

multinational research

by Teck-Chuan Voo, Jacqueline Chin, and Alastair V. Campbell

Framing the Issue

In the 1990s, the term “the 10/90 gap” was used to refer to the gross mismatch between the world’s health needs and investments in health research to meet them. Only about 10% of global spending on health research was directed at health problems of developing countries, where roughly 90% of the world’s preventable mortality occurred. While the gap has narrowed somewhat, it remains significant because finding treatments for afflictions of the developed world, such as cancer, heart disease, hypertension, and diabetes, offers greater promise of financial and political returns than researching cures for diseases such as HIV, malaria, and tuberculosis that are more prevalent in poorer countries.

Nevertheless, the research community is paying more attention to the developing world. As health problems and disease threats cross borders on a global scale, private, public, and non-profit sectors are finding compelling reasons to fund and conduct research in diagnostics, medicine, vaccines, and other lifesaving interventions in needy countries. The Global Forum for Health Research, an independent international research foundation based in Switzerland, reported in 2006 that high income countries had finally set timetables for raising the percentage of their gross national income devoted to development assistance from an average of 0.47% to approximately 0.7%. Since its inception in 2000, the Bill and Melinda Gates Foundation has made very substantial contributions—more than \$10.5 billion—to tackling the most serious health problems in developing countries. Industry-sponsored research in the emerging regions of Eastern Europe, Latin America, and Asia has also increased dramatically.

But increased research in developing countries has ambiguous ethical implications. Potential study participants there still risk exploitation due to weak socioeconomic conditions, limited health care access, and little experience and understanding of research. Pharmaceutical companies that outsource research to developing countries reportedly do so for convenience: developing countries impose fewer financial and regulatory burdens and offer opportunities to recruit subjects rapidly. The new or improved drugs resulting from this research thus reach the market in developed countries relatively quickly—a good thing—but may not ever be sold in developing host countries, since these countries have little power to purchase them. As a result, research participants and communities in developing countries may end up bearing the lion’s share of the burdens of research

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HIGHLIGHTS

- As health problems and disease threats cross borders on a global scale, developed countries are increasingly funding and conducting research in developing regions.
- Global spending on research in developing countries still lags behind that of developed countries.
- Finding treatments for afflictions of the developed world offers greater promise of financial and political returns than researching cures for diseases most prevalent in poor countries, such as HIV, malaria, and tuberculosis.
- Research in developing countries poses many ethical challenges, including the need to prevent harm and exploitation of research participants abroad and to ensure that relevant stakeholders receive a fair share of benefits.
- Investment in capacity-building—in particular, the quality of ethics review—is a key effort in forging research partnerships with developing countries.

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without receiving a fair share of benefits.

As biomedical research and development increasingly crosses international borders, researchers and policymakers must consider several ethical issues:

- What are the ethical obligations of wealthy nations engaged in funding or conducting research in the developing world?
- What values should guide this research?
- How should ethics review be handled, and by whom, in light of intercountry differences in medical and research practices and law?
- Are changes needed in the process of obtaining informed consent in these countries given cultural variations in understanding the principle of respect for persons?
- What safeguards are needed to protect research participants in developing countries from possible harm and exploitation?

Challenges to Ethical Review

To safeguard research participants abroad from harm or exploitation, several international guidelines recommend that externally sponsored research be reviewed by ethics committees or institutional review boards (IRBs) from both sponsor and host countries. However, a developing country's capacity to conduct effective ethics review may be nascent or simply absent. Another problem is that the independence of a developing country's IRB may be compromised by the prospect of collaboration with—and resources from—powerful sponsors from wealthy nations. Recognizing the deficiencies of current oversight systems for clinical drug trials conducted outside the United States, the Office of Inspector General of the Department of Health and Human Services produced a report in 2001 entitled *The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects*, which recommended that the Food and Drug Administration investigate the performance of foreign IRBs and help them to develop capacity. It also proposed that the DHHS Office for Human Research Protections encourage a voluntary accreditation system for foreign IRBs.

A standard requirement of ethical review is to ensure the informed consent of research participants. However, applying the requirements of valid informed consent may be not only difficult but even inappropriate in countries where familial and

FINANCIAL SUPPORT

Major sources of funding for research in developing countries include:

- Bill & Melinda Gates Foundation
- Fogarty International Center (National Institutes of Health)
- Global Fund to Fight AIDS, Tuberculosis and Malaria
- International Finance Facility for Immunization
- President's Emergency Plan for AIDS Relief (White House)
- Joint United Nations Programme on HIV/AIDS (UNAIDS)
- Wellcome Trust
- World Health Organization

physician-patient relationships are more hierarchical than they are in the United States. Hastings fellow Ruth Macklin, a bioethicist at Albert Einstein College of Medicine in New York, says that while procedural mechanisms should be allowed to differ between and within countries, ethical standards that pertain to universal human rights and welfare should be consistent. Using less formalized consent forms and seeking permission from community leaders or spouses may be accepted as cultural adaptations. Ensuring informed consent of each prospective research participant should, however, remain the universal standard.

Standards of Care: Whose Standards?

Ethical guidelines for clinical research stipulate that patients participating in medical studies should have access to proven treatments for their condition, if available. Such guidelines were put into place after the Tuskegee syphilis studies, in which poor black men with syphilis in Alabama were studied for decades without being treated with antibiotics. But when research is conducted in developing countries, what should be the standard of care: that of the host country or that of the sponsoring country, which is likely to be higher?

Questions about standards of care were brought into sharp focus during the 1990s, when clinical trials were conducted in parts of Africa and Southeast Asia to see if a short course of the drug zidovudine (AZT) could prevent mother-to-child transmission of HIV. The trials, funded by the U.S. government, compared the short course of AZT to a placebo, but

INTERNATIONAL GUIDELINES FOR ETHICAL RESEARCH

- World Medical Association, *Declaration of Helsinki: Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects*
- Council for International Organisations of Medical Sciences in collaboration with the World Health Organization, *International Ethical Guidelines for Biomedical Research involving Human Subjects*
- European Group on Ethics in Science and New Technologies, *Ethical Aspects of Clinical Research in Developing Countries*
- Commission of the European Communities Joint United Nations Programme on HIV/AIDS (UNAIDS), *Ethical Considerations in Biomedical HIV Prevention Trials*
- National Bioethics Advisory Commission, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries*
- Nuffield Council on Bioethics, *The Ethics of Research Related to Healthcare in Developing Countries*

critics argued that the trials should have compared it to a long-course regimen, which was the standard of care in the United States. The critics held that the trials had violated the *Declaration of Helsinki*, an international guideline on research ethics, which stipulated at that time that in “every medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method.”

The AIDS study prompted people involved in international clinical research to ask deeper questions about the standards of care to which research participants were entitled. Should the provision of care for control groups adhere to a universal standard—the best current treatment worldwide, or at least an established and effective intervention? Should it be the local *de facto* standard—the actual health care practices of the host country? Or should it perhaps adhere to the local *de jure* standard, reflecting the judgments of medical experts in the host community on the most effective treatment and care practices for that community?

In the wake of this controversy, the *Declaration of Helsinki* was revised to permit departure from a default universal standard of care on compelling scientific grounds, even as it runs the risk of subordinating individual interests to the interests of society. In 2008, the FDA stopped requiring drug company trials conducted abroad to follow the Declaration of Helsinki. This decision suggests that

the globalization of clinical trials is unlikely to be based on a universal approach to the standard of care issue.

Another ethical concern is the extent to which treatment and care not directly related to the research design—and not usually available in the host community or country—should be provided for research participants. With preventive HIV vaccine research, some argue that sponsors and researchers have an obligation to provide care and treatment, including antiretroviral therapy, to those who become infected with HIV as a result of their behavior (and not the vaccine) during the course of the trial. Others say that the huge cost and logistical burden this would impose on sponsors and would threaten the future of vaccine trials.

A few years ago, the governments of Cambodia and Cameroon suspended ongoing placebo-controlled trials of the drug tenofovir to prevent HIV infection in sex workers when both governments could not reach an agreement with the sponsors and investigators on the level of treatment and care for those who develop HIV antibodies during the trials. The Commission of the European Communities Joint United Nations Programme on HIV/AIDS, or UNAIDS, has written a guidance document, *Ethical Considerations in Biomedical HIV Prevention Trials*, which states that sponsors have the responsibility to ensure access to internationally optimal care and treatment regimens, including antiretroviral therapy, to those who become infected during HIV prevention trials.

Posttrial Benefits

For a country to bear the risks of hosting clinical trials without reaping some benefits would be unethical. But what should the benefits be? The National Bioethics Advisory Commission and the Nuffield Council recommend that posttrial benefits, such as therapies developed as a result of the research, should be discussed and agreed upon by all relevant stakeholders from sponsor and host countries *before* research begins. This difficult negotiation involves the challenges of calculating the value of the research, deciding who will receive benefits, and addressing structural issues in the host country's health system that may limit access to those benefits. Opinions differ on whether posttrial benefits and implementation strategies should be guaranteed or merely defined.

What would constitute fair posttrial benefits is

another highly contentious issue. The Council for International Organizations of Medical Sciences (CIOMS)—a group established by the WHO and the United Nations Educational, Scientific, and Cultural Organization (UNESCO)—stated in its 1993 guidelines that “as a general rule, the sponsoring agency should agree in advance of the research that any product developed through such research will be made *reasonably available* to the inhabitants of the host community or country at the completion of successful testing.” It was sharply criticized by participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries because it focused on the *type* rather than the *level* of benefit, and applied only to successful phase III clinical trials. The group suggested a framework of benefits beyond those essential to conduct the research and share in financial rewards or intellectual property rights. In response, CIOMS revised its guidelines to include under its demand for “reasonable availability” any knowledge generated from the research, in addition to any product developed.

Empowering Host Countries

In dealings between nations, there is often no shared international standard of justice. As a counterbalance to potentially exploitative research, partnership models have emerged. True partnerships require that the research capacity of developed and developing countries be bridged. Writing in the *Bulletin of the World Health Organization*, Mary Lansang and Rudolfo Dennis define capacity building as “the ongoing process of empowering individuals, institutions, organizations and nations to define and prioritize problems systematically, develop and scientifically evaluate appropriate solutions, and share and apply the knowledge generated.” During the last 10 years, several groups (see Financial Support box) have funded capacity-building initiatives, including:

- educational programs in the biomedical sciences;
- training programs in research ethics and ethics review;
- contribution to research and healthcare infrastructure; and
- creation of networks and alliances to deal with specific healthcare issues.

In the future, capacity building is likely to expand from clinical trials to emerging areas of bio-

RESOURCES

Web sites

- www.scidev.net – The Science and Development Network. The Science and Innovation Technology Research Ethics page includes policy briefs, opinions and analyses, news and features, practical guides, definitions, and links.
- www.globalforumhealth.org – The Global Forum for Health Research. Provides evidence, tools, and discussion forums for decision-makers in research funding and policy to improve the health of poor populations.
- www.fda.gov/cber – The Food and Drug Administration’s Center for Biologics Evaluation and Research. Includes the rules and regulations governing “Foreign Clinical Studies Not Conducted under an Investigational New Drug Application,” April 28, 2008.

Recent news

- Jessica Winter, “Ends and Means: Researchers Developing AIDS Drugs Must Balance the Well-Being of the People They’re Testing,” *Boston Globe*, July 2, 2006.
- Scott Kirsner, “Be Careful Not to Call It Outsourcing,” *Boston Globe*, March 21, 2005.
- Saritha Rai, “Drug Companies Cut Costs with Foreign Clinical Trials,” *New York Times*, February 24, 2005.
- Linda Marsa, “A World of Difference: A Nonprofit Drug Company Works to Wipe Out Diseases That Plague Developing Nations But Are Ignored by Western Pharmaceutical Giants,” *Los Angeles Times*, October 25, 2004.
- “Guinea Pigs Abroad” (editorial), *Washington Post*, August 13, 2001.

Further reading

- Kathryn Berndtson et al., “Grand Challenges in Global Health: Ethical, Social, and Cultural Issues Based on Key Informant Perspectives,” *PLoS Medicine*, September 11, 2007. Article available at <http://medicine.plosjournals.org>.
- Ruth Macklin, *Double Standards in Medical Research in Developing Countries*, Cambridge University Press, 2004.
- Alex John London, “Justice and the Human Development Approach to International Research,” *Hastings Center Report*, January-February 2005.
- Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries, “Moral Standards for Research in Developing Countries: From ‘Reasonable Availability’ to ‘Fair Benefits,’” *Hastings Center Report*, May-June 2004.

medical science such as nontherapeutic genetics research and research involving human tissue and embryos. Success will depend on adequate funding, sustainability, strategic resource planning and allocation, and political will. 🌳