

## FOCUS: RESEARCH AND CLINICAL ETHICS

# Conducting Research with Human Subjects in International Settings: Ethical Considerations

Sandra L. Alfano, PharmD, FASHP, CIP

*Research Scientist, General Internal Medicine, and Chair, Human Investigation Committee, Yale University, New Haven, Connecticut*

Biomedical research in international settings is undergoing expansive growth and may potentially result in far-reaching benefits, such as direction of research resources toward solving basic health care needs of world populations. However, key ethical concerns surround this expansion and must be carefully considered by international researchers. International research is impacted by differences in language, culture, regulatory structures, financial resources, and possibly ethical standards. Local community leadership involvement in the planning stages of research is imperative. Especially in resource-poor countries, the research agenda must be designed to address local needs and provide local benefit. Capacity strengthening efforts, aimed at improving institutional support for ethical conduct of human subjects research, must continue to be supported by wealthier nations.

## INTRODUCTION

Medical research is undergoing an explosive expansion into the international arena. The move toward globalization may be, in part, in recognition of the importance of mobilizing resources to address basic needs that are unmet in the world population. But many other factors have contributed to this growth, including the search

for large populations with a given disease to facilitate quick enrollments and shorter timelines to approval. Another contributing factor is the lower cost of conducting clinical trials in many international settings. Also, efforts have been made to streamline or harmonize regulatory approval [1] in multiple countries, leading to extensive multinational studies sponsored by the

---

To whom all correspondence should be addressed: Sandra L. Alfano, PharmD, FASHP, CIP, Research Scientist, General Internal Medicine, and Chair, Human Investigation Committee, Yale University, 55 College St., New Haven, CT 06520, Tele: 203-785-4688; Fax: 203-785-2847; Email: Sandra.alfano@yale.edu.

†Abbreviations: IRB, Institutional Review Board; REC, Research Ethics Committee; CIOMS, Council for International Organizations of Medical Sciences; NIH, National Institutes of Health.

Keywords: international research ethics, capacity building, institutional review boards, research ethics committees

pharmaceutical industry. While these efforts are potentially beneficial, this growth has prompted numerous concerns about the ethical acceptability, especially of researchers from wealthy countries doing human subjects research in developing countries. This article is intended to review these issues and offer a perspective of an Institutional Review Board (IRB†) Chair with experience in working with IRB counterparts in multiple foreign countries.

### SETTING THE STAGE

In 2011, Adashi [2] noted that, "... the unabated globalization of biomedical research has reached a tipping point whereupon over half of all clinical trials registered with ClinicalTrials.gov (<http://clinicaltrials.gov/>) (N100, 000) are conducted beyond the confines of the continental U.S." Economic pressures to shorten timelines to approval make some international markets with very large pools of potential subjects very attractive as settings for biomedical research. Although there may be advantages in large numbers, it must be recognized that complexity abounds in international environments. Conducting international research carries cultural, linguistic, institutional and political barriers that must be handled efficiently to be successful [3]. Researchers can be confronted by real issues in resource poor countries, including dealing with language barriers, lack of office support functions, sporadic Internet connectivity, time zone differences, lack of deep understanding of some administrative issues, and lack of funding for support personnel. Researchers must grapple with these difficult issues while still adhering to scientific and ethical principles that will drive research approvals. Indeed, Koski and Nightingale [4] argue that, "... ethics and science are not separable — a given study must conform to ethical standards or it should not be performed, and it must be scientifically sound or it cannot be ethical. The use of a good research design and adherence to sound ethical principles should result in the conduct of research that is valid, reliable, and ethically acceptable in any country."

The growth in international biomedical research leads to a number of important and difficult-to-answer questions about the economics and ethics of such research, especially in developing countries. Among these questions are the following [5,6]:

Who stands to benefit from the research conducted in developing countries? Are potential subjects free to choose to participate or seemingly forced to participate due to lack of access to ordinary health care services? Is there a potential to exploit these research subjects, and, if so, how does a researcher avoid exploitation? Are placebo-controlled trials being done in such settings simply to facilitate U.S. regulatory approvals or are they locally justifiable?

Since these questions are important and complex, it might be helpful to look to guidance for how such ethical issues can be resolved. Importantly, Levine [7] pointed out that when developing ethical guidelines for the international setting, the classical question in ethics arises: "Are ethics universal or do they differ from one culture to another?" Some argue that ethics have or should have cross-cultural validity. This is referred to as "ethical universalism" [8]. Others take the stance that ethics are necessarily based on the culture of the given population, or a "cultural pluralism" view [7]. Levine [7] aspires to what he terms "global applicability," which he defines by stating, "That means that the guidelines are, as far as we can tell, applicable currently in all the cultures and societies in the world. There is an assumption that we will be revising these guidelines from time to time as new understandings come to the fore." Despite this global applicability view, tension remains between the universalists and pluralists in the evaluation of research projects taking place in international settings.

On a more pragmatic level, one might ask how ethical issues get addressed and resolved in the United States, to see if this approach might be applicable internationally. A system of ethical review in which IRBs review and approve clinical research to ensure protection of the rights and welfare of human subjects participating in research has been in place in the United States since the 1970s.

IRBs are also charged with ensuring that research is conducted in accordance with ethical standards. In the international arena, either IRBs or Research Ethics Committees (RECs) have been created to perform similar functions. But, as Adashi [2] points out, the U.S. IRB system is viewed as overworked, inefficient, and underfunded. Current U.S. regulations are often criticized as overly bureaucratic and inattentive to a true risk-based review. It is also recognized that there can be extreme variability in practice among different U.S. IRBs. What is worrisome is that these flaws could be expected to be magnified in developing countries, which are more resource poor. Adashi [2] states, "Inevitably then, questions linger as to the ability of international IRBs to rigorously monitor clinical trials, safeguard study subjects, and ensure the integrity of the data collected." As an IRB Chair who has visited with IRBs in Asia, South America, and Russia, I have seen the difficulties that international IRBs have in complying with some IRB practices, especially administrative practices. Concepts such as the need for continuing review at no greater than annual intervals may pose burdens on a resource-poor system, leading to non-compliance with this requirement.

In order to understand ethical challenges in conducting human research in resource poor international settings, it might be helpful to first examine the ethical underpinnings of human subjects research in the United States.

### **ETHICAL PRINCIPLES IN THE UNITED STATES**

The complex environment of biomedical research and drug development in particular is highly dependent on the participation of humans in clinical trials. To promote this participation, it must be recognized that participation in research is expected to be voluntary, not forced. Over the many years of biomedical research, there have been many examples of researchers forcing participation or deceiving participants about the true nature of the research and the risks entailed therein. During World War II, Nazi physicians performed life-

threatening experiments on unwilling concentration camp detainees. Worldwide outrage over these atrocities led to development of the Nuremberg Code [9], which emphasizes that participation in research must be *voluntary* and should never cause deliberate harm. Beginning in the 1930s in the United States, Public Health Service physicians studied the natural history of syphilis over several decades in a cohort of African-American men, who subsequently were denied antibiotic use once it was shown penicillin could be an effective treatment for syphilis. This study became known as the Tuskegee Syphilis Study. Once exposed in 1972, national outrage over this reckless behavior by government-funded researchers led to passage of the National Research Act in 1974 [10], which required that institutions wishing to do federally funded research needed to set up an IRB. The IRB is charged with protecting the rights and welfare of human subjects of research and ensuring that research is conducted in accordance with accepted ethical standards.

U.S. IRBs are guided by the ethical guidelines for human subjects research as presented in the Belmont Report [11], which puts forth three ethical principles: respect for persons, beneficence, and justice. In the United States, based on a Western philosophy framework, respect for persons is articulated as respect for individual autonomy or respect for the individual's right to self-determination. This is based upon the notion that participation in research should be voluntary and is commonly translated into the concept of informed consent. One cannot "volunteer" to participate in research willingly without first being well-informed about what the research entails and then "consenting" or agreeing to participate. Consent of the individual is considered mandatory unless certain exceptions are met. Regarding beneficence, it is thought that we treat people ethically if we protect them from harm and make efforts to secure their well-being. This is ordinarily thought of as minimizing risk while maximizing benefit. Importantly, it must be recognized that research can entail exposure to risks and even to risks that are unknown. The ethical principle demands that

risks be minimized, but not eliminated. And thirdly, the principle of justice requires that there be fair distribution of both the burdens and the benefits of research. Justice demands that both exposure to the possible burdens of research, as well as access to the potential benefits of research, be fairly distributed among the population. Thus, exposure to burdens or risks without any corollary potential for benefit to the given population would almost always be considered unjust.

### **ETHICAL PRINCIPLES IN INTERNATIONAL SETTINGS**

There are also examples of ethical guidelines developed for international settings, among which the following two are best known and applicable to biomedical research. The World Medical Association has developed what is known as the Declaration of Helsinki [12] as a statement of ethical principles for conducting medical research with humans. The Declaration of Helsinki [12] asserts, "Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence." Similarly, the Council for International Organizations of Medical Sciences (CIOMS), which is representative of a substantial portion of the biomedical scientific community, has published the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects [13]. Prime components focus on ethical justification and scientific validity of human subjects research, as well as ethical review and informed consent.

### **ETHICAL CONCERNS IN INTERNATIONAL SETTINGS**

But questions remain about how well these concepts translate to the myriad international settings in which clinical research takes place. Is individual consent always pri-

mary? How do we avoid exploitation of human subjects in resource-poor countries? Is there an adequate oversight mechanism for human research? Is there fairness in exposure to risks and fairness in access to relevant trials?

#### *Individual Consent*

It must be recognized that concepts of individual autonomy may not always be considered primary in many cultures. In various cultures, there may be less dependence upon individual decision-making and more acceptance of input or decision-making by family members, spouses, or tribal leaders. This presents a tension in the provision of consent that is difficult to reconcile with Western approaches. Emanuel et al. [14] have suggested ways to reconcile cultural differences, including supplementing individual consent with community and family member consent procedures. As an IRB Chair, I have seen these supplemental processes work well, to respect different cultural practices while also respecting individual autonomy practices.

#### *Input into Setting the Research Agenda*

Another concept that interplays with the idea of community consent is the idea that in community-based participatory research, and often in international research, there is a need for participatory decision-making in development of the research agenda itself. Rather than relying solely on the consent of an individual to participate in a given trial, the concept is that the community should be consulted and have input into development of the research agenda and its implementation in the locale. This need is starkly emphasized by calling attention to the 10/90 gap as described recently by Garrafa et al. [15]:

"Since 1996 this discrepancy between prevalent health needs and research priorities have been labelled the 10/90 gap. This metaphor was introduced to depict the monstrous inequity in the world with respect to whose diseases are

favoured in ongoing or planned research programmes. In concrete terms this means that at least 90% of the economical resources spent annually on medical research are targeting the health needs of the richest 10% of the world's population, something that implies that the needs of 90% of the world's population have to be met from the remaining 10% of research funding."

Solomon Benatar has written extensively about this gap and how to address it. In 2007, he and Fleischer [6] asked, "*How do we avoid exploiting research subjects in low-income countries?*"

Others have recognized problems with relevance of the research to the local community as well. London and Zollman [16] note that developing countries often are deficient in provision of basic public health, leading to higher incidence of communicable and preventable disease. It is easy to predict that priorities for medical research in such settings would likely be quite different from priorities set in wealthier countries, which underscores the need for local input.

Benatar and Fleischer [6] advise that the community should be involved in the design and selection of appropriate trials for the given location. Through the formation of partnerships with key stakeholders, locally relevant standards of care can be determined and incorporated into the research design. Similarly, Clinton [17] emphasizes the need to meet all ethical and scientific standards in the developing country as an absolute requirement. A primary ethical standard would be to conduct research that is relevant to the local community.

In 2010, Benatar and Singer [18] brought forth an argument that underscored the need to make research locally relevant to health care needs of the community in which it is conducted. They stress that benefits must extend beyond the sponsor to the participants and their communities. They suggest that the most important value is [18]

"solidarity, which can be defined as attitudes and determination to work

for the common good across the globe in an era when interdependence is greater than ever and in which progress should be defined as enhancing capabilities and social justice rather than sustaining dependency."

### *Capacity Strengthening*

Ali et al. [19] discuss the work of the U.S. National Institutes of Health (NIH) in supporting ethics training in low and moderate income countries. This is in recognition of obligations that wealthier countries have to help lower resource countries. This capacity building effort incorporates the requirement for local IRB review [6]. Implicit in this requirement is the need for the local IRB to comply with U.S. regulations for the protection of human subjects if the project receives U.S. federal funding. In my work with international IRB/REC colleagues, understanding this requirement has sometimes been lacking and may lead to non-compliance with the regulatory requirements [20]. Capacity development likely will continue to advance the training of researchers, with a focus on cultivating a culture of recognition of the importance of research ethics and operationalizing research ethics [19]. Beyond capacity strengthening, international research projects should also provide local post-trial benefits to the participants' community, such as access to medical treatments studied in the project [21].

### *Ethics of Placebo-Controlled Trials in Resource Poor Settings*

Placebo-controlled trials in developing countries may raise especially thorny concerns [22]. There are concerns that wealthier countries are exporting risks associated with research to low and middle income countries, where the knowledge gained is of little importance to the population tested [16]. The merits of a placebo-controlled trial, taking into consideration local standard of care, must be weighed in terms of the value of the knowledge gained and its relevance to the population in which the trial is conducted [6]. The ethical principle of beneficence, with its obligation to



balance risks and benefits, requires that we reject trials that infringe upon widely accepted human rights. So again, these arguments take the focus off individual autonomy and well-being and point it toward population-based ethics. Persons in resource poor areas should not be made to bear the burdens or risks of research that will result in commercialization of products they will never see marketed in their country or that they could never afford.

### *Global Justice*

Some of the identified ethical concerns extend beyond the individuals, be they researcher or participant. Rather, the interests of whole populations and how they are impacted by corporate decision-making sets up the need for obligations being allocated to the appropriate bodies [6,23]. Only in recognition of these obligations of global justice may international clinical research be conducted ethically. Global inequities in health care challenge all of us involved in biomedical research to ensure that the health care interests of the local population are understood and addressed.

These problems are illustrated through examination of efforts to address the global HIV/AIDS crisis. Since HIV is endemic in areas of poor resource in many developing countries, international HIV/AIDS researchers have had to learn to work in a complex environment involving different cultures, languages, and laws [24]. All of these challenges are faced in the context of stigma associated with the disease, differing stances on politics and economics, influence of gender and sex roles in transmission, and decision-making about resource allocation. Each of these factors represents a challenge to the HIV/AIDS researcher trying to provide innovative approaches to the care of these people and requires research agenda-setting and ethical attentiveness in the local context. To be successful, researchers must integrate implementation of ethical standards with local applicability.

## **CONCLUSIONS AND OUTLOOK**

Investigators contemplating involvement in international research should consider the

words of Bosch and Titus [3]: “Crossing international borders to do research requires openness and flexibility, and a willingness to learn the culture and to cooperate against a background of differing institutional arrangements, educational backgrounds, research habits, funding patterns, and concerns about public policy.” These matters require commitment of time and resources in the learning process and cannot be ignored.

Hays [25] has issued a call to international researchers who author publications about their work. The call requires that the publication disclose the sponsor and all oversight bodies that approved the study; describe how the community was consulted; address how results will be disseminated to the community; and address the duration of benefits to the community. As part of the researchers’ commitment, development of IRB infrastructure and acknowledgement of the benefits to the researcher or institution should also be included.

Capacity building in low- and middle-income countries should focus on enhancing the training and education of researchers and sponsors and also focus on building capacity to conduct scientific and ethical review [26]. Beyond these efforts at capacity building, Hyder et al. [27] point out that the culture of the organization will be most important in determining whether ethical conduct on the part of researchers is supported or valued. This concept carries the idea of capacity building beyond researchers and ethics committees to emphasize the need for institutional officials and institutional support structures to promote the protection of human research participants. Such efforts will increase the sustainability of inroads that are made in individual projects and may help in the effort to mobilize worldwide resources in addressing critical health care needs internationally.

Medical research in international settings must be planned and conducted with attention to relevant ethical issues. Local community leaders must be involved in setting the research agenda, planning the implementation, ensuring the dissemination of results locally, and requiring benefit at the local level. IRBs or RECs must be available

locally to review and approve the research and provide ongoing oversight for the protection of human subjects. Institutional support for the ethical conduct of human subjects research is mandatory.

## REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [Internet]. [Accessed 2012 Oct 9]. Available from: <http://www.ich.org/>.
2. Adashi EY. International human subject research: taking stock in the wake of the Guatemala affair. *Contemp Clin Trials*. 2011;32(5):605-7.
3. Bosch X, Titus SL. Cultural challenges and international research integrity. *Lancet*. 2009;373(9664):610-12.
4. Koski G, Nightingale SL. Research involving human subjects in developing countries. *N Engl J Med*. 2001;345(2):136-8.
5. Glickman SW, McHutchison JG, Peterson ED, Cairns CB, Harrington RA, Califf RM, et al. Ethical and scientific implications of the globalization of clinical research. *N Engl J Med*. 2009;360(8):816-23.
6. Benatar SR, Fleischer TE. Ethical issues in research in low-income countries. *Int J Tuberc Lung Dis*. 2007;11(6):617-23.
7. Levine RJ. Ethical issues in international vaccine research and development. *Yale J Biol Med*. 2005;78(5):231-7.
8. Tangwa GB. Between universalism and relativism: a conceptual exploration of problems in formulating and applying international biomedical ethical guidelines. *J Med Ethics*. 2004;30(1):63-7.
9. Nuremberg Code. Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10. Volume 2. Washington, DC: U.S. Government Printing Office; 1949. pp. 181-2.
10. National Research Service Award Act of 1974 [Internet]. [Accessed 2013 May 17]. Available from: <http://history.nih.gov/research/downloads/PL93-348.pdf>.
11. The Belmont Report, Ethical Principles and Guidelines for the Protection of Human Subjects of Research. HHS.gov [Internet]. 1979. [Accessed 2013 Mar 6]. Available from: <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>.
12. Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects. World Medical Association [Internet]. [Accessed 2013 May 17]. Available from: <http://www.wma.net/en/30publications/10policies/b3/index.html>.
13. Council for International Organizations of Medical Sciences [Internet]. [Accessed 2013 May 17]. Available from: <http://www.cioms.ch/>.
14. Emanuel EJ, Wendler D, Killen J, Grady C. What makes clinical research in developing countries ethical? The benchmarks of ethical research. *J Infect Dis*. 2004;189(5):930-7.
15. Garrafa V, Solbakk JH, Vidal S, Lorenzo C. Between the needy and the greedy: the quest for a just and fair ethics of clinical research. *J Med Ethics*. 2010;36(8):500-4.
16. London AJ, Zollman KJ. Research at the Auction Block: Problems for the Fair Benefits Approach to International Research. *Hastings Cent Rep*. 2010;40(4):34-45.
17. Clinton M. Ethical conduct of research in developing countries. *Int J Evid Based Healthc*. 2010;8(2):43-4.
18. Benatar SR, Singer PA. Responsibilities in international research: a new look revisited. *J Med Ethics*. 2010;36(4):194-7.
19. Ali J, Hyder AA, Kass NE. Research ethics capacity development in Africa: exploring a model for individual success. *Dev World Bioeth*. 2012;12(2):55-62.
20. Alfano SL, Piedrahita LE, Uscinski KT, Palma GI. Strengthening Capacity for Human Research Protections: a Joint Initiative of Yale University, CIDEIM, and Univalle. *IRB*. 2012;34(5):16-20.
21. Pratt B, Zion D, Lwin KM, Cheah PY, Nosten F, Loff B. Closing the translation gap for justice requirements in international research. *J Med Ethics*. 2012;38(9):552-8.
22. Angell M. The ethics of clinical research in the third world. *N Engl J Med*. 1997;337(12):847-9.
23. Pratt B, Loff B. Justice in international clinical research. *Dev World Bioeth*. 2011;11(2):75-81.
24. Gahagan J, Sweeney E, Worthington C, Perry D, Satzinger F, Rogers E. Ethics issues for HIV/AIDS researchers in international settings - perspectives from the Canadian experience. *Int J Infect Dis*. 2008;12(6):569-72.
25. Hays JC. The ethics of international studies. *Public Health Nurs*. 2011;28(5):387-8.
26. Sidle JE, Were E, Wools-Kaloustian K, Chuani C, Salmon K, Tierney WM, et al. A needs assessment to build international research ethics capacity. *J Empir Res Hum Res Ethics*. 2006;1(2):23-38.
27. Hyder AA, Dawson L, Bachani AM, Lavery JV. Moving from research ethics review to research ethics systems in low-income and middle-income countries. *Lancet*. 2009;373(9666):862-5.