Ethical Issues in International Biomedical Research: An Overview

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ABSTRACT: Human subjects research has been the focus of numerous controversies over the years. The dilemma lies between the potential harm to individuals who participate in research and the knowledge to be gained from the research study that might benefit society. When research is conducted in developing countries by researchers and sponsors from the United States and other industrialized countries, differences in history, culture, politics, wealth, and power between the countries give rise to unique challenges. In this Article, the author identifies several ethical issues to be considered when research is conducted in developing countries and provides the legal and ethical framework for their resolution.

Over the last decade, the increasingly global nature of biomedical research on human subjects has given rise to unique and difficult ethical issues that reflect differences in history, culture, politics, wealth, and power between host countries where research is conducted and countries that sponsor and conduct research. The resolution of ethical issues in international research is particularly challenging in clinical trials conducted in

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1 Portions of this Article were taken or adapted from the author’s unpublished draft: Ethical Guidelines for the Review and Conduct of International Research (2003-2004), which is on file with the Office for Responsible Conduct of Research at Columbia University.
developing nations by the United States and other industrialized countries.\textsuperscript{2}

International research ethics has become the subject of widespread public debate in recent years. A fierce controversy erupted in 1997 over the use of placebo in the control arm of the “short course” mother-to-child human immunodeficiency virus (HIV) transmission trials conducted in Africa, Asia, and the Caribbean by sponsors from the industrialized world (the “short course” trials).\textsuperscript{3} This controversy was largely responsible for bringing the ethics of conducting research in other countries into the global spotlight.\textsuperscript{4}

Since then, the U.S. National Bioethics Advisory Commission (NBAC) and the Nuffield Council on Bioethics (United Kingdom)

\textsuperscript{2} The term “industrialized country” can include a government agency, pharmaceutical company, university, non-governmental organization (NGO), or any other entity or organization, public or private, and the individuals who represent them.

\textsuperscript{3} Opponents of the “short course” trials criticized the failure to test the experimental intervention against the standard treatment that all HIV-infected pregnant women in the United States would receive, claiming it created a double standard in research based on the level of healthcare to which a subject population had access. As will be discussed below, proponents of the trials contended that the use of placebo in the control arm was justified based on local economic circumstances and other factors in the countries where the trials were conducted. See Marcia Angell, \textit{The Ethics of Clinical Research in the Third World}, 337 NEW ENG. J. MED. 847, 847 (1997); Peter Lurie & Sidney M. Wolfe, \textit{Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries}, 337 NEW ENG. J. MED. 853, 853 (1997).

\textsuperscript{4} Short course clinical trials are trials designed to test an intervention involving a shorter duration of therapy than that which is administered under then current established regimens. Certain short course mother-to-child HIV transmission trials conducted in Africa, Asia, and the Caribbean were sharply criticized by Public Citizen’s Health Research Group and the editor of the New England Journal of Medicine. The criticism focused on their use in the control arm of placebo, rather than a long course of AZT, the standard, but very expensive and difficult to administer (in developing countries), treatment that all HIV-infected pregnant women in the U.S. would receive. The short course trials tested an intervention involving a lower dose given much later in pregnancy, which was cheaper and easier to administer than a long course of AZT. Both sides agreed that the trials could never be ethically conducted in an industrialized country, where researchers would be required to use the standard treatment as the control against which to test any experimental intervention. The trials were suspended in 1998, when the experimental short course treatment regimen was found to be effective in reducing mother-to-child HIV transmission. The short course regimen subsequently has been implemented in several resource poor settings, but it is still too expensive for some. See Angell, \textit{supra} note 3; Lurie & Wolfe, \textit{supra} note 3.
have issued reports on the ethics of conducting biomedical research in developing countries and an array of international studies and research practices has fallen under considerable ethical scrutiny in the public media.

Many U.S. researchers and Institutional Review Boards (IRBs), the vehicles established by U.S. institutions to review and approve research protocols, are not adequately prepared to deal with the ethical challenges that arise when research is conducted in other countries. In some cases, this lack of preparedness may result in a failure to protect the rights and welfare of individual research subjects or groups of subjects. In other cases, it may result in the exploitation of individuals, groups of individuals, or a host community or country where research is conducted. This is especially the case in studies in which sponsors from industrialized countries fail to make interventions or other research benefits available to developing countries after the completion of research.

This Article is divided into four parts. Part I provides a background and context for a discussion of ethical issues in international biomedical research. Part II introduces the established legal and ethical framework for the resolution of ethical issues in international biomedical research. Part III discusses a number of important ethical issues, including areas of consensus and conflict, to be considered when research is conducted in other countries and, particularly, in developing countries. Part IV offers concluding observations.

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7 See Robert A. Crouch & John D. Arras, AZT Trials and Tribulations, 28 Hastings Center Rep. 26, 30 (1998). This point is further developed in the next section of the present Article.
I. Background and Context for the Discussion of Ethical Issues in International Research

A. Why the Discussion is Important

Regardless of where research is conducted, there is always a potential risk of harm to individuals who participate in research. The advancement of scientific knowledge and human welfare often requires exposing research subjects to risk. It is this potential risk of harm, and the need to weigh it against the anticipated benefits given a particular set of circumstances, which has led to widespread agreement that research on human subjects must be ethically justified, irrespective of the setting in which it is conducted.8

During the last decade, more and more international biomedical research has been conducted, much of it in developing countries. “Part of the reason is [acquired immunodeficiency syndrome (AIDS)]—the first modern infectious disease to strike the developed and developing world simultaneously and to give both a large stake in finding a cure.”9 Another reason is that increased financial and regulatory burdens in the U.S. are driving researchers and sponsors from industry and academia to other countries able to provide certain research advantages. One important advantage of conducting research in developing countries, where research experience is often limited, is reduced research costs. Another advantage is faster accrual due to access to large numbers of subjects with particular diseases or belonging to certain racial and ethnic groups.10 “Naïve” subject populations, meaning populations who have not been treated for the disease under study, are especially sought after in clinical research.

Simultaneously with the increase in the amount of research being conducted in other countries, the international research environment has changed. First, biomedical research is increasingly becoming a collaborative effort as host countries in the developing world seek to become more equal partners with researchers and sponsors from industrialized countries in setting the research agenda and conducting research.11 Host countries are also demand-

8 NBAC, supra note 5, at 5–7.
9 Rothman, supra note 6, at 60.
11 NBAC, supra note 5, at 3.
ing a more equitable share of the benefits of biomedical research conducted within their borders, benefits that, traditionally, have almost exclusively benefited the industrialized world.\textsuperscript{12}

Second, the amount of international biomedical research sponsored and conducted by the private sector in developing countries has increased significantly. This has resulted in a dramatic shift from the public sector to the private sector as the primary source of funding for international research.\textsuperscript{13} One reason private sector research is expanding into developing countries is that these sites reportedly allow sponsors to bring their drugs to market faster.\textsuperscript{14} Another reason is to develop new markets for approved drugs.\textsuperscript{15}

The increasingly collaborative nature of international biomedical research is a reflection of a growing recognition of the need to make moral progress when research is conducted in developing countries by researchers and sponsors from industrialized countries. At the same time, the volume of research that is conducted in developing countries, driven in large part by market forces, has many concerned that protections for human subjects may be weakened when research is conducted in those countries.\textsuperscript{16} Developing countries often lack knowledge of research ethics, standards for reviewing and conducting research, and resources to conduct ethical review.\textsuperscript{17}

International research may present ethical challenges for a variety reasons. There may be historical, cultural, social, political, or legal factors that contribute to the difficulties of conducting research in other countries. These can pose obstacles to research conducted in an industrialized country by another industrialized country, as well as research conducted by an industrialized country in a developing country. Other more problematic ethical challenges are likely


\textsuperscript{15} \textit{Id.}

\textsuperscript{16} \textsc{NBAC, supra note 5, at 3.}

\textsuperscript{17} Benatar, \textit{Justice and Medical Research, supra} note 10, at 337.
to arise when research is conducted by industrialized countries in developing countries, where the existence of a disproportionately heavy disease burden,\textsuperscript{18} widespread poverty, and a lack of governmental and other resources are common. Variations in healthcare systems and standards of healthcare in countries where research is conducted, and between host countries and countries that sponsor or conduct research, raise especially difficult ethical questions.

In addition, developing country populations are often considered to be vulnerable, a term that refers to an incapacity for protecting one’s own interests.\textsuperscript{19} For a variety of reasons—such as poverty, inadequate healthcare, illiteracy, lack of female autonomy, or family or community involvement in decisionmaking—the potential for exploitation of vulnerable research subjects and their communities always exists in developing countries. Exploitation, as the term is used in this Article, refers to exploitation “in execution, or in the final analysis,” not intent.\textsuperscript{20} Special protections may be ethically required whenever research is conducted on vulnerable populations.

These challenges to conducting international research have given rise to an international discussion about how to facilitate biomedical research that is critical to global health needs while, at the same time, keeping the research ethically justifiable and protecting research subjects and their communities from exploitation. The fundamental ethical premise of all biomedical research conducted and sponsored by industrialized countries in developing countries is that it should be responsive to the health needs and priorities of the population on which it is conducted.\textsuperscript{21} The implementation of the premise, however, is much more difficult. “One of the greatest challenges in medical research is to conduct clinical trials in developing countries that will lead to therapies that benefit the citizens of these countries.”\textsuperscript{22}


\textsuperscript{20} Crouch & Arras, \textit{supra} note 7.

\textsuperscript{21} NBAC, \textit{supra} note 5, at 7–8; Ruth Macklin, \textit{After Helsinki: Unresolved Issues in International Research}, 11 \textsc{Kennedy Inst. of Ethics J.} 17, 18 (2001) [hereinafter Macklin, \textit{Unresolved Issues}].

B. Requirements for Sound Ethical Research

There are four requirements for sound ethical research with which all human subjects research conducted in other countries should comply:

1. Individual voluntary informed consent;  
2. A favorable risk-benefit assessment;  
3. An equitable distribution of the burdens and benefits of research;  
4. Prior independent ethical review.

The three substantive requirements—individual voluntary informed consent, a favorable risk-benefit assessment, and an equitable distribution of the burdens and benefits of research—are derived, respectively, from the fundamental ethical principles of respect for persons, beneficence, and justice. The fourth requirement—prior independent ethical review—is a procedural requirement. All of these requirements are embodied in the Belmont Report, the cornerstone of the U.S. system for protecting human research subjects, which is discussed below.

23 Nat’l Comm’n for the Protection of Human Subjects of BioMed. & Behavioral Research, The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research 5 (1978) [hereinafter Belmont Report]. The requirement of individual voluntary informed consent, derived from the principle of respect for persons or autonomy, is based on the individual right of self-determination. It requires that individuals who are capable of deliberation be given the opportunity to decide what should or should not happen to them. Respect for persons also encompasses the premise that individuals with diminished capacity are entitled to protection. Id. at 4.

24 Id. at 6–7. The requirement of a favorable risk-benefit ratio is derived from the principle of beneficence, with which the principle of nonmaleficence (“do no harm”) is closely linked. It suggests an obligation to act for the benefit of others and not harm them. Beneficence requires that potential benefits be maximized and potential harms be minimized to individuals and to society, thereby protecting the welfare of individuals as well as promoting the common good. Id. at 8–9. The requirement that the burdens and benefits of research be equitably distributed is derived from the principle of justice. It refers to an obligation to treat people fairly and equitably or to give them what is morally due or owed under the circumstances. Belmont Report, supra note 23, at 5.

25 Id. at 8–9. The requirement that the burdens and benefits of research be equitably distributed is derived from the principle of justice. It refers to an obligation to treat people fairly and equitably or to give them what is morally due or owed under the circumstances. Belmont Report, supra note 23, at 5.

26 NBAC, supra note 5, at 81; Nuffield Council on Bioethics, supra note 5, at 9.

II. Legal and Ethical Framework for Conducting and Reviewing International Research

A. United States Legal Framework

When research is conducted in another country by researchers and sponsors from the United States the research must be conducted in accordance with the federal regulations for the protection of human research subjects, 45 C.F.R. Part 46, Subpart A, otherwise known as the Common Rule28 (Federal Regulations). The Federal Regulations, promulgated by the Department of Health and Human Services (HHS), apply to all international research funded by HHS. All researchers and institutions engaged in HHS-supported research in another country must operate under a Federal Wide Assurance (FWA) approved by the agency.29 The Federal Regulations have the force of law, meaning that there are mechanisms for enforcement and imposing sanctions against noncompliant individuals and institutions.

The Federal Regulations, however, are almost entirely procedural. They emphasize organizational requirements related to IRBs. For example, there are requirements for IRB membership,30 record-keeping,31 and the documentation of informed consent.32 There are also provisions related to ethical principles, including informed consent,33 the risk-benefit analysis,34 and the equitable selection of subjects.35 Nevertheless, the Federal Regulations provide no guidance to IRBs or researchers about how ethics should be used

29 45 C.F.R. § 46.103(a) requires that each institution “engaged” in federally-supported human subjects research must obtain an assurance of compliance for the protection of research subjects approved by the Office for Human Research Protections (OHRP), HHS, or another federal department or agency. The assurance formalizes the institution’s commitment to protect research subjects. This means that every U.S. institution holding an assurance is responsible for ensuring that all researchers and institutions, both domestic (U.S.) and international (non-U.S.), engaged in human subjects research in another country in collaboration with that institution, operate under a Federal Wide Assurance (FWA). See id. FWAs must be obtained by the collaborating institutions prior to the start of that research.
30 Id. § 46.107.
31 Id. § 46.115.
32 Id. § 46.117.
33 Id. §§ 46.111(a)(4), 46.116.
34 45 C.F.R. § 46.111(a)(1), (2).
35 Id. § 46.111(a)(3).
as a mechanism for protecting human research subjects. With one exception rarely invoked by HHS, there are no requirements specific to international research in the Federal Regulations.36

Human subjects research regulations promulgated by other federal agencies, such as the Food and Drug Administration (FDA), may also apply when research is conducted in other countries by U.S. researchers and sponsors.37 These regulations are separate from 45 C.F.R. Part 46, Subpart A.

B. Ethical Framework

1. United States

Conducting human subjects research in compliance with the Federal Regulations does not ensure that research is ethical. Although the Federal Regulations must be considered in any ethical analysis, it is necessary to look beyond them to certain ethical principles, which must be applied to the facts and circumstances of the research study.

36 45 C.F.R. § 46.101(h) provides that, when research covered by 45 C.F.R. pt. 46(A) is conducted in foreign countries:

[I]f 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 means that if an ethics review system established in another country was declared to be “equivalent” to the protections contained in 45 C.F.R. pt. 46(A), any institution in the other country adhering to that system would not be required to obtain an assurance from an U.S. agency. NBAC, supra note 5, at 86.

37 For example, regulations promulgated by the Food and Drug Administration (FDA) apply to research conducted in other countries involving products regulated by the FDA. International research conducted under an Investigational New Drug Application or Investigational Device Exemption must comply with FDA Regulations. See, e.g., Informed Consent of Human Subjects, 21 C.F.R. pt. 50(B) (2004) (discussing the requirements of informed consent); Institutional Review Board (IRB), 21 C.F.R. pt. 56 (2004) (explaining IRB oversight requirements), Investigational New Drug (INDs) Application, 21 C.F.R. pt. 312 (providing procedures and requirements governing the use of INDs); Investigational Device Exemptions, 21 C.F.R. pt. 812 (providing procedures for the conduct of clinical investigation of devices). Federal funding for a research study is not necessary for the FDA regulations to be applicable.
In international research, this analysis requires an examination of a U.S. guidance document, the Belmont Report, produced in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. It also requires an examination of at least two international research ethics guidance documents, the World Medical Association (WMA) Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS Guidelines). Other international and national guidance documents are identified or discussed in conjunction with specific issues.

The Belmont Report provides the substantive foundation for the U.S. system for the protection of human research subjects. It applies the three ethical principles of respect for persons, beneficence, and justice to human subjects and deduces from them requirements for, respectively, informed consent, a favorable risk-benefit ratio, and an equitable selection of subjects. These requirements are designed to ensure that research is conducted ethically (i.e., in accordance with the three ethical principles).

The primary shortcoming of the Belmont Report is its failure to provide any practical guidance or examples to assist IRBs and researchers in the interpretation and application of its provisions (or those of the Federal Regulations) to individual research studies. It provides no specific requirements for, or discussion of, international research. Despite the importance of the Belmont Report to the protection of human research subjects, it is believed, in many instances, to be largely overlooked in the review and conduct of research by U.S. IRBs and researchers. Their focus, instead, is on the legal requirements imposed by the Federal Regulations.

38 BELMONT REPORT, supra note 23.
40 CIOMS, supra note 19.
41 Nancy M.P. King et al., Relationships in Research: A New Paradigm, in BEYOND REGULATIONS: ETHICS IN HUMAN SUBJECTS RESEARCH 1, 8 (Nancy M.P. King et al. eds., 1999).
42 Harold Y. Vanderpool, An Ethics Primer for IRBs, in INSTITUTIONAL REVIEW BOARD MANAGEMENT AND FUNCTION 3, 4 (Robert Amdur and Elizabeth Bankert eds., 2002).
43 Id. The extent to which this actually happens, however, is not known.
2. International Guidance Documents

The Declaration of Helsinki and the CIOMS Guidelines are the two most widely accepted international research ethics guidance documents. In contrast to the Federal Regulations, not only are the Declaration of Helsinki and the CIOMS Guidelines specific to international biomedical research, they also incorporate a more substantive approach to the application of ethical principles to the review and conduct of research.

The Declaration of Helsinki, adopted in 1964, generally is considered to be the foremost ethical guidance on biomedical research. It serves in many countries as the foundation for research-related legislation, regulations, and guidelines. The Declaration of Helsinki has undergone five revisions. The most recent revision occurred in 2000 in response to criticisms that it was unable to effectively deal with the challenges of international research, including the rapid increase in research conducted in developing countries. Today, the document consists of thirty-two ethical principles, although, like the Belmont Report, it fails to provide any specific guidance.

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44 The Declaration of Helsinki was developed by the World Medical Association (WMA), an international organization founded in 1947 to represent physicians. WMA, About the WMA?, at www.wma.net/e/about/ (last visited Sept. 9, 2004). The CIOMS Guidelines were issued by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), the leading international health organization in the world. CIOMS is an international, nongovernmental, nonprofit organization established jointly in 1949 by the WHO and the United Nations Educational, Scientific, and Cultural Organization (UNESCO) to facilitate and promote international activities in the field of biomedical sciences. CIOMS, What is CIOMS?, at www.cioms.ch/frame_what_is_cioms.htm. (last visited Sept. 9, 2004).

45 DECLARATION OF HELSINKI (as amended by the 29th WMA Gen. Assem., Tokyo, Japan, 1975); DECLARATION OF HELSINKI, (as amended by the 35th WMA Gen. Assem., Venice, Italy, 1983); DECLARATION OF HELSINKI, (as amended by the 41st WMA Gen. Assem., Hong Kong, Japan, 1989); DECLARATION OF HELSINKI, (as amended by the 48th WMA Gen. Assem., Somerset-West, South Africa, 1996); DECLARATION OF HELSINKI, (as amended by the 52nd WMA Gen. Assem., Edinburgh, Scotland, 2000).

for their application to particular studies. The most contentious issue surrounding the Declaration of Helsinki concerns the use of placebo in the control arm of a clinical trial and the standard of care (i.e., level of treatment) owed to research subjects during a study.

The CIOMS Guidelines were originally designed in 1982 as guidance for the application of the ethical principles set forth in the Declaration of Helsinki. The CIOMS Guidelines, however, were seen as ineffective in addressing the ethical issues raised by research conducted in developing countries. Consequently, they were revised in 1993 with regard to the ethics of international research involving experimentation on vulnerable population groups and large-scale drug and vaccine trials. Revised most recently in 2002, the CIOMS Guidelines contain twenty-one guidelines, each with its own commentary. The most widely discussed requirement is, perhaps, the requirement for making a product developed as a result of research “reasonably available” to the population or community in which it was tested. “Reasonably available” is a term which, thus far, has eluded definition by the international research community.

III. Issues in International Research

Resolution of ethical issues in international research may best be obtained by balancing the demands made by various ethical principles relative to the facts and circumstances of each situation. It requires reasonable flexibility in the interpretation of common principles and the accommodation of the needs of various research

(Note 46 continued)

changed the post-trial benefits for research subjects. Declaration of Helsinki 2000, supra, at Principle 30; see infra notes 135-38 and accompanying text. A third major revision, in 2002, included a provision for post-trial benefits for the host community: “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.” Declaration of Helsinki 2002, supra note 39 at Principle 19; see infra notes 139-68 and accompanying text (discussing host community benefits).

47 See Declaration of Helsinki 2002, supra note 39, at 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.”). 48 CIOMS, supra note 19, at Guideline 10 (“Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that . . . any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.”).
disciplines. Guidance documents are intended to raise general ethical issues for consideration by researchers, sponsors, IRBs, and others involved in research activities. They are not designed, however, to provide answers to specific questions or solutions to the contentious ethical problems encountered when research is conducted in other countries. Most important, ethical principles and guidelines are often open to thoughtful, but competing, interpretations by reasonable people who may disagree about solutions to particular problems.

A. Are Different Ethical Considerations Justified in Different Locations?

Perhaps the most controversial question in international biomedical research today is whether differences in ethical considerations are justified depending upon where the research is conducted. Can a research study, which could not be ethically carried out in a sponsoring industrialized country, be ethically justified in a developing country when the health problem being studied is common to both? One issue in particular—the failure to provide interventions of known efficacy to research subjects in developing countries—has polarized the international research community.

Some believe that a study, which could not be ethically conducted in a sponsoring industrialized country, may be ethically conducted in a developing country. They rely on different factors between the countries to justify different ethical standards. These factors, which affect the risk-benefit ratio, relate not only to local economic conditions, but also to the relevance of a study to the community in which it is being conducted.\footnote{Marcia Angell, \textit{Investigators’ Responsibilities for Human Subjects in Developing Countries}, 342 \textit{NEW. ENG. J. MED.} 967, 967 (2000).} Others believe that a study, which could not be ethically conducted in a sponsoring industrialized country, also may not be ethically conducted in a developing country. They contend that the same ethical standards should be applied in research conducted anywhere in the world. To do otherwise results in a double standard in research that “creates an incentive to use as research subjects those with least access to health care.”\footnote{Angell, \textit{supra} note 3, at 855.}

The question remains whether a different ethical standard is always a lower standard. Existing international guidelines are not adequate to resolve this difficult issue. The provisions in the Declaration of Helsinki governing the use of placebo in the control arm and the standard of care (i.e., level of treatment) owed to

\footnote{Marcia Angell, \textit{Investigators’ Responsibilities for Human Subjects in Developing Countries}, 342 \textit{NEW. ENG. J. MED.} 967, 967 (2000).}
research subjects during a study were at the center of the “short course” trials controversy.\(^{51}\) In 1997, when the controversy arose, the Declaration of Helsinki provided 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.”\(^{52}\) It also provided then, as it does today, that placebo should only be used in the control arm where there is no standard treatment available.\(^{53}\)

The international research community was bitterly divided over the meaning of the phrase, “best proven therapeutic method.” Did it mean the “best proven therapeutic method” anywhere in the world, as critics of the “short course” trials maintained, or that which is available in the host country, which may be nothing at all?\(^{54}\) In 2000, the Declaration of Helsinki was revised in response to this debate. The relevant provision now reads, “The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods.”\(^{55}\) Whether this revision actually will settle the debate over the standard of care remains unclear. The term “best” remains problematic, and its meaning is as open to conflicting interpretation as was its predecessor. Strong continuing disagreement over placebo-controlled trials led the WMA to establish a working group to examine this issue.\(^{56}\) The provision was further clarified the following year by way of a footnote, which provides two exceptions to the ban on the use of placebo.\(^{57}\)

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\(^{51}\) See id. at 847; Lurie & Wolfe, supra note 3 and accompanying text; see also supra text accompanying note 4.


\(^{53}\) Id.; DECLARATION OF HELSINKI 2002, supra note 39, at Principle 29.


\(^{56}\) Annabel Ferriman, WMA Agrees to Refine Changes to Declaration of Helsinki, 322 BRIT. MED. J. 1142, 1142 (2001).

\(^{57}\) DECLARATION OF HELSINKI 2002, supra note 39, at Principle 29. The first exception allows placebo to be used when a new treatment is being tested “for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.” Id. The second exception, which is clearly open to conflicting interpretation, allows the use of placebo when there are “compelling and scientifically sound methodological reasons” to do so. Id.
The CIOMS Guidelines have received far less attention than the Declaration of Helsinki concerning the issue of placebo controls and the standard of care owed to research subjects during a study. CIOMS Guideline 11 provides that, as a general rule, research subjects in the control arm of a clinical trial should be provided with “an established effective intervention.”58 It also provides several exceptions when it may be ethically acceptable to use placebo in the control arm. One notable exception, which was used to justify the “short course” trials, is where an established effective intervention is not generally available or affordable in a country. If that intervention is unlikely to become available or affordable in the foreseeable future and the health authority in that country seeks to develop an affordable intervention specifically for a health problem affecting its population, it may be ethical to use placebo in the control arm.59 The purpose of such a study is to determine whether the experimental intervention, while perhaps not as good as the standard intervention, is better than no intervention (i.e., placebo).

Since the “short course” trials have been debated extensively in the literature, this Article will use a controversial breast cancer study conducted in Vietnam in the mid-1990s (the Vietnam study) to showcase the debate over whether different ethical standards are justified depending on where the research is conducted.60 The study, about which far less has been written, raised ethical concerns not only about the failure to provide any intervention to subjects in the control arm, but also about the relevance to Vietnam of the intervention employed in the experimental arm.61 Another area of ethical concern in this study was the informed consent process, which is discussed later in the Article.62

The Vietnam study sought to study hormonal treatment as an adjuvant therapy (i.e., a therapy given after the initial primary therapy). All of the research subjects in the Vietnam study received mastectomy as the initial primary therapy. Research subjects randomized to the control arm received no adjuvant therapy after mastectomy and were merely observed. Although the study was eventually approved by the Health Sciences IRB at the University of Wisconsin-Madison, a common reaction of the reviewers of the proposed study was that this arm “should be considered inadequate

58 CIOMS, supra note 19, at Guideline 11.
59 See generally id. at Commentary on Guideline 11.
61 Id. at 426.
62 See infra text accompanying notes 92-98.
63 Love & Fost, supra note 60, at 426.
anywhere. It is exploitative of the women in Vietnam not to provide some systematic adjuvant treatment.” The researchers defended the use of the local standard treatment (i.e., no treatment), on the grounds that the women in the control group would be no worse off as a result of participating in the study. Nonetheless, they modified the study to provide the control group with both better follow-up and access to the same treatment as the experimental group in the event of cancer recurrence.

The experimental arm was also questioned on ethical grounds. Research subjects randomized to the experimental arm received two hormonal treatments, oophorectomy (the surgical removal of both ovaries), and tamoxifen (a synthetic estrogen antagonist used to prevent and treat breast cancer by inhibiting the stimulant effect of naturally occurring estrogen). There was considerable scientific support for studying the role of hormonal treatments as an adjuvant therapy for breast cancer. Nonetheless, it was not ethically or politically feasible to conduct this type of study in the United States, where the standard adjuvant therapy for breast cancer at the time of the study was (and still is) chemotherapy. Adjuvant therapy of any kind was not the standard treatment in Vietnam due to its cost.

Some questioned whether it was ethical to conduct the trial on Vietnamese women since there was nothing to indicate that the intervention was designed specifically for that population. Rather, if proven successful, it appeared that the intervention would also be appropriate for application in industrialized countries.

Though the study is done on Vietnamese women, there is no reason to expect that the results will not be seen as relevant to hormonal adjuvant therapy anywhere. It is, however, not possible to do the trial in an industrialized country. Any arguments that this trial is of particular benefit to Vietnamese women should, therefore, be viewed with suspicion. No data are given to support the claim that this is a treatment that “could be widely applied in that country.

Arguably, the Vietnam study is unethical with regard to the level of treatment provided to research subjects in two respects. First,
like the “short course” trials, research subjects in the control arm of the Vietnam study were not provided with an intervention of known efficacy. This failure violated the ethical rule advocated by one faction of the international research community, “If it is unethical to carry out a research study in a developed country, it is unethical to do the same research in a developing country.”67 Second, in contrast to the “short course” trials where, even though placebo was used in the control arm, the potential benefits accrued only to populations in developing countries where the trials were conducted, this “important feature of equity”68 appears not to have been fulfilled in the Vietnam study.

B. Host Community Involvement in Biomedical Research

Consistent with the increasingly collaborative nature of international biomedical research, prospective host communities are viewed as having the right and the responsibility to make decisions about the nature and scope of their participation in research. This is accomplished through community consultation or participation, a process in which researchers involve the affected community in all aspects of the research study. The process, which helps to make the community a more equal research partner, entails seeking guidance from various groups of community representatives, such as political and religious leaders, health officials, scientists, and prospective research subjects and their advocates. By ensuring that the role of the community goes beyond the simple participation of its individual members as research subjects, community consultation is designed to respect the culture, values, and dignity of the community and to obtain full understanding and acceptance of the research project.69

Researchers can involve the community in research in many ways. The community may help define the objectives of the research, determine how it is to be conducted and evaluated, and ensure that the research makes use of local expertise, skills, or systems, including research institutions and scientists. It may provide input relative to the manner and time frame in which the results of the research will be made available to research subjects, the community, or national policymakers and be given the opportunity to meaningfully respond to research findings and assist in implement-

68 Ruth Macklin, Justice in International Research, in BEYOND CONSENT: SEEKING JUSTICE IN RESEARCH 131, 141 (Jeffrey P. Kahn et al. eds., 1998) [hereinafter Macklin, Justice].
ing study results. Ideally, community involvement and consensus building should begin prior to the start of research.70

Along with the host community, researchers from sponsoring industrialized countries benefit from community consultation. Researchers need to be informed about cultural and logistical issues not readily apparent to them that may affect the research or its conduct. This process can help ensure that the research is sensitive toward local values and customs and ethnic or linguistic groups. It can also help enhance study credibility and recruitment, prevent unrealistic public expectations of the study, and help researchers identify risks and benefits to communities and develop strategies for addressing them. It is an effective tool by which an informed consent process can be developed and implemented and by which to promote justice by ensuring that the research is relevant to the host community.71

Community consultation is still a controversial issue in international research, however. While there is consensus that the host community should be involved, disagreement exists over the nature and scope of that involvement. The level at which a community is involved in research depends on whose interests the particular project is designed to address. Community involvement will be limited where the nature and scope of the research project has been largely determined by the interests of researchers or sponsors before the host community is consulted. Other research projects, which are actually driven by the community’s interests, will involve the community in every aspect of the project.

Another difficulty in utilizing community consultation is in defining what group or unit constitutes the community for the purpose of a particular research study.72 “Community” can mean, for example, a geopolitical unit; a religious or ethnic group; shared or common interest, occupation, or cause; activity or resource mobilization (often with conflicting views); or a target group of researchers or health policymakers.

70 Id.
71 Id.
72 Id. at 30.
As a general rule, community involvement is most appropriate for higher risk research, such as a Phase 3 clinical trial,\textsuperscript{73} HIV preventive vaccine research, or a study involving a sensitive topic or with significant social or legal risks to subjects or the community. The UNAIDS Guidance Document is the only international document that directly addresses community consultation in a guideline.\textsuperscript{74} “Guidance Point 5: Community Participation” states that “[t]o ensure the ethical and scientific quality of 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.”\textsuperscript{75} The related discussion identifies which community representatives might be involved in the vaccine development process and what benefits can be provided by community participation in that process.\textsuperscript{76}

C. Protections for Research Subjects

There are two principle safeguards designed to protect the rights and welfare of research subjects: individual voluntary informed consent and prior independent ethical review of a proposed research study. Both safeguards require special consideration when biomedical research is conducted in another country.

\textsuperscript{73} Clinical trials are categorized into four phases. Phase I trials are used to determine the toxicity and safe dosage of a new drug, and generally involve less than 100 normal research subjects, meaning individuals without the disease or condition being studied. NBAC, \textit{supra} note 5, at 21, Exhibit 2.1. Phase II trials are used to determine whether a drug produces any clinically significant effects in subjects with the targeted disease or condition. \textit{Id.} They generally involve 100 to 300 research subjects. \textit{Id.} Phase III trials, which are used to establish the efficacy, or effectiveness, of interventions that appear promising in Phase II trials, may involve thousands of research subjects at multiple sites. \textit{Id.} An intervention will be approved for use by the FDA only after the successful completion of a Phase III trial. Phase IV trials are conducted on a large number of subjects after the FDA has approved an intervention to assess its long-term effects. \textit{Id.} Phase IV trials are conducted much less frequently than Phase I, II, or III trials. \textit{Id.} Phase III trials are considered to be “higher risk” because of the large number of research subjects that is often involved.


\textsuperscript{75} \textit{Id.} at 19.

\textsuperscript{76} \textit{Id.} at 19–20.
1. Voluntary Individual Informed Consent

The requirement for obtaining voluntary informed consent is often considered to be the most important single safeguard for research subjects.\(^7\) Although not universally accepted, it is found in the Federal Regulations\(^8\) as well as in every other international\(^9\) and national\(^10\) research ethics document. Research conducted in other countries, and in developing countries in particular, presents unique challenges during the informed consent process. Researchers must find innovative ways of presenting information to ensure that prospective research subjects from different backgrounds and with varying levels of education understand the nature and purpose of the research and are able to make an informed and considered decision about whether they wish to participate in the study. It is particularly important that individuals understand the potential consequences (the risks and benefits) and the voluntary nature of their participation in research, including that they are free to withdraw from the research at anytime without penalty.

When research is conducted in another country, issues in the informed consent process, such as illiteracy, language, social, and cultural barriers, and diminished personal autonomy, must be addressed. For example, belief systems about illness may be significantly different from those in the industrialized world,\(^11\) a local language may not have words for research-related concepts (i.e., placebo, blinding, randomization),\(^12\) or common techniques used in clinical research (e.g., taking bodily fluids or tissues) may have unique significance in a particular culture.\(^13\) In some cultures, it is not customary to provide certain information, such as a diagnosis of a serious disease, to a patient.\(^14\) In other cultures, respect for the

\(^7\) Solomon R. Benatar, Reflections and Recommendations on Research Ethics in Developing Countries, 54 SOC. SCI & MED. 1131, 1135 (2002) [hereinafter Benatar, Reflections and Recommendations].
\(^8\) 45 C.F.R. § 46.116(a)(1)–(8) (2004).
\(^11\) NBAC, supra note 5, at 40–41; NUFFIELD COUNCIL ON BIOETHICS, supra note 5, at 40–41.
\(^12\) NUffield Council on Bioethics, supra note 5, at 41, 75.
\(^13\) Id. at 41.
family or community may be as important, or more important, than respect for the individual, and the role of others, such as family members or tribal leaders in the informed consent process, should be acknowledged and accommodated. In no case, however, should such influence or authorization serve as a substitute for individual informed consent.

There are circumstances in which it would be inappropriate to ask research subjects to sign a written consent document. Oral consent may be warranted, for example, when research is being conducted in a population living under a repressive regime where subjects associate signing a document with victimization by their government. Oral consent also may be warranted in any type of research setting where the creation of a record of individuals as research subjects could cause them to suffer harm. This is often the case when research is conducted on female research subjects in cultures with little or no recognition of female autonomy. In situations when consent is given orally, researchers should be able to verify that informed consent was provided and fully document the procedures used in the consent process.

The informed consent process is further complicated by the therapeutic misconception, a belief that the purpose of a clinical trial is to benefit individual subjects, rather than to generate data for the purpose of advancing scientific knowledge. There is a need to distinguish between informed consent for participation in clinical research and informed consent for clinical care. In research, the subject’s physician, who provides patient care, is also a researcher, a fact that needs to be addressed in the informed consent process. The therapeutic misconception may be particularly difficult to address when research is conducted in developing countries where the roles of researchers and physician may be impossible to separate and “grossly inadequate healthcare resources and the pressures to enroll research subjects may overshadow concern for patients’ best interests.” The use of community consultation to develop the informed consent process may be helpful in minimizing the therapeutic misconception.

86 NBAC, *supra* note 5, at 43–45, Recommendations 3.6, 3.8, 3.9.
87 *Id.* at 49.
89 Benatar, *Reflections and Recommendations*, *supra* note 77, at 1135.
Studies show that the inadequacy of informed consent is a problem not only in developing countries, but also in industrialized countries. Research subjects in both environments fail to understand that they can decline to participate, or they are free to withdraw from a study at anytime, or study participation is not part of routine medical care. There is an additional concern in developing countries that informed consent may be less than voluntary when participation in research is the only way for individuals to obtain medical care. The question is always whether such an inducement to participate in a research study is an undue inducement, such that informed consent cannot be truly voluntary.

It was mentioned earlier that the informed consent process was a major area of ethical controversy in the Vietnam study. The problem arose when it became clear that U.S. standards for informed consent would not be acceptable to physicians, political leaders, and patients in Vietnam, where a paternalistic physician/patient relationship exists. Because patients defer to their physicians in making treatment decisions, “it was necessary to withhold from potential subjects any elements of the consent process that would convey uncertainty by the treating doctor,” including alternatives to participating in the study and that randomization would determine what treatment subjects would receive. Randomization, in particular, requires the exposure of professional ignorance to enable patients to understand why it is justified. The researchers explained:

Thus, while it might be technically possible, though difficult, to inform Vietnamese women about alternative ways of treating breast cancer or options within a research protocol, Vietnamese people do not believe it is the right thing to do, and even if it were done, the informed consent that resulted would not be functionally relevant because patients, in fact, would defer judgment to their doctors. In addition, trying to force this mode of consent on the physicians risked losing their cooperation with the project because of the tone of cultural imperialism that it would convey.

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91 Nuffield Council on Bioethics, supra note 5, at 78–79.
92 Macklin, Informed Consent for Research, supra note 84, at 290.
93 Benatar, Reflections and Recommendations, supra note 77, at 1135.
94 Love & Fost, supra note 60, at 425.
After consulting with surrogate groups and political leaders, agreement was reached as to the content and form of the consent process, which included the key U.S. regulatory elements of informed consent, “though with somewhat less detail than is typical in a US consent form.”95 Consent monitoring suggested that research subjects understood the key elements: that they were enrolled in a U.S.-sponsored research study and that oophorectomy would leave them permanently sterile. It was less clear how many subjects understood they could refuse to be in the study, they could refuse to have their ovaries removed, or that randomization determined what treatment they received.96

The informed consent process used in the Vietnam study was criticized for its failure to adequately deal with the therapeutic misconception. "Research subjects who believe that the physician-investigator is choosing the best treatment for them, rather than adhering to the requirements of a research protocol, lack a proper understanding of the research enterprise and cannot truly give informed consent."97 The study might not have gone forward had researchers been required by the IRB to adhere strictly to U.S. standards for disclosing critical information to research subjects, such as alternatives to study participation and randomization to different treatments. The failure to distinguish between clinical practice and research, however, meant that the informed consent process was dictated by what was customary in clinical practice in Vietnam, rather than what is fundamental in clinical research.98

The informed consent process in the Vietnam study constituted a significant departure from recognized ethical standards. In contrast to the Vietnam study is a microbicide99 study conducted among female commercial sex workers in four developing countries.100 In this study, researchers came up with innovative ways to obtain truly informed consent after subjects were unable to grasp the concepts of a clinical trial, despite extensive counseling and explanation of the different aspects of the study.101

95 Id. at 430.
96 Id.
97 Macklin, Informed Consent for Research, supra note 84, at 291.
98 Id.
99 Malcolm Potts, Thinking About Vaginal Microbicide Testing, 90 AM. J. PUB. HEALTH 188, 188 (2000) (stating vaginal microbicides offer a promising new method for HIV and STD prevention for women in the developing world, who are often unable to compel their partners to use condoms).
100 Gita Ramjee et al., Challenges in the Conduct of Vaginal Microbicide Effectiveness Trials in the Developing World, 14 AIDS 2553 (2000).
101 Id.
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Literacy problems led researchers to employ more native language speaking counselors and translators to provide detailed and repeated counseling to subjects. These individuals were trained to explain terms such as “placebo,” “randomization,” and “double-blind.” “For example, we explained that if the women had a headache they could either be randomized to receive an aspirin or a vitamin tablet, which looks similar to aspirin. The aspirin will have an effect on the headache but the vitamin tablet will not.” Finally, role-plays were used to determine the women’s understanding of the informed consent form.

The study concluded that informed consent is an ongoing process and recommended “that future trials have a short ‘run-in’ period prior to implementation of the study to allow for difficulties in the understanding of the trial procedures. In this way the participants will have enough time to think and consult their peers before they agree to enroll in the trial.”

2. Prior Independent Ethical Review

The requirement of prior independent ethical review of a proposed research study provides an additional safeguard for research subjects, who may not be adequately protected from harm by their individual voluntary informed consent. In federally funded international research, prior independent ethical review generally involves review by committees in the sponsoring country (i.e., U.S. IRBs) as well as the host country where the research will be conducted. In other countries, ethics review committees (ERCs) or research ethics committees (RECs) serve as the equivalent of U.S. IRBs.

Ethical review of research by an IRB in the U.S. is designed to help ensure adherence to U.S. standards and regulations for protecting human research subjects when research is conducted in another country. U.S. IRBs often have greater experience reviewing biomedical research protocols than local ERCs. IRBs are required by the Federal Regulations to ensure that: (1) the risks to subjects are minimized and reasonable in relation to benefits (i.e., a favorable

102 Id. at 2554.
103 Id. at 2556.
104 NBAC, supra note 5, at 82–83; NUFFIELD COUNCIL ON BIOETHICS, supra note 5, at 107–08; CIOMS, supra note 19, at Commentary on Guideline 3.
105 CIOMS, supra note 19, at Commentary on Guideline 3.
risk-benefit ratio,\textsuperscript{107} (2) the selection of subjects is equitable,\textsuperscript{108} and (3) informed consent is obtained from subjects and documented.\textsuperscript{109} It is especially important for the IRB to determine whether conducting a research study in a developing country, rather than in the U.S. or another industrialized country, is justified.\textsuperscript{110} A researcher who has an established relationship with a host country is more likely to be conducting research there in response to a health problem identified in conjunction with that country.\textsuperscript{111}

The U.S. Office for Human Research Protections (OHRP) states that IRBs must possess sufficient knowledge of the local research context to satisfy the criteria for its approval of research in the Federal Regulations. “This responsibility endures regardless of the IRB’s geographic location relative to the institution and the research.”\textsuperscript{112} Nevertheless, in a recent survey of researchers in developing countries, about their concerns and opinions regarding the ethical review processes and the performance of U.S. and developing country IRBs, 83% of responding researchers felt that U.S. regulations were “insensitive to local culture.”\textsuperscript{113}

One way of addressing the perceived insensitivity of U.S. IRBs to local culture is to engage the services of an independent consultant who has lived or worked in the host country. The role of the consultant is to provide the IRB with a social and cultural overview of the subject population as well as an assessment of the risks and concerns associated with the study. This may be particularly useful when the U.S. researcher has neither worked nor lived in the country where the research will be conducted. The Federal Regulations permit IRBs to “invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB.”\textsuperscript{114}

In addition to review by a U.S. IRB, all human subjects research conducted in another country should be reviewed and approved by an ERC in that country. This requirement provides additional

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\textsuperscript{107} 45 C.F.R. §§ 46.111(a)(1), 46.111(a)(2) (2004)  \\
\textsuperscript{108}  Id. § 46.111(a)(3).  \\
\textsuperscript{109}  Id. §§ 46.111(a)(4), 46.111(a)(5).  \\
\textsuperscript{110}  CIOMS, supra note 19, at Commentary on Guideline 3.  \\
\textsuperscript{111}  Fitzgerald, supra note 106, at 15.  \\
\textsuperscript{112}  Memorandum from Director of Division of Human Subject Protections, OHRP, to Division of Human Subject Protections, OHRP (Aug. 27, 1998), updated July 21, 2000, at www.hhs.gov/ohrp/humansubjects/guidance/local.htm (last visited Aug. 26, 2004).  \\
\textsuperscript{113}  Adnan Ali Hyder et al., Ethical Review of Health Research: A Perspective from Developing Country Researchers, 30 J. MED. ETHICS 68, 70 (2004).  \\
\textsuperscript{114}  45 C.F.R. § 46.107(f).
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protection for research subjects by ensuring that protocols will be scientifically and ethically reviewed by individuals knowledgeable about the culture and other relevant conditions prevailing in the community where the research will be conducted. Generally, host country ERCs are in the best position to determine whether a research protocol exhibits an awareness of, and sensitivity to, the context in which research will be conducted and to monitor compliance with ethical requirements throughout the duration of the study. Host country ERCs have a “special responsibility” to determine whether a research study is responsive to the needs of the community where the research will be conducted.

Review by an institutional or organizational body in the host country can occur at a national (centralized) level or a local level in the community where the study will be conducted. If there is no biomedical ERC at the national or local level, approval from the Ministry of Health or other recognized authority may be considered. Nonetheless, the mere presence of an ERC in another country does not ensure adequate review of research to be conducted there. ERCs may be ineffective for a variety of reasons, including a lack of resources, training and experience in ethical review, and other factors. Researchers should identify any factors contributing to the ineffectiveness of such review and, where possible, invoke reasonable measures designed to address them. In most cases, U.S. IRBs and local ERCs work independently to review the same protocols. The development of enhanced communication as well as other procedures designed to facilitate collaborative review of research by U.S. IRBs and local ERCs may result in better review of research.

An important factor in the ethical review of research conducted in other countries is the need to identify those aspects of a culture or society that create conditions for potential harms and increased vulnerability of research subjects and communities. Vulnerability in research may result from “insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests.” The Declaration of Helsinki, the CIOMS

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115 CIOMS, supra note 19, at Commentary on Guideline 3.
116 Id.
117 Id.
118 NBAC, supra note 5, at 85; NUFFIELD COUNCIL ON BIOETHICS, supra note 5, at 104–06.
119 NBAC, supra note 5, at 91; NUFFIELD COUNCIL ON BIOETHICS, supra note 5, at 108–09.
120 Fitzgerald, supra note 106.
121 CIOMS, supra note 19, at Commentary on Guideline 13.
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Guidelines, \textsuperscript{123} the UNAIDS Guidance Document,\textsuperscript{124} the Belmont Report,\textsuperscript{125} and the Federal Regulations\textsuperscript{126} all reflect concerns about conducting research in vulnerable populations. The research objectives, rather than the vulnerability of the subject population, should adequately justify conducting the research in a vulnerable population. The research must not be able to be carried out equally well with less vulnerable subjects.\textsuperscript{127} Appropriate and sufficient measures should be taken to address the potential harms and increased vulnerability to research subjects and host communities. Protections for vulnerable populations might include accommodations in the informed consent process or measures to protect the fact of subjects’ participation in research or the confidentiality of research data.

Another factor to be considered during ethical review of international biomedical research is the underlying health risk that exists in a particular host community. “Research that is unacceptable in one society because its risks outweigh the risks posed by the disease may have a favorable risk-benefit ratio in another society where the risks posed by the disease are significantly greater.”\textsuperscript{128} In countries where participating in research may be the only means by which individuals can obtain access to medical care, subjects may feel that any risk is worth the possibility of a benefit, even if a benefit is unlikely to occur. This is particularly true where the research involves an intervention aimed at HIV/AIDS or other deadly diseases.

Finally, special considerations related to privacy and confidentiality may be required in international biomedical research. Protections may be needed, for example, in cultures where husbands exercise control over their wives, fathers exercise control over their unmarried daughters, or where disclosure of participation in research, or other related information, presents a risk to a female research subject. Privacy and confidentiality are especially problematic in HIV/AIDS research, where participation in research may expose subjects to significant social and legal discrimination and harm. The Federal Regulations require that the privacy of subjects be protected and that the confidentiality of data be maintained.\textsuperscript{129}

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\item \textsuperscript{123} CIOMS, \textit{supra} note 19, at Guideline 13.
\item \textsuperscript{124} UNAIDS GUIDANCE DOCUMENT, \textit{supra} note 74, at Guidance Points 3 & 7.
\item \textsuperscript{125} BELMONT REPORT, \textit{supra} note 23, at 8.
\item \textsuperscript{126} 45 C.F.R. § 46.111(b) (2004).
\item \textsuperscript{127} CIOMS, \textit{supra} note 19, at Commentary on Guideline 13.
\item \textsuperscript{128} Ezekial J. Emanuel, David Wendler & Christine Grady, \textit{What Makes Clinical Research Ethical?}, 283 JAMA 2701, 2708 (2000).
\item \textsuperscript{129} 45 C.F.R. § 46.111(a)(7).
\end{itemize}
The previously noted survey of developing country researchers’ concerns and opinions regarding ethical review processes showed significant differences between the U.S. and developing countries in the priority assigned to various ethical issues. When asked to select from a list of issues raised by IRBs and ERCs, researchers responded that developing country ERCs were most concerned about cultural appropriateness of the studies, the need for local language consent forms, the relevance of the research question to the country where the research was conducted, and the availability of the intervention to the host country after the study was over. In contrast, researchers indicated that U.S. IRBs were more likely to raise issues regarding the need for local language consent forms, the need for letters of approval from developing country representatives, and the complexity of the consent form. Interestingly, both U.S. IRBs and developing country ERCs were viewed as being more concerned with politics than with protecting the interests of research subjects. The authors admit that this perception, while serious, relies heavily on the interpretation of the term “politics.”

D. Benefit-Sharing: Justice in Research

While informed consent and prior independent ethical review provide two important safeguards to protect the rights and welfare of research subjects in international biomedical research, additional steps must be taken to promote justice in the distribution of the burdens and benefits of research. “Equity is the core concept in fair distribution in the context of research involving human subjects. Equity requires that no one group—gender, racial, ethnic, geographic, or socioeconomic—receive disproportionate benefits or bear disproportionate burdens.” There is a recent emphasis on access to research benefits in international research, which arises from the growing concern that, although research subjects and host communities in developing countries ought to benefit from research, frequently, they do not.

The fundamental ethical premise underlying biomedical research conducted in other countries is that the research should be responsive to the health needs and priorities of the population or community in which it is to be carried out. Although there is widespread agreement as to the premise itself, there is disagreement over whether proven research interventions must be made

130 Hyder et al., supra note 113.
131 Macklin, Justice, supra note 68, at 132.
132 CIOMS, supra note 19, at Guideline; NBAC, supra note 5, at 8, Recommendation 1.3.
available to the populations on which they are studied in order for the research to be responsive and, therefore, ethical.\textsuperscript{133}

Some argue there is no such obligation and that research is sufficiently responsive if a disease or other health problem prevalent in the study population is the focus of the research, and that the research is reviewed and conducted in accordance with established ethical standards. Others contend that research should not be conducted in a population that bears the burdens of research unless some post-trial benefits are made available to that population.

The issue of providing post-trial benefits to research subjects and host communities is especially significant in biomedical research conducted in developing countries where poverty afflicts so many and government health funding is often inadequate. The potential for researchers to exploit populations in developing countries is a major concern. In many cases, when an intervention is proven effective, neither the host country government nor its inhabitants can afford to buy it after the study is completed. When access to the benefits of a new intervention that has been tested in a developing country is denied to that developing country and the resulting profits go primarily to the industrialized world, the research is not responsive to the needs of the host community.

Although the principle of post-trial benefit-sharing is becoming increasingly accepted as an ethical requirement when research is conducted in developing countries by researchers and sponsors from industrialized countries, there is no agreement about the nature and scope of that obligation. In the case of an intervention, to whom should it be made available? Research subjects? The host community? Others? Subjects from earlier trials having some bearing on product development? For how long should an intervention be made available after a trial? For some designated period of time, or for as long as the intervention is needed by the individual? Who should be responsible for providing it? These are just a few of the many questions raised by the issue of benefit-sharing in research that has been conducted in developing countries.

As a general rule, however, post-trial benefits should be proportional to the size, complexity, and importance of the research project, including the possible magnitude of harm to research subjects and the probability of that harm. The greater the risks to subjects, the greater the benefits that should be afforded to subjects.

\textsuperscript{133} Macklin, \textit{Unresolved Issues}, supra note 21, at 19–21.
and the host community after a trial is completed. As one commentator explains:

While it may be difficult to undertake harm/benefit calculations in advance of knowing what research will reveal and how valuable the information may be, the debate that is beginning on how safeguards can be built into the contract to promote justice in the distribution of benefits at a later time must be encouraged in the quest to achieve greater fairness in the international research endeavour. Such considerations in the ethics of research have not yet evolved to the same level as some of the other ethical requirements that have been the focus of more attention.\textsuperscript{134}

1. Research Subjects

The protection of research subjects during a biomedical research study, through the ethical review and informed consent processes, has always been an important consideration. More recently, the international research community has begun to focus on the issue of whether subjects should receive some type of post-trial benefit. It has been suggested that research subjects should be provided with an experimental intervention, used in a study and shown to be efficacious, if subjects still need it once the study is over. When the experimental intervention is shown not to be efficacious, but the control intervention has proven to be of benefit to research subjects, and would not otherwise be available to them, consideration should be given to providing subjects with the control intervention.\textsuperscript{135}

The 2000 revision of the Declaration of Helsinki introduced a new, controversial provision directed at this issue, which states that “[a]t the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic, and therapeutic methods identified by the study.”\textsuperscript{136} The UNAIDS Guidance Document requires that effective vaccines

\textsuperscript{134} Benatar, \textit{Reflections and Recommendations}, supra note 77, at 1137.

\textsuperscript{135} NBAC, \textit{supra} note 5, at 56–61; \textit{Nuffield Council on Bioethics}, \textit{supra} note 5, at 118–21.

\textsuperscript{136} \textit{Declaration of Helsinki 2002, supra} note 39, at Principle 30. A note of clarification to and an amended version of Principle 30 are both currently under consideration by the WMA.
be made available to all trial participants as soon as possible.\textsuperscript{137} Ethics guidelines adopted by a few developing countries, such as Uganda,\textsuperscript{138} impose affirmative obligations to provide post-trial benefits to research subjects.

2. Host Communities

Many believe that the host community or country, not just research subjects, should benefit from the research if it is to be ethically sound and not exploitative.\textsuperscript{139} The primary focus of host community benefits has been the provision of interventions that were tested in developing countries and proven effective. There are, however, other types of post-trial benefits, known as derivative research benefits, which can be provided to host communities. Derivative research benefits might include transferring needed technology to the host country, training host country personnel to conduct research or the ethical review of research, or the provision of various forms of healthcare or construction of health-related infrastructure.\textsuperscript{140} Many involved in biomedical research in developing countries believe that such arrangements are preferable to those that simply make interventions available.\textsuperscript{141}

Recognition of an ethical obligation to provide post-trial benefits to host communities can be traced back to the 1979 Belmont Report.

\begin{quote}
[W]hen research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.\textsuperscript{142}
\end{quote}

\textsuperscript{137} UNAIDS GUIDANCE DOCUMENT, supra note 74, at 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”).

\textsuperscript{138} NAT’L CONSENSUS CONFERENCE, supra note 80.

\textsuperscript{139} Crouch & Arras, supra note 7, at 26; Carlos Del Rio, Is Ethical Research Feasible in Developed and Developing Countries?, 12 BIOETHICS 328, 330 (1998); Leonard H. Glantz et al., Research in Developing Countries: Taking ‘Benefit’ Seriously, HASTINGS CENTER. REP. 38, 40 (1998).

\textsuperscript{140} Alice Page, Prior Agreements in International Clinical Trials: Ensuring the Benefits of Research to Developing Countries, 3 YALE J. HEALTH POL’Y, L. & ETHICS 35, 40–41 (2002); Fair Benefits for Research, supra note 12, at 2133.


\textsuperscript{142} BELMONT REPORT, supra note 23, at 10.
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A number of international guidance documents lend support for an obligation to make effective interventions and other research benefits available to host communities, including the CIOMS Guidelines,143 the Declaration of Helsinki,144 the UNAIDS Guidance Document,145 and the WHO Operational Guidelines for Ethics Committees that Review Biomedical Research.146 In recent years, post-trial benefits have been addressed in the ethics guidelines of several industrialized and developing countries, such as the United Kingdom,147 Canada,148 Uganda,149 and Nepal.150 While all of these international and national guidance documents require discussions about post-trial product availability and benefit-sharing issues before research begins, a lesser number of them impose an affirmative obligation to provide effective interventions to a host community once a study is completed.151

One valid criticism of a requirement to provide the tested intervention is that it only applies to successful phase 3 research (i.e., research that leads to an effective intervention). “[O]nly rarely does a single research study lead to the discovery of a new intervention that can be introduced promptly into routine care.”152 The provision of derivative research benefits to host communities in phases 1 and 2 research as well as unsuccessful phase 3 research may help to negate the perception that the industrialized country is exploiting the host community.153

143 CIOMS, supra note 19, at Guideline 10.
144 DECLARATION OF HELSINKI 2002, supra note 39, at 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.”).
145 UNAIDS GUIDANCE DOCUMENT, supra note 74, at 13, Guidance Point 2 (“Any HIV preventive vaccine demonstrated to be safe and effective . . . should be made available . . . to other populations at high risk of HIV infection.”).
146 WORLD HEALTH ORG., OPERATIONAL GUIDELINES FOR ETHICS COMMITTEES THAT REVIEW BIOMEDICAL RESEARCH 13, Guideline 6.2.6 (2000) (recommending that “a description of the availability and affordability of any successful study product to the concerned communities following the research” be considered an element of review by ethics committees.)
147 MED. RESEARCH COUNCIL, RESEARCH INVOLVING HUMAN PARTICIPANTS IN DEVELOPING SOCIETIES: ETHICAL GUIDELINES FOR MRC-Sponsored Studies 3 (2004).
148 TRI-COUNCIL POLICY STATEMENT, supra note 80, at 1.12.
149 NAT’L CONSENSUS CONFERENCE, supra note 80.
150 NEPAL HEALTH RESEARCH COUNCIL, supra note 80.
151 CIOMS, supra note 19; NAT’L CONSENSUS CONFERENCE, supra note 80; UNAIDS GUIDANCE DOCUMENT, supra note 74; DECLARATION OF HELSINKI 2002, supra note 39.
152 NUFFIELD COUNCIL ON BIOETHICS, supra note 5, at 121.
153 See NBAC, supra note 5, at 21, Exhibit 2.1 (explaining phases of clinical research).
3. Capacity Building

It is generally agreed that there is a need for researchers and sponsors from industrialized countries to help build the capacity of developing countries for designing and conducting research, for conducting scientific and ethical review of proposed research, and for implementing the results of research after the study is completed.154 Research capacity building is defined as “the process by which individuals, organizations and societies develop abilities (individually and collectively) to perform functions effectively, efficiently and in a sustainable manner to define problems, set objectives and priorities, build sustainable institutions and bring solutions to key national problems.”155 These efforts are aimed at lessening the present mismatch in developing countries between the high burden of disease and the lack of technical capacity to make use of existing knowledge or generate new knowledge to independently address health problems. Capacity building, like the provision of interventions and other derivative research benefits, finds support in the ethical requirement that the benefits and burdens of research be equitably distributed between industrialized countries conducting and sponsoring research and developing countries where research is conducted.

The importance of building the capacity of developing countries to generate and apply global and country-specific knowledge to local problems through international collaboration should not be underestimated. “Although the provision of successful interventions may help developing countries address particular health problems in the short term, building research capacity better situates developing countries to solve their own health problems in the long run.”156 Many developing countries lack scientific and ethical capacities due to a lack of resources, scientific and ethical experience and capabilities, infrastructure, personnel, technical capacity for conducting research, or an inability to provide healthcare and treatment.

Research capacity building objectives should be consistent with the expectations of research subjects and communities. Most often, it involves transfer of scientific knowledge and skills to researchers or other local personnel from developing countries, provision of

154 Id. at 89–91.
156 Page, supra note 140, at 65.
facilities and equipment for conducting research, or the development of national or local ethics review capacity. The amount of capacity building reasonably expected should be proportional to the size, complexity, and importance of the research project, including the possible magnitude of harm to subjects and the probability of that harm occurring. The greater these factors, the greater the need for capacity building. Capacity building should occur in all clinical trials.

Both the CIOMS Guidelines and the UNAIDS Guidance Document expressly provide that capacity building in host countries is an ethical component of research. The UNAIDS Guidance Document expressly states that scientific and ethics infrastructures for the review of research in the host country should be developed, if they are inadequate, prior to the start of research.

4. Prior Agreements for Benefit-Sharing

The use of prior agreements to ensure the provision of interventions, capacity building, and other benefits to research subjects and host communities after a study is completed is an issue that is beginning to generate more discussion and study by the international research community. "Prior agreements . . . generally refer to arrangements [not necessarily legal ones] made before research begins that lay out a realistic plan for making effective interventions or other research benefits available to [research subjects and] the host communities after a study is completed." They “can help researchers, sponsors, ethics review committees, host governments, and other parties involved focus on whether the host community will truly benefit from the proposed research.”

157 CIOMS, supra note 19, at Commentary on Guideline 20.
158 Id. at Guideline 20 ("In externally sponsored collaborative research, sponsors and investigators have an ethical obligation to ensure that biomedical research projects for which they are responsible in such countries contribute effectively to national or local capacity to design and conduct biomedical research, and to provide scientific and ethical review and monitoring of such research."); UNAIDS GUIDANCE DOCUMENT, supra note 74, at 15, Guidance Point 3 ("Strategies should be implemented to build capacity in host countries and communities so that they can practise 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.").
159 UNAIDS GUIDANCE DOCUMENT, supra note 74, at 21, Guidance Point 6 ("If the country’s capacity for scientific and ethical review is inadequate, the sponsor should be responsible for ensuring that adequate structures are developed in the host country for scientific and ethical review prior to the start of the research.").
160 Page, supra note 140, at 38.
161 Id. at 44.
Requiring prior agreements as a condition for the approval of research has been criticized for several reasons.\textsuperscript{162} Two of the most important criticisms are: that such a requirement will only delay or prevent new drug research in developing countries since sponsors may be reluctant to commit financially to providing effective interventions and that, in practice, many aspects of prior agreements, such as product affordability, distribution, and use, are extremely problematic. Despite the criticisms, those who favor the use of prior agreements in international biomedical research believe that:

\textit{[T]he difficulties inherent in the negotiation and implementation of prior agreements do not outweigh the ethical imperative to secure them. The resolution of critical health problems always requires grappling with complex and challenging issues, and the concerted efforts and talents of multiple partners from diverse environments and disciplines are often needed.}\textsuperscript{163}

Although they are still limited in number, prior agreements have been employed in international biomedical research in developing countries by several organizations. Two of these organizations are the World Health Organization (WHO), the world’s leading international health organization, and the International AIDS Vaccine Initiative (IAVI), an international scientific, nonprofit organization founded in 1996 to develop HIV vaccines for global use.\textsuperscript{164}

WHO has successfully used prior agreements to make effective interventions available in developing countries. For years, WHO has collaborated with industry to promote research and development of \{various\} health-related products and technologies \{targeting diseases\} that are of priority to WHO. An essential element of these collaborations is the negotiation of prior agreements to ensure that final products will be made widely available to developing countries at low cost.\textsuperscript{165}

\begin{footnotesize}
\begin{enumerate}
\item \textit{Id.} at 44–54.
\item \textit{Id.} at 46.
\item \textit{Id.} at 54–64.
\item Page, \textit{supra} note 140, at 55.
\end{enumerate}
\end{footnotesize}
Currently, IAVI has six Vaccine Development Partnerships with individuals and entities from both industrialized and developing countries. It has been “instrumental in structuring prior agreements with industry partners that give developing countries access to IAVI-supported vaccines at reasonable prices and in sufficient quantities.” Although early and intermediate stage clinical trials are ongoing in a number of countries, the success of IAVI’s efforts to deal with the issue of access to AIDS vaccines by the developing world prior to the start of research awaits the test of time.

IV. Conclusion

Many opportunities and challenges remain inherent in the conducting of international biomedical research. The ethical issues are especially difficult when research is conducted in developing countries by researchers and sponsors from industrialized countries. In some cases, research in developing countries is driven by market forces, rather than the health needs of the population on which the research is conducted. Often, many of the ethical issues that arise in international research also raise corresponding concerns about disparities in wealth and power, injustice, and exploitation.

Certain requirements for the conduct of ethical research, such as informed consent and prior independent review of research, have had the benefit of more extensive discussion and actual experience. Widely accepted ethical principles and standards are established to provide guidance in these areas, although concerns remain about how best to build the capacity of developing host countries to effectively review biomedical research conducted on their populations.

Other issues in international biomedical research are at the core of the debate about what constitutes the ethical conduct of research in developing countries. The standard of care that is owed to research subjects during a study and the benefits, if any, that should be provided to subjects and host communities after a study is completed are issues that remain especially problematic. Although the international research community remains as divided as ever on the standard of care issue, there is growing agreement that something

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167 Page, supra note 140, at 59.

168 IAVI R&D PROJECTS, supra note 166.
is owed to developing countries when research is conducted by researchers and sponsors from industrialized countries.

Whether that something must be the experimental intervention or whether it can be some other type of research benefit is becoming, increasingly, the focus of that debate. Formidable financial and logistical obstacles provide the greatest challenge to making interventions available. Collaborative efforts involving multiple partners from diverse environments and disciplines may provide the most promising approach to ensure that vulnerable populations do not bear the burdens of research without receiving an equitable share of its benefits.