

# Ten Questions Institutional Review Boards Should Ask when Reviewing International Clinical Research Protocols

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As biomedical research becomes increasingly international in scope, institutional review boards in one country are often asked to review protocols that will be conducted in another country. Frequently, an IRB from a wealthy sponsor country is asked to review an international clinical protocol that will be conducted in one or more host developing countries. Unfortunately, many IRB members in wealthy countries are likely to be unfamiliar with the host country language, culture, social and ethical norms, level of health care, and other factors essential for a thorough ethical review of a clinical protocol.

Here, we draw on our experience with international HIV research in Haiti and HIV/AIDS issues in Africa to suggest questions that IRBs in sponsor country may want to ask when reviewing a clinical protocol that will be conducted in a developing country. We hope these questions will enable IRBs to conduct a more thorough review of international clinical research protocols and thereby better protect the rights of human volunteers from developing countries.

**Is there a viable ethics committee in the host country that will review the protocol and how can they be contacted?**

IRBs from a wealthy sponsor country should ensure that a viable local ethics committee in the proposed host country will review the protocol. Dual review in the sponsor country and the host country is mandated by several international guidelines for the ethical conduct of biomedical research.<sup>1,2</sup> Further, IRBs in sponsoring countries should rely on the local ethics committee for obtaining important information about the host country.

A viable local ethics committee should have broad constituency from people of the host country (as opposed to a committee of expatriates). The committee should have members with the technical capacity to understand the biomedical issues of the protocol, and all committee members should have training in the basics of international guidelines on the ethical conduct of ethics. A viable committee will have in place and follow clear operational guidelines, such as written procedures, routinely scheduled meetings, appropriate documentation practices, etc.<sup>3</sup> Finally, a viable ethics committee should have the autonomy and the power to modify or to stop a study when necessary.

A viable local IRB should be viewed as a critical resource for IRBs in sponsor countries. Unfortunately, IRBs from wealthy sponsor countries often work independently of local IRBs when reviewing a protocol. Worse, at times, the sponsor country IRB and the local IRB may disagree and demand opposing revisions in a study protocol. For example, a spon-

sor country IRB, fearing undue influence on potential research volunteers' freedom to provide consent to participate in a clinical study, may discourage providing any financial reimbursement or free medical care. But the local IRB, acutely aware of the poverty in the host country and wanting to protect the well-being of potential volunteers, may encourage generous financial reimbursements and free medical care. Better communication between the sponsor country IRB and the local IRB could help resolve such disagreements. Further, the sponsor country IRB and the local IRB may possess complementary expertise and may be able to carry out a better review working together than either could working alone. A sponsor country IRB may bring greater experience reviewing biomedical research protocols, while a local IRB most certainly has a greater understanding of the social context in which the research will be carried out.

**What is the principal investigator's relationship with the community from which research volunteers will be recruited?**

An IRB reviewing a protocol to be conducted in a developing country should know if the principal investigator is interested in a particular disease and is recruiting patients on a global scale or if the investigator is principally interested in the health issues of the host country population. It is not uncommon for wealthy country researchers interested in a specific disease to identify

geographic areas with a high disease burden and then go to those areas to find clinical sites to recruit patients for their research.<sup>4</sup> This “disease red lining” is in contrast to the practice of a researcher who has an established relationship with the people of a developing country and together identifies health problems requiring research. One situation is not a priori more ethical than the other.

However, when researchers have little investment in the host country, the situation may be ripe for ethical lapses because researchers have a limited relationship with the host country, limited understanding of the culture, and little personal investment in the health of the study population. If the research team’s connection to the host country is weak, the sponsor country IRB should ask why the clinical site was chosen and if the investigators have proof that the study site will be capable of conducting scientifically sound research. Further, the sponsor country IRB should demand proof of community support and participation in the research and ensure that the local IRB is strong.

### **Does the research protocol address the ethical challenges of conducting research in a developing country?**

Many complex ethical issues arise when clinical research is carried out in developing countries. Importantly, the socioeconomic conditions in developing countries create ethical challenges that are often not faced when research is conducted in a wealthy country—for example, obtaining informed consent from an illiterate population who speak a different language and may have a different understanding of disease causality from the investigator, or defining an appropriate level of medical care for research volunteers in a country where the standard of care may be nothing, or trying to implement the results of research in a country with little or no health care infrastructure.

Unfortunately, we have seen

many protocols for research to be conducted in developing countries that fail to address any of these ethical challenges. One senses that such protocols were written within the confines of a U.S. academic center with no input from people in the host country and no appreciation that life in Africa or Haiti is a bit different from life in Ohio.

U.S. regulation requires that investigators who receive government funds to conduct research involving human subjects document training in ethics. However, this training is relatively basic and focuses narrowly on American regulation. This minimum standard is not adequate preparation for dealing with the ethical dilemmas frequently encountered during the conduct of clinical research in developing countries.

Fortunately, several excellent resources have recently been published that address the unique challenges of conducting research in developing countries, including the U.S. National Bioethics Advisory Commission’s (NBAC) report on clinical research in developing countries<sup>1</sup> and the (U.K.) Nuffield Council report on biomedical research in developing countries.<sup>5,6</sup> These documents should be required reading for all investigators involved in research in developing countries. If research investigators fail to address the ethical challenges of conducting research in the developing world in their protocol, then the sponsor country IRB should request that the investigators read the NBAC or Nuffield Council report and revise the protocol to address the major issues contained therein.

### **Is the purpose of the research responding to the health needs of the host country?**

Our fear is that research sponsored by a wealthy country and conducted in a poor country often responds to the health needs of the wealthy country but not the needs of the poor country.

Sponsor country IRBs should

inquire if there are any local data to support that the disease under study is an important health problem in the host country. The IRB could inquire whether the host country government or the World Health Organization (WHO) has identified the disease under study as a priority health problem. Further, the sponsor country IRB should inquire whether the research protocol was discussed with members of the community from which volunteers will be enrolled to determine whether the community believes the disease under study is an important problem.

In addition, sponsor country IRBs should inquire whether the research protocol is intended to find a solution for the health problem that will be viable in the socioeconomic context of the developing country. A clinical study of an expensive new hypertension medication in a country where the majority of people do not have access to first line antihypertensive medications is not likely to be responsive to the health needs of the country. To the contrary, researchers may be exploiting a poor country in order to study a new medication in drug-naive patients with the ultimate goal of marketing the drug in wealthy countries. Thus when judging whether a study protocol is “responsive,” sponsor country IRBs must be knowledgeable about local socioeconomic conditions and sensitive to issues related to access to medical care.

### **When negotiating informed consent, how will the investigators assure that the research volunteers understand the consent procedure?**

All too often, a signature on the consent form is assumed to document that a volunteer has understood the contents of the consent form and has freely consented to participate. This assumption does not hold in developed countries and is even more problematic in developing countries, where many participants cannot read or write, are

unfamiliar with the concept of a consent form, and may be likely to sign any paper that a person wearing a white coat places in front of them.<sup>7</sup> The converse is also true, that in some communities, members are reluctant to put their signatures on documents because of suspicion based on historical injustices that may have occurred to them as a result of such signatures, for example, the signing away of land rights.<sup>8</sup>

Many sponsor country IRBs focus all their energy on the precise wording of the consent form without ever considering the awesome task of how the researcher will communicate information to prospective volunteers who may speak a different language and come from a different culture than the researcher, may have a radically different understanding of disease causality, and may have no previous concept of medical research. A sponsor country IRB should inquire not only about the specific content of the consent form but also about just how that content will be communicated to prospective participants.

Importantly, the IRB should ask whether, and how, investigators will document that volunteers do understand the information they are given in the consent process. For example, a sponsor IRB could request that volunteers take a quiz to assess their understanding prior to actual enrollment.

### **What exactly is the local standard of medical care?**

Many international research protocols state that volunteers with health problems will be referred to a local health facility for local standard of health care. There has been much debate on the appropriate level of health care for volunteers participating in international medical research, much of it focused on the level of care that should be provided to people in control groups.<sup>9,10</sup> Less attention has been paid to the availability of a minimum package of basic primary health care services to all volunteers.<sup>11</sup>

Sponsor country IRBs should not accept the stock phrase that volunteers will receive “local standard of care,” but should ask for much more detail. The sponsor country IRB should consider contacting the host country IRB to gather more information on the availability of medical care in the host country and to seek their advice. What is the local facility? How far away is it? Do trained professionals staff it? Are essential medications available? Can the volunteers afford it? What kinds of services are offered? Have any study funds been designated to provide health care to research volunteers? What medical care will be provided to individual study participants? How will this level of care be assured, especially care for the disease under study?

Unfortunately, there is no easy answer to the overarching question of what care should be provided in the context of international clinical trials, and we do not pretend to have a simple litmus test. Until a consensus emerges, we strongly believe that IRBs and researchers need to struggle with the issue of the appropriate level of care protocol by protocol. We are hopeful that from this struggle and dialogue a consensus will emerge.

We understand that many sponsor country IRBs and research sponsors are fearful that providing free medical care may be seen as “coercing” poor people to participate in research. However, this fear of coercion must be balanced by an appreciation that health care is a basic human right.<sup>12</sup> This fear should therefore be balanced by the reality that the research is being carried out on people who have other health conditions that require attention. It is not a good moral argument to justify the use of their bodies for research, while at the same time, turn a blind eye to their other medical conditions some of which might be attended to easily by research sponsors. Again, this stand might pose practical problems, for example, for how long should such treat-

ment last and should it be for every medical condition the subject has? However, we believe that to completely ignore the health of research subjects, particularly with regard to conditions traditionally linked to poverty like malnutrition, on the basis of non-coercion, is inappropriate from a justice point of view.

### **Are the risks to volunteers acceptable in the social context of the host country?**

Certain risks are the same in a sponsor country or in a developing country—an acute allergic reaction is an acute allergic reaction. However, other risks may vary according to the social context.<sup>13</sup> A risk that the sponsor country IRB views as minimal may be considered very significant in Haiti, and vice versa, what the sponsor country IRB considers a major risk may be viewed as insignificant by people in Haiti.

For example, in Haiti, people who participate in clinical studies are hesitant to have their blood sent to a laboratory outside the country, as protocols quite frequently require. They fear that their blood is being sold for use in a foreign place. Perhaps this fear stems from Haitian religious beliefs about blood or from Haiti’s history of slavery when foreigners traded African people as a commodity. Whatever its origin, it is a very real fear that must be addressed and is an important risk of some studies. In general, U.S. and European IRBs have not picked up on this issue while local Haitian ethics reviews have raised it. Sponsor country IRBs should rely upon the local IRBs to identify risks unique to the developing country and to quantify their degree within the social context of the host country.

### **Does anyone else in the host country know about the research?**

Many developing countries simply have no regulatory infrastructure to monitor biomedical

research. Developing country governments, strapped to provide even basic medical services to their populations, often do not have the manpower or the resources to oversee research and as a result investigators often work in a regulatory vacuum. The absence of regulations or enforcement mechanisms does not change the researcher's ethical obligations to protect participants, however.

Investigators proposing to carry out research internationally should first do their homework and find out if the host country has laws and regulations governing research on the books. Some developing countries have regulations but lack the resources to enforce them. In such cases, foreign researchers should make the effort to learn the rules and comply with them. In countries where there are no rules on the books, the investigators should inform the local government or health authorities about the conduct of clinical research and provide periodic updates.

If there is no appropriate government authority, then a member of a local community group, medical association, or international health organization could be asked to monitor the conduct of clinical research. At a minimum, some authority outside of the researcher's own institution should be informed about the conduct of the research. The extent of monitoring could vary with the ethical complexity of a study. For more complex studies, an independent monitor could verify that IRB approval has been obtained, that consent is documented, etc. Further, an independent monitor could serve as an ombudsman to whom volunteers could turn if they have problems. The existence of a local monitor, independent of the investigator's own institution, could provide some assurance to the sponsor country IRB that someone is in the field keeping an eye on researchers.

## research study?

The IRB should ask if the researchers plan to share the results of their research with the local Ministry of Health, with local health service providers, or with local population. There are unfortunately many examples where researchers conduct a study in a developing country, return to the sponsor country to present their data, and then publish the data in journals that are inaccessible in the host country. At a minimum, if researchers collect data in a country they have a responsibility to share the results with the people in the country. It has been argued that if the results of a research study are not shared in a timely fashion with research subjects as well as the local population, then the researchers "might be justly accused of exploiting poor, undereducated subjects for the benefit of more affluent populations of the sponsoring countries."<sup>14</sup> Researchers should state how they plan to disseminate the results of their research within the host country before the data is collected.

Further, we believe that researchers should provide a concrete plan of action that will result from their research. If researchers are testing a new vaccine and it proves effective, will it be made available in the host country? If researchers are doing a prevalence study for hepatitis in blood donors and high rates are found, will public health action be taken to screen future donors?

In countries with poor public health infrastructures, and in countries unaccustomed to acting in response to locally collected health data, there is a risk that research data will have no impact on the health of the local people. From our experience in Haiti, collecting and publishing data is the easy part; the hard part is using the data to effect change in health policy and medical practice. It is helpful to think through a plan of action prior to collecting data rather than trying to figure out what to do next only

when you have data in hand.

## Is capacity building an essential element of the research protocol?

Ideally, health research is an integral part of health improvement. And ideally, people should have control over their own health. Therefore, people in developing countries should have the capacity to conduct research themselves to help improve their own health; they should not have to depend on foreign researchers to conduct health research for them. Unfortunately, there are few well-trained medical researchers from developing countries, and for those few there is a paucity of funding and material resources available to enable them to address issues of importance in their own countries.

If sponsor country researchers are serious about using medical research to improve the health of people in poor countries, then they should be interested in training and supporting researcher colleagues in developing countries. An inherent goal of medical research conducted in developing countries should be to increase the capacity and the independence of local health researchers. When reviewing a protocol, IRBs should note whether local researchers are included as investigators, whether they are given positions of authority, whether they have been included as authors in past publications, and whether technical expertise is introduced into the host country as part of the study. Sponsor country IRBs should ask, Will the foreign researchers leave behind local capacity to conduct independent health research, or a broken-down four-wheel drive vehicle and an empty lab building?

## Meeting the Challenges of International Research

Our goal in posing these 10 questions is to encourage IRBs in countries that sponsor biomedical research to learn more about the socioeconomic context within which

**What public health action will result from the findings of the**

research will be conducted. Unfortunately, developing countries are often plagued by social injustice and economic hardship; we believe that understanding this difficult context is critical for a thorough ethical review of a research protocol. Otherwise, IRBs risk making false assumptions—that volunteers can read and write, that “local standard of care” includes medical care, that the host country government has a regulatory system to monitor research, that the local community supports or even knows about the research, or that a viable host country IRB exists. We recognize that there are no easy answers to the ethical problems that arise when medical research is carried out in developing countries. But if we do not struggle with these issues, if we do not ask the difficult questions, we will never find the answers.

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