were raised concerning challenges to voluntary consent: 1) a person's ability to comprehend the goals of the study and the risks involved; 2) the vulnerability of patients to incentives such as the provision of money, drugs, or medical treatment; 3) the power investigators have to influence a person's decision to participate because of their professional authority and social status; and 4) the impact of community pressure to participate in a study if it has been sanctioned by community elders such as tribal Chiefs.

Recommendations include the following: 1) establishing methods to ensure that individuals understand the study goals and procedures, such as providing thorough explanations of the research project; 2) providing written information about the study that individuals could read or have read to them; 3) requesting feedback that demonstrates comprehension; 4) providing considerable opportunities for discussion with family members or others; and 5) devising a process of informed consent that takes place over several encounters rather than one. Investigators and research assistants also recommended offering incentives to participate that are not coercive given the sociocultural and economic environment. Educational efforts to increase individual and community knowledge about the importance of voluntary consent were recommended to diminish the impact of community sanctions.

B. Other Issues Related to Respect for Persons

Disclosure of Medical Information to Participants. The investigators and research assistants interviewed agreed that it would be impossible to obtain voluntary consent from an individual without fully informing him or her of the relevant medical information. They acknowledged that disclosing or withholding medical information may be a consideration for physicians providing medical care when family members feel strongly about protecting loved ones from distressing news. Nevertheless, they recommended that there should be no deviation from the current standard regarding full disclosure of information in the consent discussion for participation in research.

Confidentiality. Respect for privacy and confidentiality was perceived as an essential ethical practice in the conduct of research. Investigators and research assistants commented on the possible negative consequences for individuals if information about someone's medical condition or study participation is inadvertently disclosed. Specifically, they noted concerns about stigmatization in relation to certain types of illness and disease, such as HIV/AIDS. They recommended that study participants should be provided with clear explanations and ongoing reassurances (if necessary) about procedures in place to protect individual privacy.

C. Host Country IRBs

Investigators discussed two primary issues regarding the process of obtaining approval from local ethical review committees. First, investigators commented on the difficulties of responding to what often are perceived as inconsistent requirements of funding agencies in the United States and at local Nigerian institutions. Second, investigators noted administrative difficulties associated with the bureaucracy and management of local IRBs.

Recommendations address capacity building for IRBs in host countries. Investigators suggest that regulatory agencies should develop and provide training workshops for IRB committee members and that there should be a greater financial investment in providing materials and resources in order to facilitate the smooth and effective review and implementation of research projects. Another recommendation concerns the possibility of instituting and maintaining collaborative relationships between foreign and local IRBs.

D. Moral Responsibility and Justice Issues

Investigators expressed concern about issues related to human rights and the implementation of research in nations such as Nigeria that are resource poor. Social and structural impediments that may hinder the effective application of what are considered to be international ethical standards were identified. These include factors such as poverty, illiteracy, and in some countries, the presence of dictatorial or authoritarian governmental regimes that seriously diminish the expression of individual freedom. Another factor concerns the unequal access to resources between host country and U.S. collaborators that may encourage a willingness to comply with what might be perceived as unnecessary or culturally inappropriate requirements in order to conduct a research project.

While investigators acknowledged that these issues are daunting for individual researchers to address, they recommended that every attempt should be made to encourage the protection of basic human rights, particularly in relation to enabling voluntary consent to participation in research. They recommended that host country investigators should be included at all levels in the design and implementation of research projects. They also recommended that host and foreign collaborators should consider carefully issues related to standard of care and commitments of researchers to provide treatment for study participants once the project has ended.

E. Cultural Beliefs About Disease Etiology and Biomedical Procedures

Cultural beliefs about disease etiology and the use of body tissue such as blood for harmful purposes were thought to influence the informed consent process. Additionally, social traditions such as marriage customs in which men have more than one wife were also recognized as factors in recruiting participants for genetic epidemiological studies.

In their recommendations, the investigators and research assistants emphasized the importance of understanding, respecting, and accommodating cultural traditions concerning perceptions about the nature and cause of disease, beliefs about sorcery, and social relationships within the extended families that may affect recruitment practices and informed consent. Specifically, they suggested that foreign researchers should become knowledgeable about local customs, traditions, and beliefs that are relevant to the study goals. They recommended that potential research subjects should be provided with thorough explanations about the medical conditions being researched. Strategies for implementing this recommendation include 1) allowing time in the consent discussion for questions about the particular problem; 2) providing written information to participants that they could read themselves or have read to them; and 3) ensuring that ample opportunities are available for discussion of the study with family members or others (this may include obtaining consent in a two-step process in which the study is explained and, at a later time, consent is obtained).

V. Conclusions

Results of the review of the literature and findings from the case study of genetic epidemiological research being conducted in Nigeria suggest a number of obstacles to informed consent in international scientific investigations and ethical review of protocols at host country institutions. Although concerns about ethical challenges to informed consent are not unique to research being conducted in international settings, investigators involved in collaborative studies may encounter difficulties because of cultural traditions and structural factors that influence the implementation of research.

The challenges associated with the application of informed consent are heightened in international settings because of language barriers that may inhibit effective communication, particularly regarding the translation of scientific concepts. Differences in beliefs about who has the authority to give permission to participate in research may also create obstacles to obtaining individual voluntary consent. Securing study approval from community leaders, tribal elders, or household heads is no substitute for individual consent, regardless of the cultural setting. Nevertheless, it would be naive to assume that an individual is free from community pressures or social customs regarding decisional authority. Thus, it is imperative to devise strategies for ensuring, to the degree possible, that potential research subjects comprehend adequately the goals and risks associated with the study and that their decision to participate is a choice, not a mandate.

Investigators and research assistants interviewed for the case study question the relevance of human subject regulations that seem to be impediments to conducting ethically sound research. Specifically, they noted stringent requirements for including information on consent forms that may be superfluous, culturally inappropriate, confusing and, in some cases, unnecessarily alarming for potential subjects. For example, in the United States, the inclusion of a detailed description of all possible risks, regardless of how minimal, is emphasized. Moreover, U.S. consent forms often are lengthy and complex. The investigators and research assistants noted that this gives the appearance that funding agencies are more concerned about shielding themselves from future litigation rather than protecting the individuals actually involved in studies. Thus, as Kass and Hyder (1999) and Sugarman (1999) observe in their preliminary analyses of data collected in focus groups and interviews with researchers involved in international studies, regulations serve bureaucratic purposes but do not necessarily assist investigators in meeting ethically acceptable standards of conduct.

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Comparative Analysis of International Documents Addressing the Protection of Research Participants

Staff Analysis
National Bioethics Advisory Commission

Introduction

This chart compares the texts of 25 documents that address the protection of research participants. The first seven documents were developed by various international organizations and provide general guidance:

- The Nuremberg Code (1947)
- Declaration of Helsinki (2000)
- Council of Europe – Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine (1997)
- Council for International Organizations of Medical Sciences (CIOMS) – International Ethical Guidelines for Biomedical Research Involving Human Subjects (1993)
- Council for International Organizations of Medical Sciences (CIOMS) – International Guidelines for Ethical Review of Epidemiological Studies (1991)
- International Conference on Harmonisation (ICH) – Harmonised Tripartite Guideline, Guideline for Good Clinical Practice (1996)
- UNAIDS – Ethical Considerations in HIV Preventive Vaccine Research (2000)

The remaining 18 documents come from countries around the world and provide regulations or guidance specific to that country:

- Australia – National Statement on Ethical Conduct in Research Involving Humans (1999)
- Brazil – Resolutions 196/1996, 251/1997, and 292/1999 (1996–1999)
- Canada – Tri-Council Policy Statement, Ethical Conduct for Research Involving Humans (1998)
- China – Guidelines on Ethical Review of Medical Research (1998)
- Denmark – Act on a Scientific Ethical Committee System and the Handling of Biomedical Research Subjects (1992)
- Finland – Decrees 494/1998 and 986/1999 (1992–1999)
- France – Law 88-1138 Regarding the Protection of Persons Agreeing to Biomedical Research (1988)
- India – Indian Council of Medical Research (ICMR), Ethical Guidelines on Biomedical Research Involving Human Subjects (2000)
- Netherlands – Law Regarding Medical-Scientific Research on Humans (1998)
- New Zealand – Health Research Council (HRC), Guidelines on Ethics in Health Research (1997)
- South Africa – Medical Research Council (MRC), Guidelines on Ethics for Medical Research (1993)
- Thailand – Rule of the Medical Council on the Observance of Medical Ethics (1995)
- Uganda – Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda (1997)
- United Kingdom – Medical Research Council (MRC), Guidelines for Good Clinical Practice in Clinical Trials (1998)
- United Kingdom – Medical Research Council (MRC), Interim Guidelines for Research Involving Human Participants in Developing Societies, Ethical Guidelines for MRC-Sponsored Studies (1999)
- United States – Food and Drug Administration (FDA)
- United States – Common Rule
- United States – Agency for International Development (USAID)

This chart is not intended to provide an exhaustive analysis of all 25 documents. Rather, it attempts to highlight similar and different provisions contained within them.

Explanation of Chart Headings

The chart is divided into six parts:

Part 1. Informed Consent and Disclosure

Informed Consent Process: One of the key protections for human participants participating in research is the informed consent process. Every document has specified a need for the informed consent process.

Voluntariness of Consent: All research participants should have the legal capacity to give their free and voluntary consent and not be subject to coercion or undue inducement by researchers to give consent. The language in the documents reflect these concerns and attempt to delineate what is and what is not acceptable conduct.

Disclosure to Research Participants: Essential to the informed consent process is the amount and type of information that is disclosed to research participants prior to the start of the research study. The documents include provisions that 1) require researchers to disclose certain elements to research participants and 2) address a number of related concerns.

Documentation and Other Protections: Although most organizations and countries require written informed consent, the documents have language requiring varying degrees of documentation which is reflected in the chart.

Exceptions and Waivers: Most documents have specified that exceptions and waivers to the informed consent requirements should be granted based on the type of research study being conducted, and have included language in each document to reflect this concern.

Privacy and Confidentiality: The availability of powerful computers and the Internet has made accessing and sharing data less difficult. As a result, privacy and confidentiality concerns have become more prevalent. Several documents have directly addressed this concern.

Part 2. Assessing Risks and Benefits

Risk/Potential Benefit Analysis: The other of the twin protections for human participants in research is independent review of the harms and benefits of the research. Every document has language that defines the boundaries of acceptable risk to research participants and explains the process of assessing predictable harms and foreseeable benefits.

Part 3. Selection of Participants and Distribution of Risks and Potential Benefits

Distributive Justice: In this context, distributive justice has been divided into three separate categories that vary in focus. The first column includes provisions that prohibit the exclusion of certain groups from participating in a research study. The second column includes provisions that require the equitable distribution of harms and benefits among research participants. The third column includes provisions that require the equitable distribution of harms and benefits within and among communities.

Special Protections: Almost every document has specified special groups that require additional protections which have been incorporated into each document.

Part 4. Study Design Considerations

Prior Ethical and/or Scientific Review by Independent Body: The United States relies on the Institutional Review Board (IRB) system to oversee protection of research participants at the local level. Other organizations and countries have similar oversight mechanisms in place, which are reflected in the provisions of the documents.

Level of Treatment: The phrase "best proven diagnostic and therapeutic method" in the Declaration of Helsinki has generated considerable discussion as to its meaning and implementation. Some documents have either included similar language or referred to this phrase in the Declaration of Helsinki.

Providing Research Results to Research Participants: This column refers not to publishing research results in a peer-reviewed scholarly journal but to informing research participants, the local research community, and the affected community-at-large of the research results.

Part 5. Obligations to Research Participants

Treatment and Compensation for Injured Research Participants: Many documents have provisions (although varying in specificity) that require researchers and/or sponsors to provide compensation and treatment for research participants who are injured during the course of a research study.

Duty Owed to Research Participants During/After Trial: Several documents have provisions that explicitly state the duty that researchers owe to research participants and the larger community during the course of and after the conclusion of a research study.

Successful Products Made Reasonably Available: Several documents have provisions that researchers should consider providing a therapeutic intervention to study participants after the research study has ended.

Part 6. Legal Considerations

Equivalent Protections (Harmonization of Standards): As the documents indicate, the scope of protection for research participants at the international level is uneven, but attempts continue to harmonize these standards. For example, the International Conference on Harmonization (ICH) has made strides in developing a common standard for the European Union, Japan, and the United States to facilitate the mutual acceptance of clinical data. Other documents have provisions that attempt to provide equivalent protections when research is conducted elsewhere.

Research and Review of Research Conducted in Other Countries: For international research projects, several documents require ethical review in both the country where the sponsor is located and in the country where the research is to be carried out.

Have Force and Effect of Law?: The documents use a variety of words such as *principle, guideline, law, and regulation*. After reading the compliance and/or enforcement provisions contained in each document and consulting outside experts, it was determined whether each document carried the same weight as the law of a particular country or group of countries.

Covers Privately-Funded Research?: The legal and ethical scope of each document is limited by the authority granted to it. For example, United States regulations only cover federally-funded research, while the law in Uganda explicitly covers all research regardless of whether it is publicly or privately funded.

Table Abbreviations

These are the abbreviations used in the table: CER = Committee on Ethics in Research; **DSMB** = Data Safety Monitoring Board; **GCP** = Good Clinical Practice; **HRC** = Health Research Council; **HREC** = Human Research Ethics Committee; **IEC** = Independent Ethics Committee; **IND** = Investigational New Drug Application; **IRB** = Institutional Review Board; **IRC** = Institutional Review Committee; **MOPH** = Ministry of Public Health; **MRC** = Medical Research Council; **NHMRC** = National Health and Medical Research Council; **REB** = Research Ethics Board; **RCT** = Randomized Controlled Trial; **UNCST** = Uganda National Council for Science and Technology

PART 1. Comparative Analysis of International Documents Addressing the Protection of Research Participants

	Informed Consent Process	Voluntariness of Consent	Disclosure to Research Participants	Documentation and Other Protections	Exceptions and Waivers	Privacy and Confidentiality
Nuremberg Code (1947)	**Principle 1** "The voluntary consent of the human subject is absolutely essential ..."	**Principle 1** "... the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion ..."	**Principle 1** "... the person involved ... should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision ..."	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED
Declaration of Helsinki (2000)	**Principle 20** "The subjects must be volunteers and informed participants in the research project."	**Principle 23** "When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress …"	**Principle 22** "... each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail ..."	**Principle 22** "...After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing."	**Principle 22** "…If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed."	**Principle 26** "... Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject."
Council of Europe (1997)	**Article 5** "An intervention ... may only be carried out after the person concerned has given free and informed consent to it ... The person concerned may freely withdraw consent at any time."	NOT MENTIONED	**Article 5** "... This person shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks. The person concerned may freely withdraw consent at any time."	**Article 16(v)** "... the necessary consent as provided for … has been given expressly, specifically and is documented ..."	**Article 8** "When because of an emergency situation the appropriate consent cannot be obtained, any medically necessary intervention may be carried out immediately for the benefit of the health of the individual concerned."	**Article 10** "Everyone has the right to respect for private life in relation to information about his or her health." "Everyone is entitled to know any information collected about his or her health. However, the wishes of the individuals not to be so informed shall be observed."

PART 1. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Informed Consent Process	Voluntariness of Consent	Disclosure to Research Participants	Documentation and Other Protections	Exceptions and Waivers	Privacy and Confidentiality
continued Council of Europe (1997)			**Article 16(iv)** "... persons undergoing research have been informed of their rights and safeguards prescribed by law for their protection."		**Article 9** "The previously expressed wishes related to a medical intervention by a patient who is not, at the time of the intervention, in a state to express his or her wishes shall be taken into account."	"…. restrictions may be placed by law on the exercise of the rights ... in the interests of the patient."
Council for International Organizations of Medical Sciences (CIOMS) (1993)	**Guideline 1** "... the investigator must obtain the informed consent of the prospective subject ..." **Guideline 3** obligations of investigators regarding informed consent: continuing consent **Guideline 8** "Before undertaking research involving subjects in underdeveloped communities, whether in developed or developing countries, the investigator must ensure that: … every effort will be made to secure the ethical imperative that the consent of individual subjects be informed …"	**Guideline 4** "Subjects may be paid for inconvenience and time spent, and should be reimbursed for expenses incurred, in connection with their participation in research; they may also receive free medical services. However, the payments should not be so large or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment ("undue inducement") ..." (see Guideline 3)	**Guideline 2** "Before requesting an individual's consent to participate in research, the investigator must provide the individual with the following information, in language that he or she is capable of understanding: (9 criteria)" **Guideline 3** obligations of investigators regarding informed consent: necessary information, opportunity to ask questions	**Guideline 3** obligations of investigators regarding informed consent: documentation of consent	**Commentary on Guideline 1** *"When the research design involves no more than minimal risk ... and it is not practicable to obtain informed consent from each subject ... the ethical review committee may waive some or all of the elements of informed consent ..."* **Guideline 9** "For several types of epidemiological research individual informed consent is either impracticable or inadvisable. In such cases the ethical review committee should determine whether it is ethically acceptable to proceed without individual informed consent ..."	**Guideline 12** "The investigator must establish secure safeguards of the confidentiality of research data. Subjects should be told of the limits to the investigators' ability to safeguard confidentiality and of the anticipated consequences of breaches of confidentiality."

PART 1. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Informed Consent Process	Voluntariness of Consent	Disclosure to Research Participants	Documentation and Other Protections	Exceptions and Waivers	Privacy and Confidentiality
Council for International Organizations of Medical Sciences (CIOMS) (1991)	**Principle 1** "When individuals are to be subjects of epidemiological studies, their informed consent will usually be sought ..." **Principle 2** "An investigator who proposes not to seek informed consent has the obligation to explain to an ethical review committee how the study would be ethical in its absence ..." **Principle 5** "When it is not possible to request informed consent from every individual studied, the agreement of a representative of a community or group may be sought, but the representative should be chosen according to the nature, traditions and political philosophy of the community or group. Approval given by a community representative should be consistent with ethical principles ..."	**Principle 10** "Prospective subjects may not feel free to refuse requests from those who have power or influence over them ... Investigators are expected to explain to the ethical review committee how they propose to neutralize such apparent influence." **Principle 11** "Individuals or communities should not be pressured to participate in a study. However, it can be hard to draw the line between exerting pressure or offering inappropriate inducements and creating legitimate motivation ... To determine the ethical propriety of such inducements, they must be assessed in light of the traditions of the culture." **Principle 12** "It is acceptable to repay incurred expenses … Similarly, promises of compensation and care for damage, injury or loss of income should not be considered inducements."	**Principle 1** "... Consent is informed when it is given by a person who understands the purpose and nature of the study, what participation in the study requires the person to do and to risk, and what benefits are intended from the study."	NOT MENTIONED	**Principle 2** "An investigator who proposes not to seek informed consent has the obligation to explain to an ethical review committee how the study would be ethical in its absence ..."	**Principle 3** "An ethical issue may arise when occupational records, medical records, tissue samples, etc. are used for a purpose for which consent was not given ... Individuals ... should normally be told that their data might be used in epidemiological studies ... when such information is to be used, it is understood that investigators will minimize disclosure of personally sensitive information." **Principle 26** "... investigators should make arrangements for protecting the confidentiality of such data by, for example, omitting information that might lead to the identification of individual subjects, or limiting access to the data, or by other means ..."

PART 1. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Informed Consent Process	Voluntariness of Consent	Disclosure to Research Participants	Documentation and Other Protections	Exceptions and Waivers	Privacy and Confidentiality
International Conference on Harmonisation (ICH) (1996)	**Principle 2.9** "Freely given informed consent should be obtained from every subject prior to clinical trial participation." **Principle 4.8.1** "In obtaining and documenting informed consent, the investigator… should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki …" **Principle 4.8.9** "If a subject is unable to read ... an impartial witness should be present during the entire informed consent discussion ..."	**Principle 4.8.3** "Neither the investigator, nor the trial staff, shall coerce or unduly influence a subject to participate or to continue to participate in a trial."	**Principle 4.8.2** "... The subject ... should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial." **Principle 4.8.5** "The investigator ... should fully inform the subject ... of all pertinent aspects of the trial ..." **Principle 4.8.6** "The language used ... should be as non-technical as practical and should be understandable to the subject ..." **Principle 4.8.7** "Before informed consent may be obtained, the investigator ... should provide the subject ... ample time and opportunity to inquire about details ... and to decide whether or not to participate in the trial ..." **Principle 4.8.10** 20 elements for written informed consent form	**Principle 4.8.8** "... the written informed consent form should be signed and personally dated by the subject ... and by the person who conducted the informed consent discussion."	**Principle 4.8.15** "In emergency situations, when prior consent of the subject is not possible ... enrollment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety, and well-being of the subject and to ensure compliance with acceptable regulatory requirements."	**Principle 2.11** "The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s)."

Part 1. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Informed Consent Process	Voluntariness of Consent	Disclosure to Research Participants	Documentation and Other Protections	Exceptions and Waivers	Privacy and Confidentiality
UNAIDS (2000)	**Guidance Point 12** "Independent and informed consent … should be obtained from each individual while being screened for eligibility for participation in an HIV preventive vaccine trial and before s/he is actually enrolled in the trial … Informed consent, with pre- and post-test counselling, should also be obtained for any testing for HIV status conducted before, during, and after the research."	**Guidance Point 10** "The research protocol should outline the benefits that persons participating in HIV preventive vaccine trials should experience as a result of their participation. Care should be taken so that these are not presented in a way that unduly influences freedom of choice in participation." **Guidance Point 12** "… Efforts should be taken to ensure throughout the trial that participants continue to understand and to participate freely as the trial progresses …"	**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 ..." **Guidance Point 12** "Independent and informed consent based on complete, accurate, and appropriately conveyed and understood information should be obtained from each individual …"	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED

Part 1. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Informed Consent Process	Voluntariness of Consent	Disclosure to Research Participants	Documentation and Other Protections	Exceptions and Waivers	Privacy and Confidentiality
Australia (1999)	**Principle 1.7** "Before research is undertaken … the consent of the participants must be obtained …" **Principle 1.8** "A person may refuse to participate in a research project and need give no reasons nor justification for that decision."	**Principle 1.7(b)** "… obtaining consent should involve the exercise of a voluntary choice to participate." **Principle 1.10** "The consent of a person to participate in research must not be subject to any coercion, or to any inducement or influence which could impair its voluntary character." **Principle 12.6(a)** "An HREC must examine those aspects of the budgets of clinical trials which raise ethical issues … It should be satisfied that payment in money or kind would not cause researchers to apply pressure to individuals so as to obtain their consent to participate."	**Principle 1.7(a)** "… obtaining consent should involve provision to participants, at their level of comprehension, of information about the purpose, methods, demands, risks, inconveniences, discomforts, and possible outcomes of the research …" **Principle 1.12** "A participant must be free at any time to withdraw consent to further involvement in the research. If any consequences may arise from such withdrawal, advice must be given to participants about these before consent to involvement in the research is obtained."	**Principle 1.9** "… research must be so designed that each participant's consent is clearly established, whether by a signed form, return of a survey, recorded agreement for interview or other sufficient means … In some circumstances and some communities, consent is not only a matter of individual agreement, but involves other properly interested parties … In such cases the researcher needs to obtain the consent of all properly interested parties before beginning the research."	**Principle 1.11** "It is ethically acceptable to conduct certain types of research without obtaining consent from participants in some circumstances, for example, the use of de-identified data in epidemiological research, observational research in public places, or the use of anonymous surveys."	**Principle 1.19** "… research must strive to ensure that the privacy, confidentiality and cultural sensitivities of the participants and/or the collectivity are respected ..." **Principle 12.11** "In a clinical trial ... (a) data management should comply with relevant privacy requirements ...; (b) if data are of a confidential nature, confidentiality must be observed; (c) data and records must be preserved ... as prescribed by laws of the Commonwealth, the relevant State or Territory or national policies or guidelines ..." **Principle 18.1** "An HREC must be satisfied that a research proposal conforms to all relevant Commonwealth, State or Territory privacy legislation or codes of practice." **Principle 18.2** "An HREC must be satisfied that, where a research proposal involves the collection, storage, disclosure, or other use of personal information, the privacy of persons to whom that information relates is protected ..."

PART 1. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Informed Consent Process	Voluntariness of Consent	Disclosure to Research Participants	Documentation and Other Protections	Exceptions and Waivers	Privacy and Confidentiality
Brazil (1996–1999)	Resolution No. 196/1996 **III.1.a** "Ethics in research signifies freely given and informed consent of target-individuals and the protection of vulnerable groups and the legally disabled (autonomy) …" **III.3.h** "Research involving human subjects … must … have the freely given and informed consent of the research subject …" **IV** "… research must only be carried out after informed consent has been freely given by the prospective research subjects … who have expressed their agreement to participate in the research …" **IV.3.e** "… in communities with a different culture, including Indigenous communities, prior consent must be obtained from the community, through its leaders, without foregoing, however, efforts to obtain individual consent."	Resolution No. 196/1996 **II.11** "Freely given and informed consent — agreement of the research subject … without flaws (simulation, fraud, or error), dependency, subordination, or intimidation, after a complete and detailed explanation about the nature of the research, its objectives, methods, foreseen benefits, potential risks … set forth in a term of consent, authorizing the subject's voluntary participation in the research." **IV.3.b** "… freedom of consent must be particularly guaranteed to those individuals who, although adults and capable, are exposed to specific conditioning or to the influence of authority … ensuring them complete freedom to participate, or not, in the research, without any retaliation." **IV.3.f** "… when the merit of the research depends on some restriction of information to the subjects, such fact must be duly stated and justified by the researchers … The data obtained … cannot be used for purposes other than those contemplated …"	Resolution No. 196/1996 **IV.1** "Accessible language must be used in providing the prospective subjects information about the research, always including the following: (9 elements)" **V.7** "… The form used in obtaining the freely given and informed consent of the research subjects must not contain any clause exempting the researcher from responsibility or depriving any individual of his/her legal rights, including the right to seek an indemnity for injury resulting from the research."	Resolution No. 196/1996 **IV.2.c** "The terms of freely given and informed consent must … be signed by or identified with the fingerprint of each and every research subject …"	Resolution No. 196/1996 **IV.3.c** "… in the event it is impossible to record the freely given and informed consent of the research subject, such fact must be duly documented, with an explanation of the causes and the technical opinion of the Committee for Ethics in Research …"	Resolution No. 196/1996 **III.3.i** "Research involving human subjects … must … plan procedures that will ensure confidentiality and privacy, protection of the image and non-stigmatization of the research subjects, guaranteeing that the information obtained will not be used to the detriment of individuals and/or communities …"

PART 1. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Informed Consent Process	Voluntariness of Consent	Disclosure to Research Participants	Documentation and Other Protections	Exceptions and Waivers	Privacy and Confidentiality
Canada (1998)	**Article 2.1(a)** "Research ... may begin only if (1) prospective subjects ... have been given the opportunity to give free and informed consent about participation, and (2) their free and informed consent has been given and is maintained throughout their participation in the research."	**Article 2.2** "Free and informed consent must be voluntarily given, without manipulation, undue influence, or coercion." Section 1.C1 "... There is a similar threshold regarding undue or excessive offers of benefit. As an offer of payment in relation to research participation exceeds the normal range of benefits open to the research subject, it is increasingly likely to amount to an undue incentive for participation." **Article 2.4(d)** "An assurance that prospective subjects are free not to participate, have the right to withdraw at any time without prejudice to pre-existing entitlements, and will be given continuing and meaningful opportunities for deciding whether or not to continue to participate."	**Article 2.4** "Researchers shall provide to prospective subjects ... full and frank disclosure of all information relevant to free and informed consent. Throughout the free and informed consent process, the researcher must ensure that prospective subjects are given adequate opportunity to discuss and contemplate their participation. (5 elements)" **Commentary to Article 2.4** *"Research subjects … may have cultural values different from those of the researcher … researchers must clearly explain the nature and goals of the research … in a manner appropriate for the prospective subjects' cultural settings."* (see Table 1 — additional information that may be required for some projects)	**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."	**Article 2.1(c)** "The REB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent ... or waive the requirements to obtain informed consent, provided that the REB finds and documents that: (5 criteria)" **Article 2.8** "... research involving emergency health situations shall be conducted only if it addresses the emergency needs of individuals involved, and then only in accordance with criteria established in advance of such research by the REB. The REB may allow research that involves health emergencies to be carried out without the free and informed consent of the subject ... if ALL of the following apply: (6 criteria)"	**Article 3.1** "... researchers who intend to interview a human subject to secure identifiable personal information shall secure REB approval for the interview procedure used and shall ensure the free and informed consent of the interviewee ..." **Article 3.2** "... researchers shall secure REB approval for obtaining identifiable personal information about subjects. Approval for such research shall include such considerations as: (8 considerations)" **Article 3.3** "If identifying information is involved, REB approval shall be sought for secondary uses of data. Researchers may gain access to identifying information if they have demonstrated to the satisfaction of the REB that: (3 elements)" (see Articles 3.4, 3.5, 3.6)

PART 1. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Informed Consent Process	Voluntariness of Consent	Disclosure to Research Participants	Documentation and Other Protections	Exceptions and Waivers	Privacy and Confidentiality
China (1998)	**Article 15** "… only when the informed consent signed by human subject is obtained, it can be judged that the human subject consents to participate … when the procedure or condition of the research is changed, the change must be explained to human subjects in detail, and the consent must be obtained again from them."	**Article 17** "Researcher should commit to give certain compensation or free medical services to human subjects, but the amount or services should not constitute an inducement …" **Article 15** "The researcher should respect human subjects … must not use cheating, threat and other undue means to human subjects …"	**Article 15** "The researcher should respect human subjects. Sufficient time should be given to human subjects to ask questions or give answers … must provide adequate and relevant information and knowledge to human subjects and give them adequate time to consider, and then ask them to make decision of whether to consent to participate …"	**Article 10** "All biomedical research involving human subjects must obtain written informed consent from human subjects …"	NOT MENTIONED	**Article 18** "Perfect confidential measures must be taken to the research materials. The researcher must not disclose anything involving the privacy of human subjects to media …"
Denmark (1992)	**Act No. 503 § 8 Section 1** "As a part of their evaluation of the committees will have to secure that: … their free and explicit consent will be obtained and given in writing."	**Act No. 503 § 8 Section 5** "If research subjects receive a salary or other remuneration in return for their participation in the study, the committee will have to approve such remuneration and to control that it is not influencing the consenting improperly."	**Act No. 503 § 8 Section 1** "As a part of their evaluation of the committees will have to secure that: … the patients or healthy volunteers participating in the project will be informed in writing and verbally about its content, foreseeable risks and advantages …" **Act No. 503 § 8 Section 4** "As a part of their evaluation of the committees will have to secure that: … it is obvious from the information sheets, that patients and healthy volunteers … at any time can retract their consent."	**Act No. 503 § 8 Section 1** "As a part of their evaluation of the committees will have to secure that: … their free and explicit consent will be obtained and given in writing."	NOT MENTIONED (no exceptions or waivers are permitted in Danish legislation)	NOT MENTIONED (Danish Council of Ethics has separate report entitled "Protection of Personal Sensitive Information")

PART 1. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Informed Consent Process	Voluntariness of Consent	Disclosure to Research Participants	Documentation and Other Protections	Exceptions and Waivers	Privacy and Confidentiality
Finland (1992–1999)	**Statute No. 488/1999 Section 6** "Medical research on persons may not be conducted without the research subject's informed consent in writing …"	**Statute No. 488/1999 Section 21** "No payment shall be made for participating in the research to the research subjects … However, an appropriate remuneration may be paid in respect of expenses or loss of earnings or for any other inconvenience suffered as the result of the research."	**Statute No. 785/1992 Section 5** "A patient shall be given information …. related to his/her treatment that are significant when decisions are made on the treatment given to him/her … Health care professionals should try to give the information in such a way that the patient can understand it …" **Statute No. 488/1999 Section 6** "Research subjects shall have their rights, the purpose and nature of the research and the procedures it involves properly explained to them. The potential risks and harm shall also be properly explained to them. This information shall be given so that research subjects are in a position to give their informed consent as regards issues connected with the research that have a bearing on their decision-making." "Research subjects shall be entitled to withdraw their consent at any point prior to the completion of the research. They shall be informed of this right before the start of the research."	**Statute No. 488/1999 Section 6** "Medical research on persons may not be conducted without the research subject's informed consent in writing …"	**Statute No. 488/1999 Section 6** "… Exceptions to this may be made where consent cannot be obtained owing to the urgency of the matter and the patient's state of health and the measure is expected to be of immediate benefit to the patient's health …"	**Statute No. 785/1992 Section 13** "The information in patient documents is confidential." "Health care professionals … shall not give information in patient documents to outsiders without a written consent of the patient." **Statute No. 488/1999 Section 23** "… Confidential information obtained in the course of activities … and relating to research plans, personal information concerning other persons, their state of health, personal circumstances or financial status or business or trade secrets, must not be disclosed to a third party."

PART 1. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Informed Consent Process	Voluntariness of Consent	Disclosure to Research Participants	Documentation and Other Protections	Exceptions and Waivers	Privacy and Confidentiality
France (1988)	**Title II, Article L. 209–9** "... The investigator shall inform the person whose consent is sought that he is entitled to refuse to participate in research and to revoke his consent at any time without incurring any penalty ..."	**Title I, Article L. 209–8** "Biomedical research shall not give rise to any financial consideration other than reimbursement of expenses incurred ..."	**Title II, Article L. 209–9** "Before biomedical research is conducted on a person, his free, informed, and express consent shall be obtained by the investigator ... who shall inform the person of: (3 elements)"	**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 ... wholly independent of the investigator and or the sponsor."	**Title II, Article L. 209–9** "... in biomedical research to be carried out in emergency situations ... the protocol submitted for the opinion of the Committee ... may dispense with obtaining the consent of the participant and require that only the consent of any next of kin present be obtained ..."	NOT MENTIONED
India (2000)	**General Principle 2** "…The principles of informed consent and voluntariness are cardinal principles to be observed throughout … the nature and form of the consent … shall depend upon the degree and seriousness of the invasiveness into the concerned human subject's person and privacy, health and life … and the overall purpose and the importance of the research." **General Ethical Issue 1** "For all biomedical research involving human subjects, the investigator must obtain the informed consent of the prospective subject …"	**General Principle 2** "… research subjects are fully apprised of the research and the impact and risk of such research on the research subject and others; and … retain the right to abstain from further participation in the research irrespective of any legal or other obligation …" **General Ethical Issue 2** "The investigator has a duty to: exclude the possibility of unjustified deception, undue influence and intimidation; seek consent only after prospective subject is adequately informed …; not use intimidation in any form which invalidates informed consent ..."	**General Principle 3** "[research subjects are] kept fully apprised of all the dangers arising in and out of the research so that they can appreciate all the physical and psychological risks as well as moral implications of the research …" **General Ethical Issue 3** "… the investigator must provide the individual with … information in the language he or she is able to understand which should not only be scientifically accurate but should also be sensitive to their social and cultural context: (15 elements)"	**General Ethical Issue 3** "The investigator has a duty to: … obtain from each prospective subject a signed form as an evidence of informed consent (written informed consent) preferably witnessed by a person not related with the trial …"	**General Ethical Issue 1** "When research design involves no more than minimal risk … the Institutional Ethics Committee may waive off some of the elements of informed consent. Waiver of informed consent could also be considered during conditions of emergency."	**General Principle 4** "… the identity and records of the human subjects … are as far as possible kept confidential …" **General Ethical Issue 4** "The investigator must safeguard the confidentiality of research data, which might lead to the identification of the individual subjects."

PART 1. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Informed Consent Process	Voluntariness of Consent	Disclosure to Research Participants	Documentation and Other Protections	Exceptions and Waivers	Privacy and Confidentiality
continued India (2000)	**General Ethical Issue 2** "The investigator has a duty to: communicate with prospective subject all the information necessary for informed consent. There should not be any restriction on subject's right to ask any questions related to the study …"	**General Ethical Issue 4** "Subjects may be paid for the inconvenience and time spent, and should be reimbursed for expenses incurred ... They may also receive free medical services. However, payments should not be so large or the medical services so extensive as to induce prospective subjects to consent to participate in research against their better judgement (inducement)."	**General Ethical Issue 8** **Special Concern 5** "The nature, magnitude, and probability of all foreseeable harms resulting from participation in a collaborative research programme should be specified in the research protocol and explained to the participants as fully as can be reasonably done."			
Netherlands (1998)	**Article 6.1a** "Performing scientific research is prohibited ... if the experimental subject is of adult age ... without written permission from the individual involved." **Article 6.4** "... The potential subject will be granted sufficient time to make an informed decision regarding the requested permission based on this information."	**Article 3f** "A commission may only grant a positive decision on a research protocol if ... it is reasonably plausible that the compensation to be paid to the experimental subject is not disproportionally influential in the granting of approval for participation in the research ..." **Article 5** "Performing scientific research on experimental subjects about whom a reasonable assumption exists that they are not free to decide to participate in it ... is prohibited ..."	**Article 6.3** "Before permission is requested, those who are performing the research ensure that the person whose permission is required receives written information concerning: (4 elements)" **Article 6.4** "The information will be provided in such a way that it is reasonably certain that the parties involved will completely understand its contents ..." **Article 6.5** (researchers must inform children under the age of 12 … about the research "in a manner in keeping with their comprehension level")	**Article 6.1a** "Performing scientific research is prohibited ... if the experimental subject is of adult age ... without written permission from the individual involved."	**Article 6.2** "If the scientific research can be carried out under an emergency situation in which the permission required ... cannot be granted, and may benefit the person ... actions for carrying it out may take place without permission as long as the circumstance that makes it impossible to grant permission arises."	**Article 12** "Those who are performing the scientific research will ensure that the personal life of the experimental subject is protected as much as possible."

PART 1. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Informed Consent Process	Voluntariness of Consent	Disclosure to Research Participants	Documentation and Other Protections	Exceptions and Waivers	Privacy and Confidentiality
continued Netherlands (1998)			**Article 9** "… ensure that the experimental subject may refer to a physician indicated in the research protocol who is not involved in carrying out the research for information and advice regarding the research." **Article 11** "… ensure that the experimental subject is informed in good time … about the course of the research …"			
New Zealand (1997)	**Chapter 3–Part A** "In most cases research constitutes a health care procedure and, as such, written informed consent will be required unless there are good reasons to the contrary."	**Chapter 3–Part B** "Any payment … to a research participant … which is an inducement to participate in research is unacceptable." **Chapter 3–Part A** "… The participants' consent must be voluntary and not influenced by financial reward … or by duress in any manner …" **Chapter 3–Part A** "… Participants must be able to withdraw from the investigation at any time without waiver of any rights and without giving reasons …"	**Chapter 4–Part B** "Subjects have the right to receive, in language that they will easily understand, information about proposed research in which they have been invited to participate." **Chapter 3–Part A** "Elements of informed consent include but are not limited to: … Information about the proposed research being comprehensively, properly and appropriately given, including any likely outcomes of participation in the research ..."	**Chapter 3–Part A** "In most cases research constitutes a health care procedure and, as such, written informed consent will be required unless there are good reasons to the contrary."	**Chapter 3–Part A** "If consent is not obtained in writing the justification should be given to the reviewing ethics committee, and the circumstances under which consent was obtained should be recorded. Ethics committees will be required to consider if the circumstances are appropriate ones in which to waive written consent."	**Chapter 3–Part C** "6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject." **Chapter 6–Part A** "The Health Information Privacy Code 1994 (HIPC) is the starting point for any consideration of the privacy issues which arise in health research."

PART 1. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Informed Consent Process	Voluntariness of Consent	Disclosure to Research Participants	Documentation and Other Protections	Exceptions and Waivers	Privacy and Confidentiality
South Africa (1993)	**Chapter 8** "For consent to be valid it should be offered voluntarily and be based on adequate understanding, with due regard to the patient's language and culture."	**Chapter 6** "There should … be no coercion, overt or covert, of anyone to volunteer for research, whether the pressure be financial, for academic or employment advantage, for job security, or for other reasons." **Chapter 9** ■ Inducements to healthy volunteers ■ Inducements directed towards patients ■ Offer of otherwise unobtainable treatment ■ Offer of superior care and attention	**Chapter 7** "The patient should be assured that if he agrees to participate in the research he will remain free to withdraw at any time, that no reason need be given for the withdrawal, and that withdrawal will be accepted without question, without incurring displeasure and without any disadvantage to future care." **Chapter 8** "If there is more than minimal risk, these measures are mandatory: a subject information sheet [8 elements]; time to reflect; … a responsible third party may act as an adviser to the patient …"	**Chapter 8** "Where comprehension of the research by the subject is not straightforward … the simple procedure of seeking oral consent after an oral explanation may need to be supported by additional measures … If there is more than minimal risk, these measures are mandatory: … written consent … witnessed consent may be a useful alternative in patients with impaired capacity to comprehend."	**Chapter 8** "There are some circumstances in which it is justifiable to initiate research without the consent of the patient. Prior approval of the Research Ethics Committee must be obtained in all cases." **Chapter 8** "Some research is without intrusiveness or risk and may justifiably be conducted without the patient's consent …"	**Chapter 7** "Investigators should be aware of the dangers of releasing confidential information about patients participating in a study to any third party, unless the patient … has consented to this." **Chapter 11** "It is essential that information about a patient acquired in the course of research should be regarded as completely confidential … Sensible precautions should be taken to preserve confidentiality." **Chapter 19** "The records of the patient/subject should at all times be treated as confidential."
Thailand (1995)	**# 4** "The subject … must have agreed to the study by signing the consent form after being properly informed. The consent form should follow the MOPH requirement."	NOT MENTIONED	**# 6** "Researchers have to explain clearly to potential subjects: (5 elements)" **# 10** "Subjects … are free to withdraw the consent to participate in the study. The withdrawal will not affect any entitlement to those treatments that may be required under normal circumstances."	**# 4** "The subject … must have agreed to the study by signing the consent form after being properly informed. The consent form should follow the MOPH requirement."	NOT MENTIONED	NOT MENTIONED

PART 1. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Informed Consent Process	Voluntariness of Consent	Disclosure to Research Participants	Documentation and Other Protections	Exceptions and Waivers	Privacy and Confidentiality
Uganda (1997)	**III.E.(4)** "Informed consent will be sought from each individual prospective research participant ..." **IV.A.** "... no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the individual research participant ... a community leader may not consent to the participation of community members ..." (9 required and 6 optional elements) **IV.H.(3)** privacy exception to written informed consent form	**IV.A** "... An investigator shall seek such consent under circumstances that provide the prospective research participant ... sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence ..."	**IV.A** "…. The information ... shall be in language understandable to the research participant ... whether it is conveyed orally or in writing ..."	**III.E.(5)** "Informed consent will be appropriately documented …" **IV.H.(1)** "... informed consent shall be documented by the use of a written informed consent form approved by the IRC and signed by the research participant ..."	**IV.H.(3)** "An IRC may waive the requirement for the investigator to obtain a signed consent form if the IRC finds that the only record linking the research participant and the research would be the consent document and the principal risk to the participant would be potential harm resulting from a breach of confidentiality ..."	**IV.A.(1)** "Basic elements of informed consent include the following. These elements must be included in the information provided to each research participant in order for the consent to be valid. (e) a statement describing the extent, if any, to which confidentiality of the research participants will be maintained."
United Kingdom (1998)	**Principle 2.9** "Freely given informed consent should be obtained from every participant prior to clinical trial participation." **Principle 3.1.10** "The proposal states that freely given informed consent will be sought from every participant prior to clinical trial participation whenever possible."	**Principle 2.9** "Freely given informed consent should be obtained from every participant prior to clinical trial participation."	**Principle 3.1.9** "… all potential trial participants will be informed whenever possible of the possible benefits and known risks of the intervention ... and of the possibility that there are unknown risks." **Principle 5.4.6** "Appropriate information should be provided in a form which is readily accessible and at a level	**Principle 5.4.2** "The participant's consent to participate should be obtained through signing an appropriate consent form ..."	**Principle 5.4.3** "In the case of children up to the age of 18, mentally incapacitated individuals who cannot give informed consent and the unconscious, particular considerations apply …"	**Principle 2.11** "The confidentiality of records that could identify participants should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s)."

PART 1. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Informed Consent Process	Voluntariness of Consent	Disclosure to Research Participants	Documentation and Other Protections	Exceptions and Waivers	Privacy and Confidentiality
continued United Kingdom (1998)	**Principle 5.4.2** "Whenever possible, all participants ... must give their consent to participate in the trial on the basis of appropriate information and with adequate time to consider this information and ask questions."		which will enable an informed decision by the trial participants ... regarding participation in the trial." **Principle 5.4.5** "The participants ... must be made aware before consenting to participate that they are free to withdraw without obligation at any time and that such an action will not adversely affect any aspect of their care."			
United Kingdom (1999)*	**General Principle 4** "The research must normally be done only with the full and informed consent of the individual participants; particular restrictions and safeguards are required when this is not possible ..."	**General Principle 5** "There must be neither inducement nor coercion; for certain types of non-therapeutic research participants may be recompensed for their expense, time, and inconvenience."	**Specific Consideration 8** "Special care should be taken to obtain valid informed consent from participants … in particular, all prospective participants must fully understand that their participation is entirely voluntary and that they are free to refuse to participate or withdraw at any time without loss of any entitlement."	**Specific Consideration 8** "... A permanent personalised record of consent should be retained, although this need not necessarily be in the form of a signature."	NOT MENTIONED* (see footnote)	NOT MENTIONED* (see footnote)

* "The MRC's key principles, which are underpinned by the Declaration of Helsinki and outlined in *Responsibility in Investigations on Human Participants and Material and on Personal Information,* 1992, apply to research conducted in developing societies … In addition, investigators are expected to follow the *MRC Guidelines for Good Clinical Practice in Clinical Trials*, which are based on the ICH Harmonised Tripartite Guideline for Good Clinical Practice."

PART 1. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Informed Consent Process	Voluntariness of Consent	Disclosure to Research Participants	Documentation and Other Protections	Exceptions and Waivers	Privacy and Confidentiality
United States Food and Drug Administration (FDA) Title 21 Code of Federal Regulations	**21 CFR § 50.20** "... no investigator may involve a human being as a subject in research ... unless the investigator has obtained the legally effective informed consent of the subject ..." **21 CFR § 50.23(a)** "The obtaining of informed consent shall be deemed feasible unless ... both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following: (4 criteria)"	**21 CFR § 50.20** "... An investigator shall seek such consent only under circumstances that provide the prospective subject ... sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence ..."	**21 CFR § 50.20** "... The information that is given ... shall be in language understandable to the subject ..." **21 CFR § 50.25(a)–(b)** 8 required and 6 optional elements for informed consent **21 CFR § 50.25(c)** "The informed consent requirements ... are not intended to preempt any applicable ... laws which require additional information to be disclosed for informed consent to be legally effective."	**21 CFR § 50.27** "… informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject ... at the time of consent."	**21 CFR § 50.23(a)** exception from general requirements (4 required elements) **21 CFR § 50.24** exception from informed consent requirements for emergency research	**21 CFR § 56.111(a)(7)** "… there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data."
United States Common Rule** Title 45 Code of Federal Regulations	**45 CFR § 46.116** "... no investigator may involve a human being as a subject in research ... unless the investigator has obtained the legally effective informed consent of the subject ..." **45 CFR § 46.116(d)** "An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent ... or waive the requirements to obtain informed consent provided the IRB finds and documents that: (4 criteria)"	**45 CFR § 46.116** "... An investigator shall seek such consent only under circumstances that provide the prospective subject ... sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence ..."	**45 CFR § 46.116** "... The information that is given ... shall be in language understandable to the subject ..." **45 CFR § 46.116(a)–(b)** 8 required and 6 optional elements for informed consent **45 CFR § 46.116(e)** "The informed consent requirements ... are not intended to preempt any applicable ... laws which require additional information to be disclosed for informed consent to be legally effective."	**45 CFR § 46.117(a)** "... informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject ..." **45 CFR § 46.117(b)** "... the consent form may be either of the following: (1) A written consent form that embodies the elements of informed consent ... (2) A short form written consent document stating that the elements of informed consent ... have been presented orally to the subject ..."	**45 CFR § 46.116(c)** "An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent ..."	**45 CFR 46.111(a)(7)** "… there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data."

** The Federal Policy for the Protection of Human Subjects, also known as the Common Rule, is found at 45 CFR Part 46, Subpart A. Many federal agencies that conduct research involving human participants, including the Department of Health and Human Services (DHHS) and the Agency for International Development (USAID), are signatories to the Common Rule. Note that DHHS has passed regulations that include not only Part A but also Parts B, C, and D which address special protections for pregnant women, prisoners, and children. Likewise, USAID has passed separate regulations found at 22 CFR Part 225 which mirror 45 CFR Part 46, Subpart A.

PART 1. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Informed Consent Process	Voluntariness of Consent	Disclosure to Research Participants	Documentation and Other Protections	Exceptions and Waivers	Privacy and Confidentiality
United States Agency for International Development (USAID) Title 22 Code of Federal Regulations	**22 CFR § 225.116** "... no investigator may involve a human being as a subject in research ... unless the investigator has obtained the legally effective informed consent of the subject ..." **22 CFR § 225.116(d)** "An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent ... or waive the requirements to obtain informed consent provided the IRB finds and documents that: (4 criteria)"	**22 CFR § 225.116** "... An investigator shall seek such consent only under circumstances that provide the prospective subject ... sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence ..."	**22 CFR § 225.116** "... The information that is given ... shall be in language understandable to the subject ..." **22 CFR § 225.116(a)–(b)** 8 required and 6 optional elements for informed consent **22 CFR § 225.116(e)** "The informed consent requirements ... are not intended to preempt any applicable ... laws which require additional information to be disclosed for informed consent to be legally effective."	**22 CFR § 225.117(a)** "... informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject ..."	**22 CFR § 225.116(c)** "An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent ..."	**22 CFR § 225.111(a)(7)** "… there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data."

PART 2. Comparative Analysis of International Documents Addressing the Protection of Research Participants

	Risk/Potential Benefit Analysis
Nuremberg Code (1947)	**Principle 5** "No experiment should be conducted, where there is an *a priori* reason to believe that death or disabling injury will occur ..." **Principle 6** "The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment."
Declaration of Helsinki (2000)	**Principle 5** "In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society." **Principle 7** "In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens." **Principle 16** "Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others..." **Principle 17** "Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed…" **Principle 18** "Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject…" **Principle 19** "Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research."
Council of Europe (1997)	**Article 2** "The interests and welfare of the human being shall prevail over the sole interest of society or science." **Article 16(ii)** "Research on a person may only be undertaken if all the following conditions are met ... the risks which may be incurred by that person are not disproportionate to the potential benefits of the research ..."
Council for International Organizations of Medical Sciences (CIOMS) (1993)	**Commentary on Guideline 14** *"The Declaration of Helsinki forbids the imposition of unwarranted risks on human research subjects. Article I.4 requires that 'the importance is in proportion to the inherent risk to the subject.' … The Declaration of Helsinki, Article I.7 … requires forgoing research involving human subjects unless 'the hazards involved are believed to be predictable,' and … Article I.5 … requires that clinical testing 'be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others.'*
Council for International Organizations of Medical Sciences (CIOMS) (1991)	**Principle 19** "... Investigators will inform ethical review committees and prospective subjects of perceived risks, and of proposals to prevent or mitigate them. Investigators must be able to demonstrate that the benefits outweigh the risks ..."

PART 2. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Risk/Potential Benefit Analysis
International Conference on Harmonisation (ICH) (1996)	**Principle 2.2** "Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society ..." **Principle 2.3** "The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society."
UNAIDS (2000)	**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, as well as the modalities by which to address these, including provision for the highest level of care to participants who experience adverse reactions to the vaccine, compensation for injury related to the research, and referral to psycho/social and legal support, as necessary." **Guidance Point 10** "The research protocol should outline the benefits that persons participating in HIV preventive vaccine trials should experience as a result of their participation …"
Australia (1999)	**Principle 1.3** "… the ethical principle of beneficence is expressed in researchers' responsibility to minimise risks of harm or discomfort to participants in research projects." **Principle 1.6** "The proportion of burdens for any research participant will vary. In clinical research, where patient care is combined with an intent to contribute to knowledge, the risks of participation must be balanced by the possibility of intended benefits for the participants …" **Principle 1.14** "All research proposals must be so designed as to ensure that any risks of discomfort or harm to participants are balanced by the likely benefit to be gained." **Principle 12.2(c)** "An HREC must consider all aspects of the design of a clinical trial and be satisfied that where the research is therapeutic, and is therefore intended and likely to be of direct benefit to participants, there is an acceptable balance between the risks and benefits of the trial."
Brazil (1996–1999)	**Resolution No. 196/1996** **III.1.b** "Ethics in research signifies weighing risks and benefits, both actual and potential, individual and collective (beneficence), making a commitment to maximize benefits and minimize distress and risks." **III.1.c** "Ethics in research signifies ensuring that predictable injury will be prevented (non-maleficence)." **III.3.d** "Research involving human subjects … must … always favour the probability of foreseen benefits, rather than predictable risks."

PART 2. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Risk/Potential Benefit Analysis
contined Brazil (1996–1999)	**V.1** "Despite potential risks, research involving human subjects will be admissible provided that: a) it is highly probable that it will generate knowledge that will permit understanding, preventing, or attenuating a problem that affects the well-being of the research subjects …; b) the risk is justified by the importance of the expected benefit; and c) the benefit is greater than or equal to other, already established prevention, diagnosis or treatment alternatives." **V.2** "Research without direct benefit to individuals must include conditions easily tolerated by the research subjects, considering their physical, psychological, social, and educational status." **Resolution No. 251/1997** **I.4** "… the dignity and well-being of the research subject must prevail over any other interests, whether economic, scientific, or of the community."
Canada (1998)	(see page i.6) *"… subjects are participants in the development of a research project … such collaboration entails an active involvement by research subjects, and ensures both that their interests are central to the project or study … researchers and research subjects may not always see the harms and benefits of a research project in the same way."* (see page i.7) **Section 1.C1** "If potential subjects can reasonably be expected to regard the probability and magnitude of possible harms implied by participation in the research to be no greater than those encountered by the subject in those aspects of his or her everyday life that relate to the research then the research can be regarded as within the range of minimal risk ..." **Article 1.5(a)** "The REB shall satisfy itself that the design of a research project that poses more than minimal risk is capable of addressing the questions being asked in the research." **Article 1.6** "The REB should adopt a proportionate approach based on the general principle that the more invasive the research, the greater should be the care in assessing the research."
China (1998)	NOT MENTIONED
Denmark (1992)	**Act No. 503 § 8 Section 1** "As part of their evaluation of the committees will have to secure that: the risks, that might be connected with implementation of a project, have been meticulously judged and that they not in themselves or in relation to the foreseeable advantages of the project have an unjustifiable magnitude …"
Finland (1992–1999)	**Statute No. 488/1999** **Section 4** *Weighing up benefits and harmful effects* "In medical research the interests and well-being of the research subject shall always be put before any benefits to science or society. Measures shall be taken to prevent any risks or harmful effects to the research subject, as far as possible." "Research subjects may be exposed only to measures where the expected health or scientific benefit is unequivocally greater than the potential risks or harm to the research subject."

PART 2. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Risk/Potential Benefit Analysis
France (1988)	**Title I, Article L. 209–2** "Biomedical research may not be conducted on human beings if ... the foreseeable risk to participants in the research is disproportionate to the anticipated benefit for them or to the value of such research ..." **Title IV, Article L. 209–14** "Biomedical research without direct therapeutic objectives may not entail any foreseeable risk to the health of participants ..."
India (2000)	**General Principle 5** "… due care and caution is taken at all stages … to ensure that the research subject … [is] put to the minimum risk, suffer[s] from no irreversible adverse effects and … benefit[s] from and by the research or experiment …" **General Ethical Issue 8** **Special Concern 3** "Careful consideration should be given to protect the dignity, safety and welfare of the participants when the social contexts of the proposed research can create foreseeable conditions for exploitation of the participants or increase the vulnerability to harm and the steps to be taken to overcome these should be described."
Netherlands (1998)	**Article 3c** "A commission may only grant a positive decision on a research protocol if ... it is reasonably plausible that there will be a proportional ratio of burden and risk upon the experimental subject in the research ..."
New Zealand (1997)	**Chapter 3–Part C** "4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject." "5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others."
South Africa (1993)	**Chapter 5** "A key decision in the assessment of proposed research is whether the risk or inconvenience caused to the patient is justifiable in relation to the value of the information sought." **Chapter 5** "The Research Ethics Committee needs to do more than a mere risk/benefit analysis in deciding whether research is justifiable. A proper assessment of whether the risk to the patient seems to be outweighed by the probable benefits can only be arrived at if the Research Ethics Committee itself has a proper regard for the comfort and safety of the individual participant."
Thailand (1995)	**# 7** "Researchers should select methods of study which will cause minimal impact on the subject's physical and mental health."
Uganda (1997)	**I.B.(7)** "*Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests." **III.E.(1)** "Risks to subjects are minimized (a) by using procedures which are consistent with sound research design and which do not unnecessarily expose the research participants to risk and (b) ... by using procedures already being performed on the subjects for diagnostic or treatment purposes."

PART 2. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Risk/Potential Benefit Analysis
contined Uganda (1997)	**III.E.(2)** "Risks to research participants are reasonable in relation to anticipated benefits ... and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits the UNCST should consider only those risks and benefits that may result from the research ... The UNCST should also consider possible long-range effects of applying knowledge gained in the research as among those research risks that fall within the purview of its responsibility."
United Kingdom (1998)	**Principle 2.2** "Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial participant and society." **Principle 2.3** "…the rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society." **Principle 6.6.1** "In all the deliberations of the TSC the rights, safety and wellbeing of the trial participants are the most important considerations and should prevail over the interests of science and society. The TSC should ensure that the protocol demands freely given informed consent from every trials participant. The TSC should look closely at the patient information provided and advise the investigators on its completeness and suitability."
United Kingdom (1999)*	**General Principle 3** "The potential and known risks of the research to the participants must be taken into account by participant and investigator as well as the potential benefits of the research to the participants or others." **Special Consideration 5** "The balance of risks and benefits is that pertaining to the circumstances and setting of the study."
United States Food and Drug Administration (FDA) Title 21 Code of Federal Regulations	**21 CFR § 50.3(k) and 21 CFR § 56.102(i)** "*Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." **21 CFR § 56.111(a)(1)** "Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes." **21 CFR § 56.111(a)(2)** "Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research ... The IRB should not consider possible long-range effects of applying knowledge gained in the research ... as among those research risks that fall within the purview of its responsibility."

* "The MRC's key principles, which are underpinned by the Declaration of Helsinki and outlined in *Responsibility in Investigations on Human Participants and Material and on Personal Information*, 1992, apply to research conducted in developing societies … In addition, investigators are expected to follow the *MRC Guidelines for Good Clinical Practice in Clinical Trials*, which are based on the ICH Harmonised Tripartite Guideline for Good Clinical Practice."

PART 2. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Risk/Potential Benefit Analysis
United States Common Rule** Title 45 Code of Federal Regulations	**45 CFR § 46.102 (i)** "*Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." **45 CFR § 46.111(a)(1)** "Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes." **45 CFR § 46.111(a)(2)** "Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research ... The IRB should not consider possible long-range effects of applying knowledge gained in the research ... as among those research risks that fall within the purview of its responsibility."
United States Agency for International Development (USAID) Title 22 Code of Federal Regulations	**22 CFR § 225.102(l)** "*Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

** The Federal Policy for the Protection of Human Subjects, also known as the Common Rule, is found at 45 CFR Part 46, Subpart A. Many federal agencies that conduct research involving human participants, including the Department of Health and Human Services (DHHS) and the Agency for International Development (USAID), are signatories to the Common Rule. Note that DHHS has passed regulations that include not only Part A but also Parts B, C, and D which address special protections for pregnant women, prisoners, and children. Likewise, USAID has passed separate regulations found at 22 CFR Part 225 which mirror 45 CFR Part 46, Subpart A.

PART 3. Comparative Analysis of International Documents Addressing the Protection of Research Participants

	Distributive Justice			
	1	2	3	Special Protections
Nuremberg Code (1947)	NOT MENTIONED	NOT MENTIONED	**Principle 2** "The experiment should be such as to yield fruitful results for the good of society ..."	NOT MENTIONED
Declaration of Helsinki (2000)	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED	**Principle 8** economically and medically disadvantaged human subjects unable to give or refuse consent human subjects who give consent under duress human subjects who will not benefit personally from the research human subjects in research that is combined with care **Principle 24** legal incompetence physical or mental incapacity legally incompetent minor **Principle 25** minor child
Council of Europe (1997)	NOT MENTIONED	NOT MENTIONED	**Article 3** "Parties, taking into account health needs and available resources, shall take appropriate measures with a view to providing, within their jurisdiction, equitable access to health care of appropriate quality."	**Article 6** protection of persons not able to consent **Article 7** protection of persons who have a mental disorder **Article 17** protection of persons not able to consent to research

DISTRIBUTIVE JUSTICE **Column 1:** provisions that prohibit the exclusion of certain groups from participating in a research study ■ **Column 2:** provisions that require the equitable distribution of harms and benefits among research participants ■ **Column 3:** provisions that require the equitable distribution of harms and benefits within and among communities

PART 3. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

		Distributive Justice		
	1	2	3	Special Protections
Council for International Organizations of Medical Sciences (CIOMS) (1993)	**Commentary on Guideline 11** *"Women in most societies have been discriminated against with regard to their involvement in research … A general policy of excluding from such clinical trials women biologically capable of becoming pregnant is unjust in that it deprives women as a class of persons of the benefits of the new knowledge derived from the trials. Further, it is an affront to their right of self-determination."*	**Guideline 10** "Individuals or communities to be subjects of research should be selected in such a way that the burdens and benefits of the research will be equitably distributed ..."	NOT MENTIONED	**Guidelines 5–7** children; persons with mental or behavioural disorders; prisoners **Guideline 8** research involving subjects in underdeveloped countries **Guideline 11** selection of pregnant or nursing women as research subjects
Council for International Organizations of Medical Sciences (CIOMS) (1991)	NOT MENTIONED	NOT MENTIONED	**Principle 42** "... Potential benefits and harm should be distributed equitably within and among communities that differ on grounds of age, gender, race, or culture, or other variables."	**Principle 43** vulnerable and dependent groups
International Conference on Harmonisation (ICH) (1996)	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED	**Principle 4.8.12** "When a clinical trial … includes subjects who can only be enrolled in a trial with the consent of the subject's legally acceptable representative … the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent."

DISTRIBUTIVE JUSTICE **Column 1:** provisions that prohibit the exclusion of certain groups from participating in a research study ■ **Column 2:** provisions that require the equitable distribution of harms and benefits among research participants ■ **Column 3:** provisions that require the equitable distribution of harms and benefits within and among communities

PART 3. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Distributive Justice			
	1	2	3	Special Protections
UNAIDS (2000)	**Guidance Point 17** "… women should be included in clinical trials in order to verify safety, immunogenicity, and efficacy from their standpoint …" **Guidance Point 18** "… children should be included in clinical trials in order to verify safety, immunogenicity, and efficacy from their standpoint …"	NOT MENTIONED	**Guidance Point 4** "… the desired outcome of the research protocol should potentially benefit the population from which the research participants are drawn."	**Guidance Point 7** "Where relevant, the research protocol should describe the social contexts of a proposed research population (country or community) that create conditions for possible exploitation or increased vulnerability among potential research participants, as well as the steps that will be taken to overcome these and protect the dignity, the safety, and the welfare of the participants." **Guidance Point 8** "… the choice of study populations for each trial phase should be justified in advance in scientific and ethical terms in all cases, regardless of where the study population is found. Generally, early clinical phases of HIV vaccine research should be conducted in communities that are less vulnerable to harm or exploitation, usually within the sponsor country …" **Guidance Point 13** "Special measures should be taken to protect persons who are, or may be, limited in their ability to provide informed consent due to their social or legal status." **Guidance Point 17** "… During such research, women should receive adequate information to make informed choices about risks to themselves, as well as to their fetus or breastfed infant, where applicable." **Guidance Point 18** "… Efforts should be taken to design vaccine development programmes that address the particular ethical and legal considerations relevant for children, and safeguard their rights and welfare during participation."
Australia (1999)	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED

DISTRIBUTIVE JUSTICE **Column 1:** provisions that prohibit the exclusion of certain groups from participating in a research study ■ **Column 2:** provisions that require the equitable distribution of harms and benefits among research participants ■ **Column 3:** provisions that require the equitable distribution of harms and benefits within and among communities

PART 3. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

		Distributive Justice		
	1	2	3	Special Protections
Brazil (1996–1999)	**Resolution No. 196/1996 III.3.j** "… Vulnerable individuals or groups should not be research subjects when the desired information can be obtained from fully capable individuals, unless the research is to directly benefit the vulnerable individuals or groups …"	**Resolution No. 196/1996 III.1.d** "Ethics in research signifies social relevance of the research, with significant advantages to the research subjects and minimization of the burden to vulnerable individuals, which guarantees equal consideration of all interests involved and preserves the socio-humanitarian purpose of research (justice and equality)."	**Resolution No. 196/1996 III.3.m** "Research involving human subjects … must … guarantee that, whenever possible, research in communities is translated into benefits whose effects continue to be felt after the research is concluded …" **Resolution No. 292/1999 IV** "The burden and benefits arising from the investigation [coordinated abroad or with foreign participation] and the research results must be distributed fairly among the parts involved and should be clearly set forth in the protocol."	**Resolution No. 196/1996 III.1.a** "Ethics in research signifies freely given and informed consent of target-individuals and the protection of vulnerable groups and the legally disabled (autonomy) …" **III.3.u** "Research involving human subjects … must … take into account, in research carried out in women in the reproductive age or pregnant women, the evaluation of risks and benefits, as well as possible interference with the fertility, pregnancy, embryo, or fetus, labor, puerperium, nursing and the new born."
Canada (1998)	**Commentary to Article 2.1** *"The requirement of free and informed consent should not disqualify research subjects who are not proficient in the language used by researchers from the opportunity to participate in the potential research."* (see Articles 5.1, 5.2 (women), 5.3 (incompetent persons))	(see page i.6)	(see page i.6)	**Article 2.5** research involving incompetent individuals **Article 2.6** 4 minimum requirements to obtain informed consent from incompetent individuals **Article 2.7** "... the researcher shall seek to ascertain the wishes of the individual concerning participation ..." where "... the legally incompetent individual understands the nature and consequences of the research ..."

DISTRIBUTIVE JUSTICE **Column 1:** provisions that prohibit the exclusion of certain groups from participating in a research study ■ **Column 2:** provisions that require the equitable distribution of harms and benefits among research participants ■ **Column 3:** provisions that require the equitable distribution of harms and benefits within and among communities

PART 3. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Distributive Justice			
	1	2	3	Special Protections
China (1998)	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED	**Article 11** children **Article 12** mental patients **Article 16** pregnant or nursing women
Denmark (1992)	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED	
Finland (1992–1999)	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED	**Statute No. 488/1999** Section 7 (persons not able to consent) Section 8 (minors) Section 9 (pregnant women and nursing mothers) Section 10 (prisoners)
France (1988)	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED	**Title I , Article L. 209–4** pregnant or nursing women **Title I, Article L. 209–5** persons deprived of liberty (solicitation) **Title I, Article L. 209–6** minors, mentally ill, critically ill (solicitation) **Title II, Article L. 209–10** minors
India (2000)	NOT MENTIONED	**General Principle 3** "Such human subjects should be selected so that the burdens and benefits of the research are distributed without arbitrariness, discrimination or caprice."	**General Principle 8** "… the research or experiment and its subsequent applicative use are conducted to benefit all human kind and not just those who are socially better off but also the least advantaged; and in particular, the research subjects themselves."	**General Ethical Issues 5** Research involving pregnant or nursing women, children, and vulnerable groups

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PART 3. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Distributive Justice			
	1	2	3	Special Protections
Netherlands (1998)	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED	**Article 4.1** "Performing scientific research with experimental subjects who have not reached 18 years of age, or who are not in a condition to assess their interests reasonably, is prohibited. This prohibition does not apply to scientific research that may also benefit the experimental subjects involved or to scientific research that cannot be performed with the cooperation of the experimental subjects from the category to which the experimental subject belongs for whom the risks and burdens are minimal." **Article 6.1 b–d** minors **Article 6.7** "If … the experimental subject is not competent to give permission, those who are competent in his place may withdraw it at any time without explanation …"
New Zealand (1997)	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED
South Africa (1993)	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED	**Chapter 6** Special Groups (including women, children, the elderly, the mentally handicapped, prisoners, and students)
Thailand (1995)	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED
Uganda (1997)	NOT MENTIONED	**III.E.(3)** "The selection of research participants is equitable …"	NOT MENTIONED	**II.E.(8)** "When some or all of the research participants are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these research participants." **IV.B–IV.G** pregnant women; children; prisoners; soldiers; mentally ill and behaviorally disordered; refugees

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PART 3. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

		Distributive Justice		
	1	2	3	Special Protections
United Kingdom (1998) (Guidance Notes are available on the Internet at: *http://www.mrc.ac.uk/Clinical_trials/ct_gn.html)*	**Guidance Notes** "We require that, in full proposals, any proposed lower and upper age limits for trial participants should be justified on scientific grounds. Normally, for example, there should be no upper age limit on recruitment. Similarly, exclusion on the grounds of gender should be justifiable on scientific grounds."	**Principle 5.4** "The principles of informed consent in the current version of the Helsinki Declaration …. and those laid out in the 13 principles at the beginning of this document should be implemented in all RCTs."*	NOT MENTIONED	**Principle 5.4.3** children, mentally incapacitated persons who cannot give full informed consent, unconscious
United Kingdom (1999)*	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED
United States Food and Drug Administration (FDA) Title 21 Code of Federal Regulations	NOT MENTIONED	**21 CFR § 56.111(a)(3)** "Selection of subjects is equitable …"	NOT MENTIONED	**21 CFR § 56.111(a)(3)** "… the IRB … should be particularly cognizant of the special problems of research involving vulnerable populations …" **21 CFR § 56.111(b)** "When some of the subjects … are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects."

* "The MRC's key principles, which are underpinned by the Declaration of Helsinki and outlined in *Responsibility in Investigations on Human Participants and Material and on Personal Information*, 1992, apply to research conducted in developing societies … In addition, investigators are expected to follow the *MRC Guidelines for Good Clinical Practice in Clinical Trials*, which are based on the ICH Harmonised Tripartite Guideline for Good Clinical Practice."

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PART 3. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

		Distributive Justice		
	1	2	3	Special Protections
United States Common Rule** Title 45 Code of Federal Regulations	NOT MENTIONED	**45 CFR § 46.111(a)(3)** "Selection of subjects is equitable ..."	NOT MENTIONED	**45 CFR § 46.111(a)(3)** "... the IRB ... should be particularly cognizant of the special problems of research involving vulnerable populations ..." **45 CFR § 46.111(b)** "When some of the subjects ... are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects."
United States Agency for International Development (USAID) Title 22 Code of Federal Regulations	NOT MENTIONED	**22 CFR § 225.111(a)(3)** "Selection of subjects is equitable ..."	NOT MENTIONED	**22 CFR § 225.111(a)(3)** "... the IRB ... should be particularly cognizant of the special problems of research involving vulnerable populations ..." **22 CFR § 225.111(b)** "When some of the subjects ... are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects."

** The Federal Policy for the Protection of Human Subjects, also known as the Common Rule, is found at 45 CFR Part 46, Subpart A. Many federal agencies that conduct research involving human participants, including the Department of Health and Human Services (DHHS) and the Agency for International Development (USAID), are signatories to the Common Rule. Note that DHHS has passed regulations that include not only Part A but also Parts B, C, and D which address special protections for pregnant women, prisoners, and children. Likewise, USAID has passed separate regulations found at 22 CFR Part 225 which mirror 45 CFR Part 46, Subpart A.

PART 4. Comparative Analysis of International Documents Addressing the Protection of Research Participants

	Prior Ethical and/or Scientific Review by Independent Body	Level of Treatment	Providing Research Results to Research Participants
Nuremberg Code (1947)	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED
Declaration of Helsinki (2000)	**Principle 13** "The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed…" **Principle 14** "The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration."	**Principle 29** "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists."	NOT MENTIONED
Council of Europe (1997)	**Article 16(iii)** "The research project has been approved by the competent body after independent examination of its scientific merit and multidisciplinary review of its ethical acceptability … "	NOT MENTIONED	NOT MENTIONED
Council for International Organizations of Medical Sciences (CIOMS) (1993)	**Guideline 14** "All proposals to conduct research involving human subjects must be submitted for review and approval to one or more independent ethical and scientific review committees ..."	**Commentary on Guideline 14** *"… as required by the Declaration of Helsinki, Article III.3, '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."*	NOT MENTIONED

PART 4. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Prior Ethical and/or Scientific Review by Independent Body	Level of Treatment	Providing Research Results to Research Participants
Council for International Organizations of Medical Sciences (CIOMS) (1991)	**Principle 33** "The requirement that proposals for epidemiological studies be submitted to independent ethical review applies irrespective of the source ..." **Principle 40** "... Scientific review and ethical review cannot be considered separately; a study that is scientifically unsound is unethical in exposing subjects to risk … and achieving no benefit in knowledge ..."	NOT MENTIONED	**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 ..."
International Conference on Harmonization (ICH) (1996)	**Principle 2.6** "A trial should be conducted in compliance with the protocol that has received prior IRB/IEC approval/favorable opinion."	**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(s)." **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."	NOT MENTIONED
UNAIDS (2000)	**Guidance Point 5** "To ensure the ethical and scientific quality of the proposed research, its relevance to the affected community, and its acceptance by the affected community, community representatives should be involved in an early and sustained manner in the design, development, implementation, and distribution of results of HIV vaccine research."	**Guidance Point 11** "As long as there is no known effective HIV preventive vaccine, a placebo control arm should be considered ethically acceptable in a phase III HIV preventive vaccine trial. However, where it is ethically and scientifically acceptable, consideration should be given to the use in the control arm of a vaccine to prevent a relevant condition apart from HIV."	**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 …"

PART 4. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Prior Ethical and/or Scientific Review by Independent Body	Level of Treatment	Providing Research Results to Research Participants
continued UNAIDS (2000)	**Guidance Point 6** "HIV preventive vaccine trials should only be carried out in countries and communities that have appropriate capacity to conduct independent and competent scientific and ethical review." **Guidance Point 15** "A plan for monitoring the initial and continuing adequacy of the informed consent process and risk-reduction interventions, including counselling and access to prevention methods, should be agreed upon before the trial commences."	**Guidance Point 16** "Care and treatment for HIV/AIDS and its associated complications should be provided to participants in HIV preventive vaccine trials, with the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country in light of circumstances listed …A comprehensive care package should be agreed upon through a host/community/sponsor dialogue which reaches consensus prior to initiation of a trial …"	
Australia (1999)	**Principle 1.13** "Every research proposal must demonstrate that the research is justifiable in terms of its potential contribution to knowledge …" **Principle 1.16** "Research projects involving humans must be reviewed by a Human Research Ethics Committee (HREC) and must not be undertaken or funded unless and until approval has been granted." **Principle 12.2** "An HREC must consider all aspects of the design of a clinical trial …"	**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."	**Principle 1.18** "… Normally, research results should be made available to research participants."
Brazil (1996–1999)	**Resolution No. 196/1996** **III.3.r** "Research involving human subjects … must … guarantee the absence of conflicts of interest between the researcher and the research subjects or sponsor of the research project." **VII.13.a** "[The Committee for Ethics in Research will] review all protocols of research involving human subjects, including multicentre research; the CER will be responsible for all	NOT MENTIONED	**Resolution No. 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."

PART 4. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Prior Ethical and/or Scientific Review by Independent Body	Level of Treatment	Providing Research Results to Research Participants
continued Brazil (1996–1999)	decisions pertaining [to] the ethics of the research to be developed by the institution, so as to ensure the integrity and rights of volunteers participating in said research." **VII.14** "The ethical review of each and every proposal of research involving human subjects cannot be dissociated from the scientific analysis of said proposal …"		
Canada (1998)	**Article 1.1(a)** "All research that involves living human subjects requires review and approval by an REB ... before the research is started ... " **Article 1.2** "The institution in which research involving human subjects is carried out shall mandate the REB to approve, reject, propose modifications to, or terminate any proposed or ongoing research involving human subjects ..." **Article 1.13(a)** "Ongoing research shall be subject to continuing ethics review." **Article 4.1** "Researchers and REB members shall disclose actual, perceived or potential conflicts of interest to the REB. REBs should develop mechanisms to address and resolve conflicts of interest."	**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."	(see pages 6.3 and 6.4)
China (1998)	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED

PART 4. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Prior Ethical and/or Scientific Review by Independent Body	Level of Treatment	Providing Research Results to Research Participants
Denmark (1992)	**Act No. 503 § 6 Section 1** "Every biomedical research project which includes research on: live human subjects … has to be notified to the regional committee within the area, where the person responsible for the project works." **Act No. 503 § 7 Section 1** "Projects … must not be initiated until they have been subject to a scientific ethical evaluation and a permission to start has been given by the regional committee …" **Act No. 503 § 7 Section 3** "Dealing with projects, of which a clinical trial of medicinal products is a part, and thus covered by the Medicines Act, the regional committee submits its report on the scientific ethical evaluation of the project to the National Board of Health … The National Board of Health gives the final license to initiate the project." **Act No. 503 § 7 Section 4** "If no consensus can be reached in judging a given project in a regional committee, or if the committee finds that the project brings up questions of a principal character, the project will have to be referred to the Central Committee."	NOT MENTIONED	NOT MENTIONED

PART 4. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Prior Ethical and/or Scientific Review by Independent Body	Level of Treatment	Providing Research Results to Research Participants
Finland (1992–1999)	**Statute No. 488/1999** **Section 3** "Before any research … is undertaken, the ethics committee shall have given a favourable opinion on the research plan." **Statute No. 488/1999** **Section 17** "Ethics committees shall be responsible for prior evaluation of research projects and delivering opinions on them. Projects shall be considered by the ethics committee of the region where the person in charge of the research is based or of the region where the research is to be principally conducted …" **Statute No. 986/1999** **Section 1** "The research plan shall be submitted for the opinion of the ethics committee … to the ethics committee of the hospital district in whose area the person responsible for the research operates and in whose area the major part of the research is to be carried out …"	**Statute No. 785/1992** **Section 3** "Every person who stays permanently in Finland is without discrimination entitled to health and medical care required by his state of health within the limits of those resources which are available to health care at the time in question … The patient has a right to qualitatively good health care and medical care … The mother tongue of the patient, his/her individual needs and culture have to be taken into account according to possibilities in his/her medical care and other treatment."	NOT MENTIONED
France (1988)	**Title III, Article L. 209–12** "Before conducting research on human beings, the investigator shall submit his proposal for the opinion of the Advisory Committee for the Protection of Participants in Biomedical Research ..."	NOT MENTIONED	NOT MENTIONED
India (2000)	**Ethical Review Procedures** "It is mandatory that all proposals on bio-medical research involving human subjects should be cleared by an appropriately constituted Institutional Ethics Committee (IEC) … to safeguard the welfare and the rights of the participants."	NOT MENTIONED	**General Principle 2** "The principles of informed consent and voluntariness are cardinal principles to be observed throughout … so that research subjects are continually kept informed of any and all developments in so far as they affect them and others."

PART 4. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Prior Ethical and/or Scientific Review by Independent Body	Level of Treatment	Providing Research Results to Research Participants
Netherlands (1998)	**Article 2.2 a–b** "A positive decision must be obtained on this research protocol: from a recognized commission [for the purpose of testing research protocols in agreement with what is defined in or by virtue of this law] …; from the central commission [for medical and scientific research] when it involves a decision of an administrative nature [or] scientific research …. that an involved experimental subject may not benefit and whereby his/her condition is changed deliberately …"	NOT MENTIONED	NOT MENTIONED
New Zealand (1997)	**Chapter 1–Part A** "… ethical approval from an accredited ethics committee must be obtained before HRC funding for any research proposal may commence." **Chapter 2–Part A** "… every application for funding received by the HRC is required to have been reviewed by an accredited ethics committee."	**Chapter 3–Part E** "When the administration of effective treatment is important for the well-being of the patient, a controlled trial can only be undertaken where there is genuine uncertainty about whether the trial treatment is more effective (or has less risk) than the standard treatment with which it is being compared."	**Chapter 2** "… investigators should ensure that the results of their research and an account of the methods employed are adequately and appropriately disseminated in a manner accessible to the research participants …" **Chapter 4–Part B** "… the results of any investigation should be appropriately disseminated in a full and frank manner [to research participants]."
South Africa (1993)	**Chapter 4** "All medical research involving healthy people and patients should be subject to independent ethical review and this should be accomplished by a Research Ethics Committee." **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 …"	**Chapter 10** "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)." **Chapter 10** "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."	**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 small gift in the case of children."

PART 4. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Prior Ethical and/or Scientific Review by Independent Body	Level of Treatment	Providing Research Results to Research Participants
Thailand (1995)	**# 1** "The MOPH is responsible for reviewing ethical issues in the medical research which meet the following criteria: (1) conducted by the MOPH's personnel or organizations, or conducted in geographical areas under responsibility of the MOPH; (2) requested by other organizations for ethical review; (3) requiring national authority approval."	NOT MENTIONED	NOT MENTIONED
Uganda (1997)	**V.C.(2)** "Pre-clinical studies that provide sufficient documentation of the potential safety of the pharmaceutical product ... are a prerequisite to a clinical trial ..."	NOT MENTIONED	NOT MENTIONED
United Kingdom (1998)	**Principle 2.6** "A trial should be conducted in compliance with the protocol that has received prior Ethical Committee favourable opinion." **Principle 3.1.11** "Any necessary approval has been, or will be, obtained from the relevant ethical and regulatory bodies before the trial's implementation." **Principle 5.2.1** "Any material amendments or alterations to or deviations from the protocol ... must have approval of the relevant ethics committees ... before their implementation."	**Principle 5.3.1** "The ... Declaration of Helsinki is the accepted basis for clinical trial ethics and must be known and implemented by those engaged in research involving human participants. The personal integrity and welfare of the trial participants is the ultimate responsibility of the doctor responsible for their care."	**Principle 5.4.8** "... Where feasible, trial participants should also be notified of progress with the trial and the eventual outcome of the trial."

PART 4. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Prior Ethical and/or Scientific Review by Independent Body	Level of Treatment	Providing Research Results to Research Participants
United Kingdom (1999)*	**General Principle 1** "The research must be of potential scientific or practical value; it must address an important question relevant to Council's overall objectives, and be feasible and well-designed." **General Principle 6** "The research should be done only with the approval of an independent research ethics body ..." **Specific Consideration 7** "Local ethical review of research proposals is required to judge the ethical acceptability of the research in accordance with the customs and traditions of the particular community."	**Specific Consideration 6** "The Helsinki principle II.3 — … best proven diagnostic and therapeutic method … — should take into account 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, but the information given to patients should set out the position unequivocally.)"	**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."
United States Food and Drug Administration (FDA) Title 21 Code of Federal Regulations	**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 ..." **21 CFR § 56.109** "An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities ..." **21 CFR § 312.22(b)** "The amount of information on a particular drug that must be submitted in an IND to assure the accomplishment of the objectives ... depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug."	NOT MENTIONED	NOT MENTIONED

* "The MRC's key principles, which are underpinned by the Declaration of Helsinki and outlined in *Responsibility in Investigations on Human Participants and Material and on Personal Information*, 1992, apply to research conducted in developing societies … In addition, investigators are expected to follow the *MRC Guidelines for Good Clinical Practice in Clinical Trials*, which are based on the ICH Harmonised Tripartite Guideline for Good Clinical Practice."

PART 4. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Prior Ethical and/or Scientific Review by Independent Body	Level of Treatment	Providing Research Results to Research Participants
United States Common Rule** Title 45 Code of Federal Regulations	**45 CFR § 46.103(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 ..." **45 CFR § 46.109(a)** "An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities ..."	NOT MENTIONED	NOT MENTIONED
United States Agency for International Development (USAID) Title 22 Code of Federal Regulations	**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 ..." **22 CFR § 225.109(a)** "An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities ..."	NOT MENTIONED	NOT MENTIONED

** The Federal Policy for the Protection of Human Subjects, also known as the Common Rule, is found at 45 CFR Part 46, Subpart A. Many federal agencies that conduct research involving human participants, including the Department of Health and Human Services (DHHS) and the Agency for International Development (USAID), are signatories to the Common Rule. Note that DHHS has passed regulations that include not only Part A but also Parts B, C, and D which address special protections for pregnant women, prisoners, and children. Likewise, USAID has passed separate regulations found at 22 CFR Part 225 which mirror 45 CFR Part 46, Subpart A.

PART 5. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Treatment and Compensation for Injured Human Participants	Duty Owed to Research Participants During/After Trial	Successful Products Made Reasonably Available
Nuremberg Code (1947)	NOT MENTIONED	**Principle 7** "Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death." **Principle 10** "During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe ... that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject."	NOT MENTIONED
Declaration of Helsinki (2000)	NOT MENTIONED	**Principle 1.7** "... Physicians should cease any investigation if the hazards are found to outweigh the potential benefits."	**Principle 30** "At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study."
Council of Europe (1997)	**Article 24** "The person who has suffered undue damage resulting from an intervention is entitled to fair compensation according to the conditions and procedures prescribed by law."	**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."	NOT MENTIONED
Council for International Organizations of Medical Sciences (CIOMS) (1993)	**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. In the case of death, their dependents are entitled to material compensation. The right to compensation may not be waived." **Commentary on Guideline 13** accidental injury; equitable compensation; obligation of sponsor to pay	**Commentary on Guideline 2** *"If the investigator is a physician, the subject must be told clearly whether the investigator will act … both as an investigator and a physician to the subject … an investigator who agrees to act as physician-investigator undertakes all of the legal and ethical responsibilities of the subject's primary-care physician."* **Commentary for Guideline 15** *"When indicated, sponsors should also provide facilities and personnel to make necessary health-care services available to the population from which research subjects are recruited ..."*	**Guideline 8** "Before undertaking research involving subjects in underdeveloped communities, whether in developed or developing countries, the investigator must ensure that: ■ persons in underdeveloped countries will not ordinarily be involved in research that could be carried out reasonably well in developed communities; ■ the research is responsive to the health needs and the priorities of the community in which it is to be carried out…"

PART 5. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Treatment and Compensation for Injured Human Participants	Duty Owed to Research Participants During/After Trial	Successful Products Made Reasonably Available
continued Council for International Organizations of Medical Sciences (CIOMS) (1993)			**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 ..."*
Council for International Organizations of Medical Sciences (CIOMS) (1991)	**Principle 47** "Compensation is difficult when it is not appropriate to make monetary payments ... When harm results from a study, the body that has sponsored or endorsed the study should be prepared to make good the injury, by public apology or reparation."	**Principle 16** "... the expectation in the community ... that it will be provided with health care ... should not be frustrated and where people need health care, arrangements should be made to have them treated ..."	NOT MENTIONED
International Conference on Harmonisation (ICH) (1996)	**Principle 4.8.4** "None of the oral and written information ... should contain any language that causes the subject ... to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor ... from liability for negligence." **Principle 5.8** compensation to subjects and investigators	**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."	NOT MENTIONED

PART 5. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Treatment and Compensation for Injured Human Participants	Duty Owed to Research Participants During/After Trial	Successful Products Made Reasonably Available
UNAIDS (2000)	**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, as well as the modalities by which to address these, including provision for the highest level of care to participants who experience adverse reactions to the vaccine, compensation for injury related to the research, and referral to psycho/social and legal support, as necessary."	**Guidance Point 3** "Strategies should be implemented to build capacity in host countries and communities so that they can practice meaningful self-determination in vaccine development, can ensure the scientific and ethical conduct of vaccine development, and can function as equal partners with sponsors and others in a collaborative process." **Guidance Point 14** "Appropriate risk-reduction counselling and access to prevention methods should be provided to all vaccine trial participants, with new methods being added as they are discovered and validated." **Guidance Point 16** "Care and treatment for HIV/AIDS and its associated complications should be provided to participants in HIV preventive vaccine trials …"	**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 …"
Australia (1999)	**Principle 12.7** "An HREC must be satisfied, before approving a clinical trial, that arrangements exist to ensure adequate compensation to participants for any injury suffered as a result of participation in the trial."	**Principle 12.10** "It may be unethical for a researcher to continue a trial if: (a) there are or have been substantial deviations from the trial protocol; (b) side effects of unexpected type, severity, or frequency are encountered; (c) as the trial progresses, one of several treatments or procedures being compared proves to be so much better, or worse, than other(s) that continuation of the trial would disadvantage some of the participants."	NOT MENTIONED

PART 5. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Treatment and Compensation for Injured Human Participants	Duty Owed to Research Participants During/After Trial	Successful Products Made Reasonably Available
Brazil (1996–1999)	**Resolution No. 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." **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 an indemnity."	**Resolution No. 196/1996** **III.3.q** "Research involving human subjects … must … ensure the research subjects the required follow-up, treatment, or orientation, in screening surveys …" **III.3.s** "… Studies sponsored by external organizations must also respond to training needs in Brazil, so that the country be able to independently develop similar projects." **V.3** "If the main researcher perceives any risk or injury to the health of the research subjects … he/she must interrupt the research immediately. Likewise, as soon as the advantage of a method under study has been demonstrated, the project must be interrupted and all research subjects must be offered the benefits of the best regime."	**Resolution No. 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." **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 No. 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 proven."
Canada (1998)	NOT MENTIONED	**Commentary to Article 1.14** *"… researchers should ensure the benefits of their research are available in the host country. Benefits may … take the form of information-sharing, training for local personnel both in the host country and in Canada, or health care or similar services."* (see pages 6.3 and 6.4)	**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."*
China (1998)	**Article 19** "Those human subjects who got temporary or permanent harm owing to participating [in] the research should get treatment and financial compensation; if the death of human subject is caused, his/her family should get compensation. Any research, any institution or any individual must not deprive this right from human subjects."	**Article 17** "Researcher should commit to give certain compensation or free medical services to human subjects …"	NOT MENTIONED

PART 5. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Treatment and Compensation for Injured Human Participants	Duty Owed to Research Participants During/After Trial	Successful Products Made Reasonably Available
Denmark (1992)	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED
Finland (1992–1999)	NOT MENTIONED	**Statute No. 785/1992** **Section 6** "The patient has to be cared in mutual understanding with him/her. If the patient refuses certain treatment or measure, he/she has to be cared according to possibilities in another medically acceptable way in mutual understanding with him/her." **Statute No. 785/1992** **Section 10** "A patient who is not satisfied with the health care or medical care and the related treatment received by him/her has the right to make a complaint on the matter to the director responsible for health care in the health care unit in question …" **Statute No. 785/1992** **Section 3** "Every person who stays permanently in Finland is without discrimination entitled to health and medical care required by his state of health within the limits of those resources which are available to health care at the time in question … The patient has a right to qualitatively good health care and medical care … The mother tongue of the patient, his/her individual needs and culture have to be taken into account according to possibilities in his/her medical care and other treatment."	NOT MENTIONED
France (1988)	**Title I, Article L. 209–7** "In the case of biomedical research without direct therapeutic benefit, the sponsor shall be subject to strict and vicarious liability to provide full compensation for the harmful consequences of research suffered by a participant ... In all biomedical research, the sponsor shall take out an insurance policy covering his own civil liability ..."	NOT MENTIONED	NOT MENTIONED

PART 5. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Treatment and Compensation for Injured Human Participants	Duty Owed to Research Participants During/After Trial	Successful Products Made Reasonably Available
India (2000)	**General Principle 3** "Each research shall include an inbuilt mechanism for compensation for the human subjects either through insurance cover or any other appropriate means to cover all foreseeable and unforeseeable risks by providing for remedial action and comprehensive after-care, including treatment during and after the research or experiment …" **General Ethical Issue 7** "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 whether a pharmaceutical company, a government, or an institution, should agree, before the research begins, to provide compensation for any physical injury for which subjects are entitled to compensation or agree to provide insurance coverage for an unforeseen injury whenever possible."	**General Principle 12** "… there is a general and positive duty on all persons conducting, associated or connected with any research entailing the use of a human subject to ensure that both the letter and the spirit of these guidelines, as well as any other norms, directions, and guidelines … are scrupulously observed and duly complied with."	NOT MENTIONED
Netherlands (1998)	**Article 7.1** "The scientific research will only be performed if, at the time the research begins, insurance is in place covering damages for death or injury to the experimental subject caused by the research ..." **Article 7.4** "The manner in which the first paragraph is to be executed is established in the research protocol." **Article 7.5** "If the party performing the scientific research is responsible for death or injury damages vis-à-vis the experimental subject, then the party sponsoring the scientific research is also responsible ..." **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."	**Article 10** "If the scientific research proceeds along a course that is less favorable for the experimental subject than that which is provided in the research protocol, the individual who is carrying out the research is to inform the experimental subject at once ... Until a closer positive decision is granted, the performance of the research will be suspended unless the health of the experimental subject does not allow suspension or cessation."	NOT MENTIONED

PART 5. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Treatment and Compensation for Injured Human Participants	Duty Owed to Research Participants During/After Trial	Successful Products Made Reasonably Available
New Zealand (1997)	**Chapter 5–Part G** "… where personal injury results from medical error or medical mishap that occurs in a clinical trial the personal injury shall constitute medical misadventure only where the trial—(a) (i) Has been approved by an ethics committee accredited by the HRC or the Director-General of Health, and (ii) The ethics committee has certified that it is satisfied that the trial is not conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is carried out; or (b) The person has not agreed, in writing, to participate in the trial." **Chapter 5–Part H** "Where personal injury results from negligence during a non-approved clinical trial, or a clinical trial conducted by a manufacturer or distributor principally for the purpose of testing or proving a product, the injured person will have a right to sue for common law damages … it will be necessary for the researcher that all parties (including the researcher, the manufacturer, the distributor and the host institution) are adequately insured to meet any potential liabilities."	NOT MENTIONED	NOT MENTIONED
South Africa (1993)	**Chapter 14** "It is recommended that researchers or sponsors of research take out professional indemnity insurance to cover them against eventual liability for claims arising from research activities." **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."	**Chapter 10** "In trials where the consequences of one treatment being found to be more effective than others could have profound implications for the future health of participants, the trial should be terminated as soon as evidence has accumulated from enough patients to establish the point." **Chapter 11** "It is important that the ordinary requirements — medical and other — are not neglected as a consequence of the involvement in research, and that the identity of the person in overall clinical charge of the patient's care is clear."	**Chapter 10** "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."

PART 5. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Treatment and Compensation for Injured Human Participants	Duty Owed to Research Participants During/After Trial	Successful Products Made Reasonably Available
Thailand (1995)	NOT MENTIONED	**# 5** "… Command facilities are required for the safe and efficient treatment of the subject when needed." **#8** "Each activity involving human subjects must be conducted under caution based on medical standards. Any methods found to indicate potential hazards to the subjects must be ceased." **# 9** "Researchers must report to the Committee or the monitor/DSMB in case of serious adverse reaction as determined in the Guidelines for Good Clinical Practice (GCP)."	NOT MENTIONED
Uganda (1997)	**V.D.(6)** "The investigator must provide evidence of insurance to cover claims of injuries, disabilities, or death of a clinical trial participant that has resulted from participation in a clinical trial." **V.E.(6)** "The sponsor is responsible for providing compensation or indemnity in the event of trial-related serious injury, disability, or death …"	**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 …"	**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."
United Kingdom (1998)	**Principle 5.4.12** "The participant should have access to information about the procedures for obtaining compensation and treatment following harm through negligence or non-negligence as a direct result of participating in the trial."	**Principle 2.7** "The medical care given to, and medical decisions made on behalf of, participants should always be the responsibility of a qualified physician, or, when appropriate, a qualified dentist." **Principle 5.3.1** "… The personal integrity and welfare of the trial participants is the ultimate responsibility of the doctor responsible for their care."	NOT MENTIONED

PART 5. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Treatment and Compensation for Injured Human Participants	Duty Owed to Research Participants During/After Trial	Successful Products Made Reasonably Available
continued United Kingdom (1998)	**Principle 6.10** "The MRC ... accepts responsibility for its sponsorship of the trial, and as such would give sympathetic consideration to claims for any non-negligent harm suffered by individuals as a result of participating in the trial ... the Council is unable to insure and thus cannot offer advance indemnity cover for participants in MRC-funded studies."	**Principle 5.3.2** "The medical care given to, and medical decisions made on behalf of, participants should always be the responsibility of a qualified physician, or, when appropriate, a qualified dentist or other qualified health care professional ..." **Principle 6.10.3** "Where studies are carried out in a hospital, the hospital continues to have a duty of care to the patient being treated within that hospital, whether or not that patient is participating in an MRC-supported study." ***Footnote to Principle 2*** *"In the UK there may be situations where it would be appropriate for other qualified health care professionals, such as midwives etc. to be responsible for patient care."*	
United Kingdom (1999)*	NOT MENTIONED	NOT MENTIONED	**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."
United States Food and Drug Administration (FDA) Title 21 Code of Federal Regulations	**21 CFR § 50.20** ".. No informed consent .... may include any exculpatory language through which the subject of the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence."	NOT MENTIONED	**21 CFR § 312.34** "In case of a serious disease, a drug ordinarily may be made available for treatment use … during Phase 3 investigations or after all clinical trials have been completed …" (see 21 CFR § 812.36 — medical devices)

* "The MRC's key principles, which are underpinned by the Declaration of Helsinki and outlined in *Responsibility in Investigations on Human Participants and Material and on Personal Information*, 1992, apply to research conducted in developing societies … In addition, investigators are expected to follow the *MRC Guidelines for Good Clinical Practice in Clinical Trials*, which are based on the ICH Harmonised Tripartite Guideline for Good Clinical Practice."

PART 5. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Treatment and Compensation for Injured Human Participants	Duty Owed to Research Participants During/After Trial	Successful Products Made Reasonably Available
United States Common Rule** Title 45 Code of Federal Regulations	**45 CFR § 46.116** ".. No informed consent .... may include any exculpatory language through which the subject of the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence."	NOT MENTIONED	NOT MENTIONED
United States Agency for International Development (USAID) Title 22 Code of Federal Regulations	**22 CFR § 225.116** ".. No informed consent .... may include any exculpatory language through which the subject of the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence."	NOT MENTIONED	NOT MENTIONED

** The Federal Policy for the Protection of Human Subjects, also known as the Common Rule, is found at 45 CFR Part 46, Subpart A. Many federal agencies that conduct research involving human participants, including the Department of Health and Human Services (DHHS) and the Agency for International Development (USAID), are signatories to the Common Rule. Note that DHHS has passed regulations that include not only Part A but also Parts B, C, and D which address special protections for pregnant women, prisoners, and children. Likewise, USAID has passed separate regulations found at 22 CFR Part 225 which mirror 45 CFR Part 46, Subpart A.

PART 6. Comparative Analysis of International Documents Addressing the Protection of Research Participants

	Equivalent Protections (Harmonization of Standards)	Research and Review Conducted in Other Countries	Have Force and Effect of Law?	Covers Privately Funded Research?
Nuremberg Code (1947)	NOT MENTIONED	NOT MENTIONED	NO	YES
Declaration of Helsinki (2000)	**Principle 9** "Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration."	NOT MENTIONED	NO	YES
Council of Europe (1997)	**Article 26** "No restrictions shall be placed on the exercise of the rights and protective provisions ... other than such as are prescribed by law and are necessary in a democratic society ..." **Article 27** "None of the provisions ... shall be interpreted as limiting or otherwise affecting the possibility for a Party to grant a wider measure of protection with regard to the application of biology and medicine than is stipulated ..."	NOT MENTIONED	NO **Article 23** "The parties shall provide appropriate judicial protection to prevent or to put a stop to an unlawful infringement of the rights and principles set forth ... at short notice." **Article 25** "Parties shall provide for appropriate sanctions to be applied in the event of infringement of the provisions ..."	YES

PART 6. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Equivalent Protections (Harmonization of Standards)	Research and Review Conducted in Other Countries	Have Force and Effect of Law?	Covers Privately Funded Research?
Council for International Organizations of Medical Sciences (CIOMS) (1993)	**Guideline 15** "Externally sponsored research entails two ethical obligations … An external sponsoring agency should submit the research protocol to ethical and scientific review according to the standards of the country of the sponsoring agency, and the ethical standards applied should be no less exacting than they would be in the case of research carried out in that country."	**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." **Guideline 15** "Externally sponsored research entails two ethical obligations … After scientific and ethical approval in the country of the sponsoring agency, the appropriate authorities of the host country, including a national or local ethical review committee or its equivalent, should satisfy themselves that the proposed research meets their own ethical requirements."	NO **Commentary for Guideline 14** *"Ethical review committees generally have no authority to impose sanctions on investigators who violate ethical standards in the conduct of research involving human subjects. However, they should be required to report to institutional or governmental authorities any serious or continuing noncompliance with ethical standards ... Sanctions imposed by institutional, governmental, professional or other authorities possessing disciplinary power should be employed as a last resort ..."*	YES
Council for International Organizations of Medical Sciences (CIOMS) (1991)	**Principle 48** "Such a study implies two ethical obligations: 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." **Principle 51** "Investigators must comply with the ethical rules of the funding country and host country ..."	**Principle 49** "It is in the interest of the host country to require that proposals initiated and financed externally be submitted for ethical approval in the initiating country ..."	NO	YES

PART 6. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Equivalent Protections (Harmonization of Standards)	Research and Review Conducted in Other Countries	Have Force and Effect of Law?	Covers Privately Funded Research?
International Conference on Harmonisation (ICH) (1996)	**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."	NOT MENTIONED	YES (certain member states of the European Union, Japan, Russia, Hungary, and Poland have adopted ICH-GCP as national law; the United States, Canada, India and the Philippines have adopted ICH-GCP as official guidance) **Principle 5.20.1** "Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) … should lead to prompt action by the sponsor to ensure compliance." (in practice, the local health authority or drug regulatory authority may require inspections to ensure compliance) **Principle 5.20.2** "If the monitoring and/or auditing identifies serious and/or persistent noncompliance, the sponsor should terminate the investigator's/ institution's participation in the trial. When … participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies)."	DEPENDS
UNAIDS (2000)	NOT MENTIONED	**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."	NO	YES

PART 6. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Equivalent Protections (Harmonization of Standards)	Research and Review Conducted in Other Countries	Have Force and Effect of Law?	Covers Privately Funded Research?
Australia (1999)	**Principle 12.3** "An HREC, before granting approval to a clinical trial, must be satisfied that the protocol conforms to: (a) this Statement; (b) the … *Declaration of Helsinki;* (c) where relevant, the CPMP/ICH *Note for Guidance on Good Clinical Practice* … and the ISO 14155 *Clinical Investigation of Medical Devices* and the requirements of the TGA [Therapeutic Goods Administration]; and (d) any requirements of relevant Commonwealth or State/Territory laws."	**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."	YES **Preamble** *"The NHMRC requires all institutions or organisations that receive NHMRC funding for research to establish a Human Research Ethics Committee (HREC) and to subject all research involving humans ... to ethical review by that committee. The NHMRC expects this Statement to be used as the standard for that review ..."* (in practice, the National Statement has been comprehensively endorsed as the national standard for the ethical review of research involving humans. However, non-compliance with the National Statement is not an issue of legality or illegality)	YES **Preamble** *"... this Statement is recommended for use by any individual, institution or organisation conducting research involving humans as an inclusive, reliable and informative guide to the ethical considerations relevant to the review of that research. This would include any research involving humans undertaken by industry."*
Brazil (1996–1999)	**Resolution No. 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 No. 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)." **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."	**Resolution No. 196/1996** **III.3.l** "Research involving human subjects … must … respect the cultural, social, moral, religious, and ethical values, as well as the mores and habits, when research involves communities."	YES	YES

PART 6. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Equivalent Protections (Harmonization of Standards)	Research and Review Conducted in Other Countries	Have Force and Effect of Law?	Covers Privately Funded Research?
Canada (1998)	**Commentary to Article 1.14** *"Rules pertaining to research abroad should be created and interpreted in the spirit of the Helsinki Accords and subsequent documents that encourage the free movement of researchers across national boundaries."* **Commentary to Article 7.2** *"Clinical investigators undertaking research intended for use in seeking regulatory approval for pharmaceuticals should also generally respect the ICH Guidelines which were developed by the United States, Europe and Japan and have been adopted by Canada."*	**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."	YES **Introduction** *"The Councils will consider funding (or continued funding) only to individuals and institutions which certify compliance with this policy regarding research involving human subjects."* (note that, although the Councils are prepared to withhold funds from institutions that do not comply with the Policy Statement, non-compliance is not an issue of legality or illegality)	YES (academic institutions are applying the Policy Statement to all research, irrespective of the funding source. An average of 60–80% of health research conducted at academic institutions is sponsored by industry)
China (1998)	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED	NOT MENTIONED
Denmark (1992)	NOT MENTIONED	**Recommendation No. 4** "… Danish biomedical research projects in foreign countries including developing countries are not required to be notified to a scientific ethical committee … However, the scientific ethical committee system is, if requested, willing to conduct an advisory ethical evaluation of biomedical research projects carried out by Danish researchers in a developing country in accordance with the fundamental recommendation by the World Health Organization (WHO)." "Danish biomedical research projects that are *solely* conducted in a developing country are handled on an advisory base by the Central Scientific Ethical Committee to whom the research protocol shall be submitted. A scientific ethical evaluation shall also be performed in the developing country in question according to local regulations."	YES **Act No. 503 § 17 Section 1** "Anyone that initiates a project against § 6, § 7, § 14, sections 2, 3, 4 and 55, and § 15 can be punished with fine or ordinary imprisonment."	YES **Act No. 503 § 7 Section 1** "[Every biomedical research project which includes research on live-born human subjects] must not be initiated until they have been subject to a scientific ethical evaluation and a permission to start has been given by the regional committee …"

PART 6. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Equivalent Protections (Harmonization of Standards)	Research and Review Conducted in Other Countries	Have Force and Effect of Law?	Covers Privately Funded Research?
continued Denmark (1992)		"The ... Danish biomedical research projects conducted *both* in Denmark *and* in a developing country shall be evaluated according to the Act on a scientific ethical committee system and the handling of biomedical research projects."		
Finland (1992–1999)	**Statute No. 488/1999** **Section 17** "… For the purposes of delivering opinions, ethics committees shall examine whether the research plan has taken account of … international obligations covering the status of research subjects and the rules and guidelines that govern medical research …"	NOT MENTIONED	YES (see e.g. Statute No. 488/1999, Section 27)	YES **Statute No. 488/1999** **Section 1** "This Act applies to medical research carried out on persons … save as otherwise provided in law."
France (1988)	NOT MENTIONED	NOT MENTIONED	YES **Title III, Article L. 209–12** "... The Minister may at any time suspend or prohibit biomedical research if there is a risk to public health or a breach of the provisions ..." **Title III, Article L. 209–13** "Medical Inspectors of Health and Pharmaceutical Inspectors of Health shall be empowered to ensure that the provisions ... are complied with."	NOT MENTIONED

PART 6. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Equivalent Protections (Harmonization of Standards)	Research and Review Conducted in Other Countries	Have Force and Effect of Law?	Covers Privately Funded Research?
India (2000)	**General Ethical Issue 8 Special Concern 7** "Guidelines, rules, regulations, and laws of all countries participating in collaborative research projects should be respected, especially by researchers in the host country and the sponsor country."	**Statement of Specific Principles for Clinical Evaluation of Drugs … Specific Principle 1** "The proposed trial should be carried out, only after approval of the Drugs Controller General of India … All 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."	YES	NOT MENTIONED
Netherlands (1998)	NOT MENTIONED	NOT MENTIONED	YES **Article 33.1** "Parties who do not comply with the prohibition contained in Article 6, first paragraph, will be punished with a prison sentence of a maximum of one year or a monetary fine …" **Article 33.2** "Parties who do not comply with the obligation to fulfill article 2, first paragraph or second paragraph … or who do not comply with the obligation contained in article 29, will be punished by being taken into custody for a maximum of six months or will be required to pay a monetary fine … Those who disobey the prohibitions contained in articles 4 and 5 and parties who carry out scientific research without a protocol on which a positive decision has been received will receive the same penalty." **Article 39** "… the law will be enforced for accurate execution on the part of all ministries, authorities, universities and officials concerned."	YES

PART 6. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Equivalent Protections (Harmonization of Standards)	Research and Review Conducted in Other Countries	Have Force and Effect of Law?	Covers Privately Funded Research?
New Zealand (1997)	NOT MENTIONED	**Chapter 4–Part B** "Practices and beliefs of an ethnic and/or religious nature must be fully respected. Research must be undertaken in a culturally sensitive and appropriate manner, in full discussion and partnership with the research participants whatever their ethnicity or religious affiliation …" **Chapter 4–Part H** "Any investigator participating in international collaborative research whose project is funded … by the HRC will require ethical approval from an accredited New Zealand ethics committee for the research. Research conducted overseas having human … involvement will also require ethical approval from an ethics committee (or equivalent body) in the country concerned … Any international collaborative research project, whether funded by HRC or not, which involves investigations in New Zealand or its territories, will be required to undergo ethical review by an accredited ethics committee within New Zealand."	YES	NO
South Africa (1993)	NOT MENTIONED	**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 … This is of paramount importance for medical research in an African context."	NO	NOT MENTIONED

PART 6. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Equivalent Protections (Harmonization of Standards)	Research and Review Conducted in Other Countries	Have Force and Effect of Law?	Covers Privately Funded Research?
Thailand (1995)	NOT MENTIONED	NOT MENTIONED	YES **# 11** "The Ethics Committee has the right to set any future guidance or regulation as deemed necessary."	YES
Uganda (1997)	**I.A.3** "Research covered by this policy may take place in a foreign country. The procedures enumerated in these rules may differ from those followed in the foreign country. In such instances, 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. This substitution is not, however, required by these rules."	NOT MENTIONED	YES **I.C.1** "Each institution which is engaged in research that is covered by this policy shall provide written assurance to the Uganda National Council on Science and Technology (UNCST) and the Uganda National Health Research Organisation (UNHRO) when it is established, that it will comply with the requirements ..." **III.F** "The UNCST shall have authority to temporarily suspend or permanently terminate approval of research that is not being conducted in accordance with the UNCST's requirements or that has been associated with unexpected serious harm to research participants ..." **VI.B** "Failure to comply with the provisions ... may result in termination of the research, fine, imprisonment, and/or deportation."	YES **I.B.1** "An *institution* means any entity or agency, whether public or private." **I.C.1** "Each institution which is engaged in research that is covered by this policy shall provide written assurance to the Uganda National Council on Science and Technology (UNCST) and the Uganda National Health Research Organisation (UNHRO) when it is established, that it will comply with the requirements ..."
United Kingdom (1998)	**Principle 2** "The principles for Good Clinical Practice in MRC-funded trials are the same as those laid down in the ICH Harmonised Tripartite Guideline for Good Clinical Practice …"	NOT MENTIONED	NO **Introduction** *"The Council expects that this framework for good practice will be implemented in all MRC-funded trials that involve human participants, including all trials involving medicinal products."*	NO

PART 6. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Equivalent Protections (Harmonization of Standards)	Research and Review Conducted in Other Countries	Have Force and Effect of Law?	Covers Privately Funded Research?
United Kingdom (1999)*	NOT MENTIONED	**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 ..."	NO	NO
United States Food and Drug Administration (FDA) Title 21 Code of Federal Regulations	**21 CFR § 312.120(c)(1)** "Foreign clinical research is required to have been conducted in accordance with the ethical principles stated in the Declaration of Helsinki or the laws and regulations of the country in which the research was conducted, whichever represents the greater protection of the individual." (see 21 CFR § 814.15–medical devices)	(see 21 CFR § 312.120 and 21 CFR § 814.15)	YES	YES (if it involves FDA regulated products)
United States Common Rule** Title 45 Code of Federal Regulations	**45 CFR § 46.101(h)** "When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy ... the procedures prescribed by the institution afford protections that are least equivalent to those provided in this policy ... may [be substituted] in lieu of the procedural requirements provided in this policy."	NOT MENTIONED	YES	DEPENDS (all privately funded research conducted at institutions, whose multiple project assurance (MPA) requires adherence to the Common Rule for "all research conducted at that institution," is covered)

* "The MRC's key principles, which are underpinned by the Declaration of Helsinki and outlined in *Responsibility in Investigations on Human Participants and Material and on Personal Information*, 1992, apply to research conducted in developing societies … In addition, investigators are expected to follow the *MRC Guidelines for Good Clinical Practice in Clinical Trials*, which are based on the ICH Harmonised Tripartite Guideline for Good Clinical Practice."

** The Federal Policy for the Protection of Human Subjects, also known as the Common Rule, is found at 45 CFR Part 46, Subpart A. Many federal agencies that conduct research involving human participants, including the Department of Health and Human Services (DHHS) and the Agency for International Development (USAID), are signatories to the Common Rule. Note that DHHS has passed regulations that include not only Part A but also Parts B, C, and D which address special protections for pregnant women, prisoners, and children. Likewise, USAID has passed separate regulations found at 22 CFR Part 225 which mirror 45 CFR Part 46, Subpart A.

PART 6. Comparative Analysis of International Documents Addressing the Protection of Research Participants *continued*

	Equivalent Protections (Harmonization of Standards)	Research and Review Conducted in Other Countries	Have Force and Effect of Law?	Covers Privately Funded Research?
United States Agency for International Development (USAID) Title 22 Code of Federal Regulations	**22 CFR § 225.101(h)** "When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy ... the procedures prescribed by the institution afford protections that are least equivalent to those provided in this policy ... may [be substituted] in lieu of the procedural requirements provided in this policy."	NOT MENTIONED	YES	DEPENDS (all privately funded research conducted at institutions, whose multiple project assurance (MPA) requires adherence to the Common Rule for "all research conducted at that institution," is covered)

INTERNATIONAL PERSPECTIVES ON PROTECTING HUMAN RESEARCH SUBJECTS

Commissioned Paper

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Executive Summary

By conducting focused site visits to countries in which research funded by the United States has been conducted, this project illuminates some of the ways in which U.S. human subjects protections and research practices may affect local investigators and others involved in the research enterprise. To obtain these perspectives, conversations with local researchers and members of committees charged with oversight of research were conducted in eight countries (Chile, Guatemala, Haiti, Kenya, Mexico, Taiwan, Thailand, and the United Kingdom).

Overall, there seems to be a high degree of commitment to conducting ethically sound research as well as much consonance between the values of foreign researchers and U.S. guidelines. However, researchers with whom we spoke commonly expressed concern that despite its importance in conducting research, the review process is unnecessarily burdensome—that is, it is time consuming and often difficult. At times, the specific procedures outlined in U.S. regulations regarding how this review should take place and how it should be documented pose substantial challenges, due to limited staffing, space, and resources. Local researchers and those charged with the oversight of research sometimes perceived that there is little flexibility in applying U.S. regulations in the face of cultural variability.

Similarly, while local researchers generally support the need to obtain consent for research, in some settings, cultural barriers exist (such as a tendency to withhold information about certain diagnoses or procedures) to obtaining individual informed consent. Nonetheless, even where such challenges to the informed consent process were absent, widespread concern was expressed that U.S. regulations regarding informed consent place undue emphasis on detailed documentation that seems to serve U.S. needs rather than local needs. In one instance, the documents themselves posed a risk to subjects. Although, arguably, Institutional Review Boards (IRBs) could properly waive the need for written consent in such situations, this approach can be difficult to implement in international collaborative research.

Despite some discordance between local and U.S. approaches, local researchers and those charged with the oversight of research tended to see this discordance not as one that poses irreconcilable conflicts, but as one that provides opportunities for negotiation and compromise. However, local researchers and IRB members perceived that their well-intentioned offers for negotiation and compromise can be met with a lack of trust in local investigators, institutions, and IRB members.

Although exploratory, this project makes it possible to provide some recommendations to investigators, IRB members, regulators, and sponsors regarding ways to enhance the protection of human subjects in international collaborative research, such as the following:

1. Work with local colleagues to make the research relevant to local issues and priorities.
2. In designing research, assess whether any relevant cultural barriers (such as whether placebos are culturally appropriate) exist to conducting research in a given location.
3. Develop informed consent documents in collaboration with local colleagues, paying special attention to potential problems in translation of particular concepts.
4. Exercise a degree of flexibility with regard to written consent documents, which may be awkward for research participants unaccustomed to receiving documentation of any important transaction.
5. Develop means of simplifying requirements for documentation that retain the ability to audit, both for the oversight of research (initial review, direct oversight, and continuing review) and for informed consent.
6. Consider having a local ombudsman available to answer subjects' concerns about the study as well as their rights as research subjects.

7. Encourage international discussion about the role of trusting the integrity of local investigators and those charged with the oversight of research to adopt and enforce mechanisms for ensuring that the rights and interests of human subjects are protected.
8. Provide education and training for local investigators and IRB members about U.S. regulatory requirements that include information about the rationale for those regulatory requirements.

Background

The National Bioethics Advisory Commission (NBAC) has been charged with examining selected ethical and legal issues in international research conducted and/or supported by the United States. In order to meet this charge, NBAC has initiated several projects to assist in deciding whether changes in federal regulations and policies are warranted, and if so, to develop recommendations for such changes.

By conducting focused site visits to countries in which research funded by the United States has been conducted, this project illuminates some of the ways in which U.S. human subjects protections and research practices may affect local investigators and others involved in the research enterprise. These perspectives were obtained through a series of visits to eight countries and involved conversations with local researchers and members of committees charged with the oversight of research.

Methods

The project was approved by the Duke University Medical Center (DUMC) IRB. Site visits were conducted in eight countries: Chile, Guatemala, Haiti, Kenya, Mexico, Taiwan, Thailand, and the United Kingdom. Sites were selected according to three main criteria. First, investigators who are now or have in the past been affiliated with DUMC or Family Health International (FHI) and have conducted internationally funded research were identified. Among this group, senior staff then identified those researchers with significant experience in international collaborative research who would be most able to provide informed responses relating to the project domains (described below). Next, a preliminary list of sites was selected to achieve a balanced geographic distribution. Finally, because of the significant time and financial constraints inherent to the project, most of the final sites selected for inclusion were among those to which travel by FHI personnel on unrelated business was already scheduled.

Once all of these factors were taken into account, a key respondent in each country was identified and asked to facilitate project staff in gaining an appreciation of how U.S. human subjects protections are perceived as well as their consonance with local values and concerns. To provide as complete a picture as possible, key respondents then identified others who could provide additional perspectives and information. Oral informed consent to participate in this project was obtained from individuals before they were engaged in formal discussions.

Standardized discussion guidelines were developed for use in conversations with local investigators, those involved in the local oversight of research, and those who obtain informed consent for research. The guidelines covered several domains including experiences with U.S. regulations regarding research (e.g., how they function, who carries them out, and a review of the standard U.S. elements of informed consent); how U.S. regulations correspond to international investigators' own moral rules and how situations of conflict are reconciled; and recommendations for changes or improvements in current U.S. regulations and research practices. Following three initial site visits by senior project staff, minor modifications were made to the discussion guidelines. The final guidelines are included as appendices to this paper.

Based on the experiences garnered during the initial three visits by senior staff, a training session was developed for staff who would make the subsequent site visits. The training session covered study domains; use of discussion guidelines; information to be included in trip reports and site visit reports; and intended application of study results.

Site visitors prepared a brief trip report as well as a more extensive site visit report. Each site visitor attended at least one of two group debriefing sessions (in person, and in one case by telephone). These sessions focused on uncovering general themes as well as other information that might not have been included in individual site visit reports. The debriefing sessions were tape recorded and transcribed. Then, site visit guidelines, site visit reports, and transcripts from the group debriefing sessions were reviewed to identify themes that emerged as a result of the site visits.

Findings

The findings from this project are reported according to the major themes that emerged: informed consent; IRBs; justice; research design; contrasting approaches to oversight; and trust. In this report, the term IRB is used to refer to local committees charged with reviewing and overseeing the conduct of research, recognizing that in international research, these committees commonly have different names, such as Research Ethics Committee or Ethics Committee.

In interpreting these findings, it is essential to note that the design of this project makes it inappropriate to generalize about the research practices of specific countries. In addition, because the ethical issues that arise in research can be controversial, it is essential to protect the confidentiality of key respondents and others with whom discussions were held. Accordingly, details that might provide a richer picture of the issues encountered are necessarily omitted from this report.

Informed Consent

The topic of informed consent engendered significant interest. In general, those who participated believed that it was important to obtain informed consent comprised of the basic elements outlined in U.S. regulations. For example, one IRB member mentioned that a "person must understand 100 percent what the research is about—must be able to say in her/his own words what the study is about. No coercion, pressure. Freedom to leave [the] study. That information [should] be given at the 'right/best' moment—not when the woman is in labor, for example."

However, frequent comments were made about the legalistic nature of U.S. guidelines for informed consent and the fact that they seem more oriented towards protecting institutions, researchers, and sponsoring agencies rather than research participants. For example, one person commented that "[c]onsent forms should protect participants (up to a point) not the provider."

There were also reports of investigators having difficulty translating the concept of informed consent to potential research participants, because of cultural practices and expectations. In addition, the process of documenting informed consent according to U.S. regulations seems to create a substantial amount of difficulty. In one study, it was described ironically as placing research participants at risk. Each of these issues will be described in greater detail.

The concept of individual consent. The concept of informed consent is challenging in some settings because of different attitudes and levels of concern about individual versus family decisionmaking; perceived expectations about telling the truth concerning certain diagnoses, treatments, and the details of research; and the degree of regard for women's roles in decisionmaking.

In some settings, the notion of individual informed consent can seem inappropriate, because important decisions are often made in conjunction with families or are even left to communities. For instance, 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 decisionmaking process. In another country, a research project ultimately included a multistep consent process beginning with community consent and followed by individual parental consent for research involving children. Finally, village elders were invited to sit in on sessions with children, because of community suspicions that children might be abducted and used as servants or be subject to having their organs harvested.

In one country, complete information about medical diagnoses and prognoses is withheld routinely from patients with certain diseases, such as cancer. Consequently, obtaining valid informed consent (for either treatment or research participation) can be difficult or impossible. While these patients are sometimes enrolled in research, family members may be asked to provide permission in lieu of consent even when the patient retains adequate decisionmaking capacity.

Consent documents. Although there was broad agreement that the basic elements of informed consent are important, repeated concerns were expressed about the amount of detail that was expected to be provided in consent documents according to U.S. standards. U.S. consent forms are viewed universally as too long, too detailed, and too complex. As recorded by one site visitor, "The process should be shorter. Information should be shorter." Some researchers questioned the need to include highly technical information, such as the pharmacological pathways of drugs. Others indicated that detailed consent forms might lead to a perception of exploitation, because providing detailed information to patients in some settings is uncommon. Similarly, there may be a perception among potential participants that complex forms would not be used unless the research in question involved substantial risk. One site visitor recounted the beliefs of an investigator regarding a lengthy consent document: "Nobody reads it, and it will just scare away individuals who would have participated in the study."

Investigators and those charged with overseeing research told stories about awkward translations of consent documents. According to an investigator in one study, "[t]he informed consent [form] had to be changed many times; in our culture the wording was not as strong as in the U.S. proposed wording." At another site, in a study that required a careful assessment of frequency of vaginal intercourse, the term *coitus* was translated to "with your husband," yet this may have led to an incomplete measure of the frequency of vaginal intercourse with all partners.

At times, working with U.S. IRBs on clarifying these issues has been difficult. One IRB chair was especially unhappy over a project funded by the National Institutes of Health in which a U.S. IRB insisted on retaining what the local IRB believed was inappropriate wording. Specifically, in this study the U.S. IRB wanted to retain a clause indicating that the participant would "pay for care even in the case of an adverse event." However, even though in the country in which the research was proposed, this clause was inappropriate because health care is provided at no charge, no flexibility was permitted in creating a local form that did not include this text. As a result, participation in the study was discontinued. A similar concern was expressed about inflexibility in changing terminology to refer to a *midwife* rather than a *doctor*, even though the appropriate clinician in the local setting was a midwife.

Avoiding such conflicts should not be difficult. As local researchers in one setting mentioned, "[we] are presented with informed consent documents already finished by the sponsors, and there is almost no opportunity to change them." These researchers concluded that they should participate in the development of informed consent forms.

In contrast to the standard practice of including contact information for someone in the United States in the consent form, most local investigators and IRB members believed that the contact person listed on the consent

form should be a citizen of the country in which the research was being conducted and who was located in that country. However, some favored including the names of both a local contact person and someone in the country of the sponsoring organization.

Documenting consent. In an occasional setting, documenting individual consent itself was seen as inappropriate. For instance, in one project involving many illiterate subjects, although thumbprints might be considered to be an appropriate means of documenting individual consent, local investigators did not use such an approach because it was too closely related to past police tactics and was 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. This point was summarized by a site visitor: "Signing a form in this country means 'asking for trouble;' whereas signing a form in the United States means 'self-protection.'"

Institutional Review Boards

Researchers and IRB members viewed the process of conducting local IRB review as important. Nevertheless, in some cases, the goal of IRB review in protecting human subjects seems lost amidst concerns about meeting U.S. regulations regarding appropriate procedures and the emphasis on documentation of these procedures. As indicated in a conversation with one investigator, "Everyone is in agreement that the patient's well-being is of [the] utmost concern, and everyone's goal is to look out for [the] subject—but IRBs ultimately shouldn't interfere with the research process. IRBs in [the] United States [are] looking out for legal protection of [their] institution—they lose sight of the subject's protection. This is not the way things work [here]."

In some settings, there seem to be impediments to implementing IRB review as stipulated in U.S. regulations. These include lack of resources to support comprehensive oversight that includes detailed documentation; concerns regarding the composition and function of IRBs; and the need for training of IRB members and investigators.

Resources. Conducting meaningful IRB review requires substantial resources that may not be available in some settings. In many poor countries where physicians are considerably overburdened, it is difficult to encourage their participation on IRBs. Yet, some members are very dedicated despite the burden on their time and the opportunity cost.

Shortage of office space and a lack of computers add to the difficulty of conducting some of the administrative work expected of IRBs. Compounding this problem is the fact that U.S. regulations can require substantially greater documentation of the entire oversight process than is the local norm (and with documentation requirements that may differ by sponsor). In addition, maintaining detailed records of IRB meetings and informed consent forms is difficult, particularly when resources for this work are not made available. In one research institution that does not have secure storage areas, it has been difficult to find sufficient room to retain documentation for the length of time that is sometimes required or expected. When faced with office shortages for existing staff and faculty, maintaining secure storage areas for files that may or may not ever be reviewed seems to be a low priority or a misallocation of resources. Finally, some observers mentioned that they face a conflict concerning the need to spend resources without this being recognized by sponsors.

Composition and function. Although many investigators know about U.S. federal requirements for the composition and function of IRBs, in some settings, "[l]ocal IRBs are not constituted according to these requirements, [and are] comprised of only physicians without community representatives." Further, some local and national IRBs seem to have operated without written guidelines, whereas others have very explicit guidelines. In some places without such guidelines, efforts are under way to develop them. In one IRB, members do not know each other and do not meet. They also do not know if the studies are followed up or even approved. This is not a national requirement, but is apparently done for historical reasons or perhaps because of the personality of the IRB chair.

Training. In many settings, U.S. regulations are not well known, and there may also be a good deal of confusion regarding which U.S. guidelines should be followed (e.g., those of the Department of Health and Human Services or those of the Food and Drug Administration). Furthermore, it is often difficult for international researchers and IRB members to keep apace with changing U.S. regulations.

Clearly, however, investigators and IRB members expressed a desire to learn about the U.S. regulatory approach. One group created the following list:

- Training of IRB members.
- Exchanges between U.S. and overseas IRBs.
- Dissemination of U.S. regulations.
- Need for more information/education/training for researchers and IRB members.

IRB members cited a similar list:

- More involvement of local IRBs in the development of informed consent.
- Need for training/information for IRB members and researchers.
- Dissemination of U.S. federal regulations.
- Development of local guidelines.

Justice

Considerations of justice abound in international research, yet in these site visits, comments related to justice focused on the responsibility to subjects once research has been completed and the importance of incorporating local priorities into the selection of study topics for international collaborative research based on their relevance in the United States and in the host country. For example, a site visitor summarized that while it was understood that "Foreign donors want to address issues that are important to them, [they] should involve issues that are of interest to local people too. [The] study must have relevance to local people and humanity in general." Similarly, IRBs need to evaluate research questions to make sure they are relevant for the population. Such a task would seem to require collaboration in the design of international research. In the words of one IRB member, "[f]oreign research must be genuinely collaborative, not a facade [of] collaboration."

Research Design

In some settings, explicit interest was expressed in having a role in research design. Of particular interest were stories regarding local perceptions concerning cultural barriers to randomization and the use of placebos. While local investigators understood the scientific rationale for using these techniques, they spoke of conflicts arising from cultural expectations on the part of patient-subjects.

In one setting, local researchers were dedicated to conducting a Phase III randomized, placebo-controlled trial, but were unable to engage patients in the study by using a standardized informed consent process. The investigators believed that obtaining informed consent was a barrier to the trial because participants in that setting did not expect physicians to be uncertain about which "treatment" was appropriate, regardless of the scientific uncertainty involved. These investigators deliberated extensively about the appropriate course of action, verifying the need for data obtained from a randomized trial and the need for consent. They entertained the possibility of conducting a pre-randomized study, but decided against doing so, because they believed it to be unethical. Ultimately, the trial was abandoned in favor of a Phase II trial.

In another setting, local researchers indicated that if a trial involves the use of a placebo, it is simply not included in the informed consent process. According to an IRB member, the "…community would not like placebo, but they don't know…." Moreover, since there is no direct translation of the term placebo in the local language, it is apparently translated in such a way that it might be misleading. Thus, research participants in this study were left without accurate information.

Contrasting Approaches to Oversight

Local researchers and those charged with the oversight of research reflected on the possibility of contrasting approaches to oversight in collaborative international research. Some suggested that local and national standards should prevail over U.S. approaches because they more adequately reflect cultural expectations than do international guidelines. Others argued that foreign researchers had an obligation to use their own standards when conducting research abroad. For example, one investigator said that "Researcher[s] from abroad should not carry out research [that would be considered] repugnant in his/her own culture in a second country." Still others believed that there are, or should be, universal principles that should be applied internationally and that the implementation of these principles must be sensitive to local needs. That is, international guidelines "should leave room for compromise…valid standards for everyone…not be too specific."

Although faced frequently with contrasting approaches to oversight from local and U.S. guidelines, such contrasts were not viewed as representing conflict. Rather, these situations generally prompted a search for negotiation and compromise. As indicated by a site visitor, one investigator mentioned that "he's never seen a conflict which couldn't be resolved; it comes down to understanding local cultures."

Nevertheless, a site visitor noted that in certain situations there is "[a] perception of a double standard, U.S. agencies do research [in this region]…that would not be possible in the United States because of ethical problems….[Also] an economic imposition: if you do not do it our way you will not get the money."

Some investigators emphasized that collaborative research involves continuing discussion and review and that there is a need to attend not only to meeting U.S. regulations, but also to respecting local regulations and expectations. One group of investigators expressed "a need for cultural communication" and made the following recommendations:

- Need for more involvement of local researchers.
- Need for education on use/meaning of the regulations.
- Need for clear definition of concepts.
- Need for agencies to understand the difference between a language problem and a substance problem.

Trust

IRB members and researchers questioned frequently the extent to which U.S. sponsoring institutions appeared to distrust the integrity of local researchers. Yet, "Trust is the basic component." Furthermore, the degree of inflexibility expressed by U.S. regulatory approaches is viewed as disrespectful, if not offensive, particularly by researchers and institutions with a great deal of experience and long-term relationships with American sponsors and research institutions.

Local investigators perceived some differences between the amount of trust inherent to collaborative research with U.S. sponsors compared to other governments. One site visitor observed that when "working with European Community, [Investigators are] only required to sign that they'll follow…guidelines of Helsinki…i.e., much less red tape, no inappropriate forms, and more trust and respect for them as researchers and as ethical moral beings."

Comments

Through a series of international site visits, much can be learned about how U.S. regulations and research practices are perceived and how these regulations correspond to international investigators' own moral rules. Nevertheless, these results should be interpreted with several limitations in mind:

1. The primary respondents in this study had extensive experience conducting research and were therefore aware of generally accepted international approaches for protecting human research subjects. Therefore, these respondents may have already decided to accept the U.S. regulatory approach, even if they had cultural reservations about doing so.
2. It is possible that site visitors may have been guided to colleagues with an interest in ethics.
3. Because of the high profile of this study, the information obtained may be overly positive.
4. The perspectives of research subjects are absent from this study.
5. Official local policies, procedures, laws, and regulations that guide the conduct of research with human subjects were beyond the scope of this study and thus were not analyzed.
6. These qualitative data were derived in a fashion that does not permit making generalizations about international research in general, or even for all research in specific countries.

Although many of these limitations might be overcome in subsequent evaluations using both qualitative and quantitative techniques, several of the findings from this study provide new, rich, and important information.

Overall, there seems to be a high degree of commitment to conducting ethically sound research as well as much consonance between the values of foreign researchers and U.S. guidelines. However, researchers with whom we spoke commonly expressed concern that the review process is burdensome in that is it time consuming and often difficult, despite its importance in conducting research. At times, the specific procedures outlined in U.S. regulations regarding how this review should take place and how it should be documented pose substantial challenges because of lack of staffing, space, and resources. Local researchers and those charged with oversight of research sometimes perceived that there is almost no flexibility in those procedures in the face of cultural variability.

Similarly, while local investigators generally support the need to obtain consent, in some settings, there are cultural barriers (such as a tendency to withhold information about certain diagnoses or procedures) to obtaining individual informed consent. Nonetheless, even where such challenges to the informed consent process were absent, widespread concern was evident that U.S. regulations regarding informed consent place undue emphasis on detailed documentation that seems to serve U.S. rather than local needs. In one instance, the documents themselves posed a risk to subjects. Although arguably IRBs could properly waive the need for written consent in such situations, this approach can be difficult to implement in international collaborative research.

Despite some discordance between U.S. and local approaches, local researchers and IRB members tended not to view the discordance as one that posed irreconcilable conflicts. Rather, they were considered to be opportunities for negotiation and compromise. However, local researchers and IRB members perceived that their well-intentioned offers for negotiation and compromise can be met with a lack of trust in local investigators, institutions, and IRB members.

Recommendations

Although exploratory, this project makes it possible to offer some recommendations to investigators, IRB members, regulators, and sponsors regarding ways to enhance the protection of human subjects in international collaborative research:

1. Work with local colleagues to make the research relevant to local issues and priorities.
2. In designing research, assess whether any relevant cultural barriers (such as whether placebos are culturally appropriate) exist to conducting research in a given location.
3. Develop informed consent documents in collaboration with local colleagues, paying particular attention to potential problems in the translation of particular concepts.
4. Exercise a degree of flexibility regarding written consent documents that may be awkward for research participants who are unaccustomed to receiving documentation of any important transaction.
5. Develop ways to simplify documentation requirements that retain the ability to audit, both for the oversight of research (initial review, direct oversight, and continuing review) and for informed consent.
6. Consider having a local ombudsman available to address subjects' concerns about the study and their rights as research subjects.
7. Encourage international discussion about the role of trusting the integrity of local investigators and those charged with the oversight of research to adopt and enforce mechanisms for ensuring that the rights and interests of human subjects are protected.
8. Provide education and training for local investigators and IRB members about U.S. regulatory requirements that include information about their rationale.

Appendix A

National Bioethics Advisory Commission

Assessment of the Impact of U.S. Federal Ethics Regulations on Research in Other Countries

Implemented by

Duke University
Family Health International

SITE VISIT GUIDELINES FOR IRB MEMBERS AND MEMBERS OF NATIONAL ETHICS COMMITTEES

Site Visit Guidelines for IRB and National Ethics Committee Members

The purpose of our conversation is to learn about the impact of research that is funded by the United States. Foreign funding can influence research in many ways, but we are mainly interested in the impact on various ethical issues. What we learn from this may be used to modify U.S. policies. Your comments and recommendations will be kept confidential, and your name will not be used in our reports.

Have you any questions before we start?

[Write down questions.]

Do you consent to discussing these issues with me?
Yes ☐ No ☐

I have a consent form here that we need to go through before we start. [OBTAIN CONSENT.]
Would you like to have a signed copy of it?
Yes ☐ No ☐

Site Visit Guidelines for IRB and National Ethics Committee Members

Ask the Respondent about his or her background–who s/he represents on the IRB/NEC (law, clergy, consumer, researcher, etc). Find out who appointed the Respondent and why s/he thinks s/he was asked. Find out whether s/he serves on any other IRBs (currently or formerly), and how long s/he has served on this one. How are members appointed? Is there any special training for members?

Learn as much as you can about this IRB/NEC. What is the committee's role? Ask about number of members, frequency of meetings, whether documents are sent for review in advance, whether decisions are made by vote or by consensus, and if by vote whether a simple majority is required. Ask how many proposals are reviewed per year. For NEC members, are biomedical issues other than those involving research examined by the committee?

Ask about the nature and source of the guidelines used by this IRB/NEC. Please cover the following:

- Are there written guidelines, and do all members of the IRB/NEC and all researchers have a copy?
- Who wrote the guidelines—this IRB/NEC, a national committee, another body? Were they adapted from other guidelines (which)?
- Does the IRB/NEC follow up studies that they have approved? How are regulations enforced?

Determine what procedures researchers must go through to get ethics approval for research. Determine if there are differences depending on whether the source of funding is local, bilateral (e.g., U.S.), multilateral (e.g., WHO), private (e.g., pharmaceutical), or public (e.g., government agencies). How does this IRB/NEC relate to others in the process? Are there multiple steps in review? If so, what are they? Ask for detailed descriptions, and take extensive notes. Ask the Respondent how burdensome s/he feels this process is and whether s/he feels the process is good and/or necessary.

Is the documentation of the IRB/NEC process different for research funded from different sources? If so, how?

Now we want to learn about areas of similarity and discrepancies or conflicts between different sets of ethical guidelines and how they are resolved. Ask about differences of opinion/rules between

- Individual committee members.
- Researchers and local IRB.
- Researchers and national guidelines.
- National guidelines and those of the funding or collaborating agency.

Write down all examples, and for each determine whether this happened on this committee or another.

Ask the Respondent what, in his or her opinion, are the most common sources of similarities and differences regarding ethical issues in research. Although the focus here is on agreement and disagreement between national and international ethical standards, local situations are also instructive. [Write down the responses.]

When the Respondent has finished, ask about each of the following if it HAS NOT ALREADY BEEN MENTIONED:

- Diagnostic testing and screening (probe: confidentiality, treatment availability, informing of test results).
- Experimental treatments.
- Use of placebos.
- Payment for iatrogenically caused injury or disease.
- Use of animals.
- Randomization.
- Other.

Sometimes local scientific communities feel that U.S. regulations for informed consent for research participation are inappropriate to their situation. Please tell what you feel are the most important components of informed consent. Explain.

When the Respondent is finished, ask how s/he feels about the importance of the following IF NOT ALREADY MENTIONED:

- Purpose of research.
- Risks of procedure/drug/contraceptive.
- Benefits of procedure/drug/contraceptive.
- Effectiveness of procedure/drug/contraceptive.
- Voluntary nature of participation.
- Freedom to drop out.
- Confidentiality.
- Burden of participation.
- Name of person to contact with questions or problems.
- Payment.

Now ask about any examples of complaints on the part of study participants about their treatment in the course of their participation. Ask whether the IRB was involved in the resolution. Ask about the process of resolution of complaints and the final outcomes. Does the Respondent feel the complaints were justified? Did they lead to any change in IRB or institutional procedures or policies?

Ask the Respondent to give examples of how this committee made research projects more ethical or participants in research projects safer. Learn if any of these examples involved internationally funded research.

Ask the Respondent to make recommendations to enhance resolving conflicts or discrepancies between different sets of ethical guidelines and making external guidelines function more effectively.

Explain that all research is governed by some code of ethics. Then read the Respondent the following two sentences and ask which one more closely reflects his or her own thinking:

☐ When foreign researchers and funders work in your country, they should use your local standards of ethics.

☐ When foreign researchers and funders work in your country, they should use the same standards of ethics as they use in research in their own country.

Ask the Respondent to elaborate on his or her answer.

Ask the Respondent if there are any other topics related to the subject of ethical conduct of research that s/he would like to discuss.

DUKE UNIVERSITY MEDICAL CENTER

CONSENT FOR RESEARCH

Respondent:_____

International Research: Case Studies

(Protocol Number: 1869-98-12ER)

Form M30

We are asking you to take part in a research study sponsored by the National Bioethics Advisory Commission.

PURPOSE OF THE STUDY

The purpose of the study is to document the effect that American research regulations have when applied in international settings. You are being asked to participate because of your experience with research studies that take place in foreign countries but are funded by the U.S. government. The results of this study will help inform U.S. policymakers about ways in which current regulations may need to be modified to help ensure the adequate and appropriate protection of participants in international research.

PROCEDURES

If you agree to be in this study, you will be interviewed about your experience with international research.

POTENTIAL RISKS

There are no physical risks associated with participation in this study. However, there is a small risk to your privacy by responding to the interviewer's questions and by sharing information about your experiences. In order to preserve the confidentiality of your responses to the interview, an identification number will be assigned to you. A list linking your name and identification number will be maintained in a secure location, accessible only by the study's technical monitor located at FHI.

ANTICIPATED BENEFITS

Information gathered during this interview will be reported to those charged with formulating policies and regulations governing federally funded research. Your responses will help inform policymakers of the possible effects that changes to U.S. research regulations may have upon foreign-based researchers and any individuals involved in their research studies.

Your participation in this study is entirely voluntary. You may refuse to answer any questions posed to you during this interview.

"I have read the above and have been given the opportunity to discuss it and ask questions. I have been informed that I may contact Benjamin Popkin, the FHI technical monitor, at (919) 544-7040, ext 229, to answer any questions I may have during the investigation and that I may contact the Office of Risk Management at (919) 684-3277 for any questions regarding my rights as a research subject. I agree to participate as a subject with the understanding that I may withdraw at any time."

_____
Name of person obtaining consent

_____ _____
Date Signature of person obtaining consent

Appendix B

National Bioethics Advisory Commission

Assessment of the Impact of U.S. Federal Ethics Regulations on Research in Other Countries

Implemented by

Duke University
Family Health International

SITE VISIT GUIDELINES FOR PERSONS WHO OBTAIN INFORMED CONSENT

Site Visit Guidelines for Persons Who Obtain Informed Consent

The purpose of our conversation is to learn about the impact of research that is funded by the United States. Foreign funding can influence research in many ways, but we are mainly interested in the impact on various ethical issues. What we learn from this may be used to modify U.S. policies. Your comments and recommendations will be kept confidential, and your name will not be used in our reports.

Have you any questions before we start?

[Write down questions.]

Do you consent to discussing these issues with me?
Yes ☐ No ☐

I have a consent form here that we need to go through before we start. [OBTAIN CONSENT.]
Would you like to have a signed copy of it?
Yes ☐ No ☐

Site Visit Guidelines for Persons Who Obtain Informed Consent

What is his or her professional background? How did s/he get involved in clinical research? Did s/he receive any special training?

Ask the Respondent about his or her understanding of the details of the studies s/he is or has worked on. For each project, make sure you cover the following topics:

- The sponsor.
- The purpose of the research.
- How participants are recruited.
- Policies for withdrawing from the study.
- Risks.
- Benefits.
- Additional burden due to research.
- To whom participants would turn if they think they are not being properly treated in the study.

Ask the Respondent

- What s/he believes is the most important information to give study participants.
- Whether there is information not on the consent form that s/he would give participants. Specify.
- Whether there is information on the consent form that is not necessary. What is it?

Ask the Respondent about his or her general perceptions about informed consent. Be sure to cover

- Whether study participants seem to desire additional information about the studies in which they participate.
- Whether most participants seem to understand what they are getting into when they agree to join a research study.
- If participants do not understand, why might that be?
- Recommendations for improving the informed consent process.

Explain that all research is governed by some code of ethics. Then read the following two sentences to the Respondent and ask which one is closest to his or her own thinking:

☐ When foreign researchers and funders work in your country, they should use your local standards of ethics.

☐ When foreign researchers and funders work in your country, they should use the same standards of ethics as they use in research in their own country.

Ask the Respondent to explain why s/he feels this way.

Ask the Respondent if there are any other topics related to the subject of ethical conduct of research that s/he would like to discuss.

DUKE UNIVERSITY MEDICAL CENTER

CONSENT FOR RESEARCH

Respondent:_____

International Research: Case Studies

(Protocol Number: 1869-98-12ER)

Form M30

We are asking you to take part in a research study sponsored by the National Bioethics Advisory Commission.

PURPOSE OF THE STUDY

The purpose of the study is to document the effect that American research regulations have when applied in international settings. You are being asked to participate because of your experience with research studies that take place in foreign countries but are funded by the U.S. government. The results of this study will help inform U.S. policymakers about ways in which current regulations may need to be modified to help ensure the adequate and appropriate protection of participants in international research.

PROCEDURES

If you agree to be in this study, you will be interviewed about your experience with international research.

POTENTIAL RISKS

There are no physical risks associated with participation in this study. However, there is a small risk to your privacy by responding to the interviewer's questions and by sharing information about your experiences. In order to preserve the confidentiality of your responses to the interview, an identification number will be assigned to you. A list linking your name and identification number will be maintained in a secure location, accessible only by the study's technical monitor located at FHI.

ANTICIPATED BENEFITS

Information gathered during this interview will be reported to those charged with formulating policies and regulations governing federally funded research. Your responses will help inform policymakers of the possible effects that changes to U.S. research regulations may have upon foreign-based researchers and any individuals involved in their research studies.

Your participation in this study is entirely voluntary. You may refuse to answer any questions posed to you during this interview.

"I have read the above and have been given the opportunity to discuss it and ask questions. I have been informed that I may contact Benjamin Popkin, the FHI technical monitor, at (919) 544-7040, ext 229, to answer any questions I may have during the investigation and that I may contact the Office of Risk Management at (919) 684-3277 for any questions regarding my rights as a research subject. I agree to participate as a subject with the understanding that I may withdraw at any time."

_____
Name of person obtaining consent

_____ _____
Date Signature of person obtaining consent

Appendix C

National Bioethics Advisory Commission

Assessment of the Impact of U.S. Federal Ethics Regulations on Research in Other Countries

Implemented by

Duke University
Family Health International

SITE VISIT GUIDELINES FOR RESEARCHERS

Site Visit Guidelines for Researchers

The purpose of our conversation is to learn about the impact of research that is funded by the United States. Foreign funding can influence research in many ways, but we are mainly interested in the impact on various ethical issues. What we learn from this may be used to modify U.S. policies. Your comments and recommendations will be kept confidential, and your name will not be used in our reports.

Have you any questions before we start?

[Write down questions.]

Do you consent to discussing these issues with me?
Yes ☐ No ☐

I have a consent form here that we need to go through before we start. [OBTAIN CONSENT.]
Would you like to have a signed copy of it?
Yes ☐ No ☐

Site Visit Guidelines for Researchers

Ask the Respondent about the nature of his or her research. Be sure to cover the following topics:

- Type of research (bench, clinical trials, epidemiology, service delivery, etc.).
- The substantive area (family planning, STDs, HIV/AIDS, oncology, etc.).
- Whether the Respondent has a current research project(s).
- How extensive the Respondent considers his or her experience with international collaborative research, as well as national research conducted with external funding and local funding.

Ask the Respondent whether s/he plays a role in other aspects of research.
Yes ☐ No ☐

If yes, which roles:

☐ Chair of IRB.
☐ Member of IRB.
☐ National ethics committee member.
☐ Person who obtains informed consent.
☐ Participant in research.
☐ Other, explain _____.

Now ask about sources of funding. The point is to get the *variety* of sources and the *extensiveness of experience*.

- Number and type of different donors on current projects.
- Approximate value of current projects.
- Number and type of different donors on projects in the last five years.
- Approximate value in last five years.

What is the general procedure that the Respondent must follow for a protocol to undergo ethical review and receive approval? How did s/he learn about this process?

Does this process vary according to the source of funding (i.e., funding source is local, bilateral [e.g., U.S.], multilateral [e.g., WHO], private [e.g., pharmaceutical], or public [e.g., government agencies])?
Yes ☐ No ☐ How?

Ask the Respondent how burdensome s/he feels this process is and whether s/he feels the process as it currently exists is good and/or necessary. Ask the Respondent for personal recommendations as to how to improve this process.

Write down *all examples* that this Respondent can give you about any differences in ethical guidelines (i.e., between individual researchers, researchers and local IRB, researchers and national guidelines, national guidelines and those of funding or collaborating agency) with which they or their colleagues have had direct experience. If it was with a colleague, ask if it would be okay to talk with that person. Obtain contact information and record it on the *next to last* page (which is otherwise blank), which will be removed before processing.

Learn how any moral differences that surfaced during the research review and approval process were resolved. What reviews and committees were involved? What was the resolution? How long did it take? Was the scientific design of the study jeopardized? Did the research proceed as planned? Was the Respondent satisfied with the resolution?

[NOTE: This refers to the *process* of resolution.]

Ask the Respondent what, in his or her opinion, are the most common sources of similarities and differences regarding ethical issues in research. Although the focus here is on agreement and disagreement between national and international ethical standards, local situations are also instructive. [Write down the responses.]

[NOTE: This refers to substantive areas of research or techniques.]

When the Respondent has finished, ask about each of the following IF THEY HAVE NOT ALREADY BEEN MENTIONED:

- Diagnostic testing and screening (Probe: confidentiality, treatment availability, informing of test results).
- Experimental treatments.
- Use of placebos.
- Written consent.
- Payment for iatrogenically caused injury or disease.
- Use of animals.
- Other methods of seeking approval or consent.
- Randomization.
- Other.

Is the *documentation* of the IRB process different for research funded from different sources? Please elaborate on your answer.

Sometimes local scientific communities feel that U.S. regulations for informed consent for research participation are inappropriate to their situation. Please say what you feel are the most important components of informed consent. Explain.

When the Respondent has finished, ask how s/he feels about the importance of the following IF THEY HAVE NOT BEEN MENTIONED:

- Purpose of the research.
- Risks of procedure/drug/contraceptive.
- Benefits of the procedure/drug/contraceptive.
- Effectiveness of the procedure/drug/contraceptive.
- Voluntary nature of participation.
- Freedom to drop out.
- Confidentiality.
- Burden of participation.
- Name of person to contact with questions or problems.
- Payment for participation.

Now ask about any examples of complaints on the part of study participants about their treatment in the course of their participation. Ask about the process of resolution of complaints and the final outcomes. Does the Respondent feel the complaints were justified? Did they lead to any change in institutional procedures or policies?

Ask the Respondent to make recommendations to enhance the current method for resolving differences or discrepancies between different sets of ethical guidelines and making external guidelines function more effectively.

Explain that all research is governed by some code of ethics. Then read the Respondent the following two sentences and ask which one more closely reflects his or her own thinking:

☐ When foreign researchers and funders work in your country, they should use your local standards of ethics.

☐ When foreign researchers and funders work in your country, they should use the same standards of ethics that they use in research in their own country.

Ask the Respondent to elaborate on his or her answer.

Ask the Respondent if there are any other topics related to the subject of ethical conduct of research that s/he would like to discuss.

Ask the Respondent if there are colleagues who have experienced conflicts or discrepancies in ethical guidelines relevant to their work.

You may use the rest of the page to make contact and scheduling notes. They will be removed before these discussion notes are processed.

DUKE UNIVERSITY MEDICAL CENTER

CONSENT FOR RESEARCH

Respondent:_____

International Research: Case Studies

(Protocol Number: 1869-98-12ER)

Form M30

We are asking you to take part in a research study sponsored by the National Bioethics Advisory Commission.

PURPOSE OF THE STUDY

The purpose of the study is to document the effect that American research regulations have when applied in international settings. You are being asked to participate because of your experience with research studies that take place in foreign countries but are funded by the U.S. government. The results of this study will help inform U.S. policymakers about ways in which current regulations may need to be modified to help ensure the adequate and appropriate protection of participants in international research.

PROCEDURES

If you agree to be in this study, you will be interviewed about your experience with international research.

POTENTIAL RISKS

There are no physical risks associated with participation in this study. However, there is a small risk to your privacy by responding to the interviewer's questions and by sharing information about your experiences. In order to preserve the confidentiality of your responses to the interview, an identification number will be assigned to you. A list linking your name and identification number will be maintained in a secure location, accessible only by the study's technical monitor located at FHI.

ANTICIPATED BENEFITS

Information gathered during this interview will be reported to those charged with formulating policies and regulations governing federally funded research. Your responses will help inform policymakers of the possible effects that changes to U.S. research regulations may have upon foreign-based researchers and any individuals involved in their research studies.

Your participation in this study is entirely voluntary. You may refuse to answer any questions posed to you during this interview.

"I have read the above and have been given the opportunity to discuss it and ask questions. I have been informed that I may contact Benjamin Popkin, the FHI technical monitor, at (919) 544-7040, ext 229, to answer any questions I may have during the investigation and that I may contact the Office of Risk Management at (919) 684-3277 for any questions regarding my rights as a research subject. I agree to participate as a subject with the understanding that I may withdraw at any time."

_____
Name of person obtaining consent

_____ _____
Date Signature of person obtaining consent

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