1 International research contested: controversies and debates

At an international meeting devoted to ethics in research, one participant from a developing country remarked: "It is important to specify that research should be conducted in developing countries only when it cannot reasonably be carried out in developed countries. Research should not be carried out in developing countries solely for economic reasons."

A participant from the United States replied: "It's proving useful to conduct studies on allergy and depression in developing countries. The people who do the studies do them well. Do people want to discourage that sort of thing? It's going on now, with consent of the countries."[1]

These comments illustrate two responses to a question that has given rise to international debate and controversy: Should medical research be conducted in Third World countries when it could equally well be carried out in the United States or Western Europe? According to one view, the answer is a probable "no":

> We fear . . . a major increase in studies that could easily be done in an industrialized country, but where the participants are denied optimal medical care and the products are not made available afterward. The benefits to the pharmaceutical industry are obvious: potentially lower costs, less red tape, larger pools of "naïve" subjects and lower ethical requirements.[2]

This position considers populations in developing countries to be vulnerable, and therefore it is inappropriate to involve them in research when the same studies could be done in an industrialized country.

An opposing view maintains that requiring research to be conducted in industrialized countries before initiating a similar study in a developing country is an unacceptable form of paternalism. It treats developing country decision-makers, researchers, and research subjects like children, incapable of knowing their own interests and protecting those interests in the way the rights and welfare of research subjects are protected in industrialized countries.

A great deal of research is conducted in both industrialized and developing countries when the same health problem exists in both places.

Spokespersons from developing countries are among those who encourage this trend, arguing that their countries are capable of protecting their own citizens from harm or exploitation at the hands of local and foreign researchers alike. If the population in these countries has to wait for drug trials to be completed in industrialized countries before the medications can be tested and approved by their own regulatory authorities, the delay can result in untreated diseases and loss of lives.

Yet another question looms large: are developing countries and their citizens able to afford the cost of drugs that are the products of successful research once they are approved for sale? Will the treatments, in fact, become available when research is concluded? According to one view, all that is required is to conduct research according to the highest ethical standards. Researchers and sponsors have no further obligations. Once the research is over, it is a matter for national or local health systems to provide any resulting health benefits for the population. An opposing view argues that when wealthy countries or pharmaceutical companies sponsor research in resource-poor countries, they should not simply pack up and leave, with any resulting health benefits going to the sponsoring country and economic benefits to industry. This debate poses the question of what justice requires in the conduct of multinational research, the topic addressed in chapter 3.

An even more intense debate has arisen over research that could not – for ethical reasons – be conducted in an industrialized country, but is carried out in a developing country. In considering this possibility, the US National Bioethics Advisory Commission acknowledged the ethical dilemma but did not recommend prohibition of such research. The Commission's report on international research says that when the US or another industrialized country seeks to conduct research in another country, when that same research could not be conducted ethically in the sponsoring country, "the ethical concerns are more profound, and the research accordingly requires a more rigorous justification."[3]

Can there be a good justification for conducting research in a developing country when that same research could not ethically be conducted in the United States or Europe? One answer is a clear "no":

> [O]ur ethical standards should not depend on where the research is performed . . . [T]he nature of investigators' responsibility for the welfare of their subjects should not be influenced by the political and economic conditions of the region . . . [A]ny other position could lead to the exploitation of people in developing countries, in order to conduct research that could not be performed in the sponsoring countries.[4]

The possibility that vulnerable people might be exploited is a cause for concern in developing countries that lack sufficient protections for human subjects of research. Yet the concept of exploitation remains fuzzy, and disagreements have arisen with regard to specific instances in which exploitation has been alleged. Chapter 4 examines the concept of exploitation, its different applications, and mechanisms to guard against it. One supposition underlying concerns about exploitation is that research subjects are exposed to risks, possibly unacceptable risks. This ethical worry focuses on the potential harms research subjects may experience.

However, a researcher from the Uganda Cancer Institute expressed an equally strong view defending research in his country that could not have been conducted in the United States or Western Europe:

> Ugandan studies are responsive to the health needs and the priorities of the nation . . . [T]he appropriate authorities, including the national ethics review committee, have satisfied themselves that the research meets their own ethical requirements. With these requirements met, if Ugandans cannot carry out research on their people for the good of their nation, applying ethical standards in their local circumstances, then who will?[5]

This scenario puts a different twist on the matter. In the absence of research conducted in developing countries, the inhabitants are denied the potential benefits that may result. In many such places, the majority of people lack access to treatments available in industrialized countries or, for that matter, any treatments at all. If research is not conducted in developing countries, the public health benefits that could result may never be available to the population.

Still, the Ugandan researcher's comments pose another thorny question about the protection of human subjects of research in developing countries. Are the mechanisms for protecting the rights and welfare of human subjects adequate in those countries? According to one side in the debate, the ethical standards employed in the United States and Western European countries, and stipulated in international guidelines, should prevail wherever research is conducted, and review by an ethics committee should be required in both the sponsoring and the host countries. This is the position of the Public Citizen Health Research Group, as expressed in a letter criticizing a draft provision of the report of the US National Bioethics Advisory Commission:

> We are dismayed and deeply disappointed that the National Bioethics Advisory Commission (NBAC) has seen fit to radically alter its draft report on the ethics of research in developing countries . . . to no longer require review by a US Institutional Review Board (IRB) of US government-funded research in

developing countries. This ill-considered proposal would effectively remove the requirement for American ethical review of some American research and frequently leave participant protection solely to often inexperienced and unregulated foreign IRBs.[6]

Exactly the opposite position has been expressed by the Pharmaceutical Research and Manufacturers of America (PhRMA), the trade association for the US pharmaceutical manufacturers:

We understand that there is a strong movement to ensure that consistent ethical standards are applied to research globally. However, requiring ethics committee review in the sponsor's country as well as local ethics committee review would impose the standards of the sponsor's country on the host country. Moreover, we are not confident that ethics committees in sponsoring countries will have the resources to be involved routinely in such activity, given the demands already placed on such committees for review of protocols to be conducted in their own country.[7]

These opposing views call for an exploration of what ethical standards are in use or have been proposed in recent efforts to revise international guidelines, and whether it is a form of "ethical imperialism" for an industrialized country to impose its own standards on a developing country where it is sponsoring or conducting research. As discussed in chapter 2, a great deal of confusion surrounds the meaning of "ethical standards" in the review and conduct of research. One common shortcoming is a failure to distinguish between *ethical standards* and *procedural mechanisms*.

If it can be shown that the procedural mechanisms for protecting the rights and welfare of human subjects of research in developing countries are equivalent to the protections in place in the US and other industrialized countries, then it would surely be paternalistic to insist on ethical review of proposed research by a committee sitting in the US. On the other hand, someone from a developing country might argue that people there would balk at the requirement for obtaining informed consent in research because patients trust doctors to do what is in their best interest, and a local research ethics committee could accept that argument at face value. However, to abandon the requirement to obtain voluntary, informed consent from each prospective subject of research would amount to a significant departure from an internationally accepted ethical *standard* in the conduct of research. The question of what constitutes adequate safeguards for the protection of research subjects in developing countries is explored in chapter 5.

It is not uncommon to find references to ethical principles governing research as "American," "North American," or "Western," implying a

contrast with "Asian," "African," or "Eastern" ethics. Such references misconceive the nature and scope of ethical principles. The author of an article about research in Africa on a preventive vaccine for AIDS, published in the *New Yorker*, makes this mistake when he asks: "Will scientific objectives drive the search for an AIDS vaccine, or will a series of ethical imperatives imposed by the West take precedence?"[8] This question actually embodies at least three mistakes; the same errors appear in a similar question under the article's title: "Has the race to save Africa from AIDS put Western science at odds with Western ethics?"[9]

The first mistake is in characterizing ethical imperatives for research as "imposed by the West." Three prominent documents containing guidelines for ethics in research were developed by international organizations and intended to apply to research that is multinational, as well as intranational. These are the Declaration of Helsinki, issued by the World Medical Association;[10] international ethical guidelines issued by the Council for International Organizations of Medical Sciences (CIOMS), a nongovernmental organization that works in collaboration with the World Health Organization (WHO);[11] and a guidance document for research on preventive HIV/AIDS vaccines, issued by the Joint United Nations Programme on HIV/AIDS (UNAIDS).[12]

The second error by the author of the *New Yorker* article is the presupposition that everyone in the "West" agrees on ethical imperatives. Researchers, ethicists, and health advocates from both industrialized and developing countries stand on both sides of debates that have occurred regarding key provisions in these international guidelines, especially the question of what is owed to research subjects during and after a trial. What the author of this misleading article identifies as "Western ethics" is the view that there exists an ethical obligation to provide antiretroviral treatment to research subjects who become infected while participating in a preventive HIV/AIDS vaccine trial in Africa. This is a question that assumes great importance as preventive HIV vaccine trials are going forward.

The vigorous and prolonged debate over what level of care should be provided to research subjects during a trial has, for the most part, occurred in a quite different context from that of HIV/AIDS preventive vaccine trials (see chapter 2). Contrary to the *New Yorker* author's statement, the strongest defenders of a "double standard" in research have been spokespersons from the West: officials at the US National Institutes of Health (NIH) and the Food and Drug Administration (FDA), and some of their counterparts from the UK. They have argued that it is ethically acceptable to provide a lower level of care and treatment to research subjects in less developed countries than research subjects receive in

the US and in Europe (their views are discussed in detail in chapters 2 and 4).

The third error is setting scientific objectives in opposition to ethics in research. Guidelines for research that rest on universal ethical principles do not set science and ethics in opposition to one another. On the contrary, these documents proclaim the importance and necessity of conducting scientific research in striving for the goal of improving public health. The purpose of ethical guidelines is not to halt or slow scientific progress, but rather to ensure that the fruits of research are obtained with full attention to the rights and welfare of human beings.

In chapter 8 we return to the debate over whether researchers and sponsors of preventive HIV vaccine trials have an obligation to provide antiretroviral treatment to participants who become HIV-infected during the trial. We examine the merits of arguments on both sides of that debate, without the distracting assumptions that there exists a "Western" ethics, and that ethics and science are somehow incompatible elements in research.

Why do clinical research in developing countries?

A matter of growing concern is the increasing the number of studies that drug companies conduct in developing countries because the research can be done there more quickly and with less oversight, thereby enabling the companies to gain approval for marketing and realize a profit as soon as possible. Especially in countries that lack adequate mechanisms for the protection of human subjects, the dramatic rise in the testing of experimental drugs has become a matter of deep ethical concern. When the US National Bioethics Advisory Commission was holding meetings of its international project, one commissioner asked a fundamental question: "When is it ethically acceptable to conduct a trial in another country?" Another member responded that if all the ethical requirements are satisfied, the fact that it is cheaper to conduct the trial in another country is irrelevant.[13] Other commissioners disagreed.

When the Commission sought testimony from industry spokespersons at public hearings, that effort was thwarted by the refusal of industry to cooperate. However, a study commissioned by NBAC did succeed in getting a candid response from one pharmaceutical researcher regarding the reasons why industry conducts studies in developing countries:

> The vast majority of the trials I have done in the third world possibly are dose response trials. Developing the profile of the knowledge on the drug to get profit and benefit elsewhere. That's extremely clear . . . I'm sure the simple fact that the

pharmaceutical industry is a profitable business with all the drugs that we use just tells me that. It's not a charitable business. It's a Wall Street hardcore business. And doing clinical trials in the third world sometimes may be motivated by a variety of reasons. In general, the vast majority is access to the patient in large numbers and a faster rate. And sometimes the third argument, nevertheless, is also at a cheaper price.[14]

The pharmaceutical industry obtains unquestionable gains – scientific as well as financial – from testing new products in developing countries. One scientific reason for testing experimental medications on research subjects in developing countries is that they have been exposed to fewer other drugs than have patients in industrialized countries. As one industry spokesman is quoted as saying: "You want patients with no other disease states and no other treatments. Then you can say relatively clearly that whatever happens to those patients is from the drug."[15] Drug companies and researchers refer to such individuals as "naïve subjects," meaning that they have not been exposed to existing treatments for their condition and, therefore, are likely to yield more reliable results. A darker meaning of "naïve" may also be pertinent – a reference to people who are not well-educated, who are unacquainted with the precepts of modern science, or who submit themselves without questions to medical authority.

The financial advantages are several. It is unquestionably cheaper to carry out the research in countries that have lower costs for all of the ancillary goods and services necessary to set up and support the research, including labor costs for technical and scientific personnel in resource-poor countries. If the research can also be completed more rapidly, that is also a financial advantage because industrial sponsors can bring successful products to market more quickly and ensure an earlier profit. In the not-too-distant past, a factor that enabled research to be conducted more rapidly in developing countries was the virtual absence of prior ethical review by research ethics committees, a mechanism that has been required for decades in industrialized countries. Avoidance of the often time-consuming requirement for local or national ethical review is fast disappearing as an option, as an increasing number of developing countries have established such requirements and US agencies that oversee research also mandate such protections.

The US Department of Health and Human Services reported a significant increase in the number of foreign countries where US-supported clinical trials are carried out. In 1990, research involving human subjects was conducted in twenty-nine foreign countries; by 1999 that figure jumped to seventy-nine. The largest growth in these studies occurred in Russia, Eastern Europe, and Latin America.[16] By the middle of 2002, members of the US Congress had become concerned about reports of

unethical overseas research and a representative from California introduced a bill entitled "To promote safe and ethical clinical trials of drugs and other test articles on people overseas." Among the findings in the bill were that "Some researchers exploit the fragile regulatory systems, high illiteracy rates, and public health failures of developing countries to test their experimental drugs and devices on misinformed and unwilling human participants"; and that "existing law permits manufacturers to profit from the misery and pain of uninformed, misinformed, and unwilling patients in developing countries."[17] On the day the bill was introduced, it was referred to the House Committee on International Relations, where it has remained ever since.[18]

When asked whether India is increasingly becoming a favored destination for human trials, a distinguished Indian physician–researcher, who established one of the first research ethics committees in that country, made these observations.

> The reasons for the popularity of the developing world are the following: (a) Large population (b) Low cost (c) Legislative vacuum or infirmities (d) Ignorance about the legal and ethical issues of human trials among the public and even health care professionals and (e) Craze among the developing countries to link up with Western institutions and at any cost.[19]

The Indian researcher added the important observation that adequate readiness to conduct clinical trials should be assessed on an institution-by-institution basis, and not for a developing country in general.

Still another factor that provides an advantage to the pharmaceutical industry is the much greater opportunity in many developing countries to conduct clinical research testing an experimental product against a placebo, an inactive substance. Placebo-controlled studies can be completed with fewer research subjects and in a shorter period of time than clinical studies that compare an experimental drug to an existing medication. In addition, the US Food and Drug Administration prefers a placebo-controlled study whenever that design is ethically defensible[20] (see chapter 2 for an extensive discussion of this issue). To industry's advantage, the ability to compare a new drug with placebo shortens the time of the study and makes the data more readily acceptable to the FDA, both of which lead to quicker profits for experimental products that prove to be efficacious.[21]

Of course, the single best reason to conduct clinical research in developing countries is that the diseases for which products are being tested are prevalent in those countries and a public-health need exists to develop effective prevention or treatment. But the investment in research on tropical diseases has been paltry compared to the amount of money

and number of studies devoted to research on diseases prevalent in the United States, Europe, and Japan – the leading markets for pharmaceuticals. According to one estimate: "Just 0.3 percent of the drug industry's much-touted R&D [research and development] resulted in the handful of drugs approved for tropical diseases between 1975 and 1997, despite tens of thousands of industry-sponsored clinical trials conducted around the world every year."[22]

A leading example of this imbalance is the case of malaria. In 1993, the United Kingdom spent over $200 million on cancer research, whereas the total amount spent on malaria research throughout the world was only $84 million.[23] Yet in 2000, more than 1 million people died of malaria, most of them children in Africa. In contrast, only about 1,200 cases of malaria are diagnosed in the United States each year, most of them occurring in immigrants or travelers who have returned from areas where malaria is prevalent such as Africa, India, and Central America. There appears to be more basic research, such as studies of the mechanisms of action of drugs and disease transmission, and less research on ways of providing treatment against malaria to people in developing countries.[24] It is worth pondering what the expenditures on research would be if the toll malaria were to take in the United States even remotely approached the figures in developing countries.

Which countries are "developing"?

At a workshop on research ethics in which I participated in Buenos Aires in 2002, the need arose to distinguish between different countries typically referred to as "developing." I commented that Argentina is not in the same category as Rwanda: to which one participant, referring to the severe and worsening financial crisis the country was undergoing, replied: "We're getting there."

The terms "developed," "developing," and "underdeveloped" have typically been used to refer primarily, if not exclusively, to the comparative economic level of countries. In recent years, the requirement to use politically correct terminology led to a rejection of "underdeveloped" in favor of "developing." As late as 1993, however, the CIOMS international ethical guidelines included a guideline entitled "Research involving subjects in underdeveloped communities."[25] The revised version of the CIOMS guidelines, issued in 2002, abandons the term "underdeveloped," and the relevant guideline is entitled "Research in populations and communities with limited resources."[26] Other international documents now refer to "least developed countries" with the abbreviation LDCs.[27] An analogous move has resulted in a more frequent use of "industrialized"

to replace "developed" when referring to wealthier countries. Another term used to refer to countries such as Brazil and Thailand is "newly industrialized," reflecting their status as somewhere between the richest countries in North America and Europe, and the poorest in Africa and Southeast Asia.

Nevertheless, a problem remains whenever a label is applied to countries, lumping them together as "industrialized' or "developing." For one thing, not all non-industrialized countries are moving in that direction at the same rate. Some may never become industrialized like European countries, the United States and Canada. Some are likely to remain poor indefinitely. Some countries characterized as "developing" have extremely low literacy rates, whereas others – such as Argentina, Costa Rica, and Chile – have a population whose literacy rate is as high as that of leading industrialized countries. In addition, it is not clear exactly how to characterize the countries that emerged from domination by the former Soviet Union at the end of the Cold War. Scientific and technological expertise has long been in the forefront in some of those countries, but awareness and implementation of ethical rules for the conduct of research has been rare, if present at all.

Is it a mistake to lump together as "developing" all countries except those in Western Europe, North America, Japan, Australia, and New Zealand? The answer is both "yes" and "no." It depends on the specific features of a country that bear on the research enterprise. It is appropriate to lump together countries that are resource-poor, since neither the government nor the majority of citizens can afford medical treatments that become largely available to residents of wealthier countries once research is concluded. It is appropriate to lump together countries that have few trained scientists and little experience of conducting biomedical research. And it is appropriate to lump together countries that lack ethical guidelines for research and have little or no capacity for conducting ethical review of research conducted there by industry or by scientists from industrialized countries.

Yet there is surely a continuum along which countries typically called "developing" fall with regard to the above characteristics. Most of the countries in sub-Saharan Africa are desperately poor, have little or no manufacturing capability, and have few highly trained and experienced biomedical researchers. South Africa is the key exception, with Uganda, Kenya, and Nigeria ranking somewhat above most other countries in these respects. A look at South America reveals that Brazil and Argentina boast many highly trained and experienced biomedical researchers. These countries have had an industrial infrastructure for many years. Yet Brazil is the country with the widest gap between the richest and poorest members