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OPINION

Enhancing research ethics capacity: implications for protection of research subjects, avoiding exploitation and achieving global health*

Henry Silverman, M D , M A

University of Maryland School of Medicine Baltimore Maryland U S A.

ABSTRACT

Research sponsored by developed countries is increasingly being conducted in developing countries While many celebrate the enhanced funding of foreign sponsors, others are concerned with the ethics of such research Ethical issues usually center on the protection of the rights and welfare of human subjects involved in research Another important issue involves avoiding exploitation by ensuring that developing countries receive a fair share of the benefits of foreign-sponsored research A fair exchange of benefits between resource-rich and resource-scarce counties can help achieve global health To ensure that research conducted in developing countries undergo proper ethical oversight and is responsive to the local context, measures to enhance research ethics capacity needs to be instituted in the developing world.

Key Words: Research Ethics, International, Justice, Research Capacity

It is estimated that less than 10 percent of the world's resources for health research are devoted to ninety percent of the world's health problems, which reside mainly in resource-scarce countries in Africa, Asia, Eastern Europe, and the Middle East This disparity has since become known as the "10/90 Gap" (1) The existence of this Gap will have serious implications for Global Health, due to the increasingly interconnectedness of and increasing cultural interactions between all health environments To help redress this imbalance, the past decade has seen an unprecedented expansion in international health research, particularly clinical drug and vaccine trials funded by sponsors in wealthy countries and conducted in resource-scarce countries.

Research Ethics - Why?

Biomedical research in the developing world faces many challenges, dilemmas, and difficulties But, it is imperative that these efforts are undertaken in ethical ways that respect and honor those many individuals and communities that agree to participate in the investigations

Unfortunately, clinical trials have been accompanied in some instances by abuses not unlike those which historically led to ethical concerns in medical research (2-5) An illustrative case is that of a clinical trial designed to test a drug called trovafloxacine, which was carried out on

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Corresponding Author: Henry Silverman, MD, MA, Department of Medicine, University of Maryland School of Medicine, 10 S Pine St , Suite 800, Baltimore, MD 21201, Tel: + 410-706-6250, Fax: + 410-706-8162, E-mail: hsilverm@medicine umaryland edu

children in northern Nigeria in 2001, during a meningitis epidemic This trial resulted in eleven deaths, while a further two hundred of the children became blind, deaf, or lame.

Although research ethics standards exist in Western countries, standards must be developed that are sensitive and relevant to the local context of the developing world For example, researchers need to develop an understanding of the unique ways in which different cultural groups make decisions (6-8). Strategies for obtaining informed consent might need to deviate from the traditional Western model of a single meeting with a prospective subject. Frequently, in resource-scarce communities, where illiteracy rates are high and cultural norms define persons in relation to others, the informed consent process might need to pursue a stepwise process that begins with discussions with the group of village elders followed by convened focused group discussions with the heads of extended families Subsequently, similar discussions can occur with prospective subjects.

Although the signing of informed consent documents is frequently mandated by U.S. regulations (9), many individuals in Middle Eastern countries are opposed to signing such documents, because they strongly believe that giving their verbal agreement should be sufficient Also, many are fearful of signing documents that contain legal language, which seem to have more to do with protecting the investigators and sponsors than the subjects Finally, the difficulty of such legal language might prevent many to discern the purpose and the risks and benefits of the clinical trial.

The existence of illiteracy also contributes to what has been called the "therapeutic misconception", whereby research subjects continue to believe, even against all explanation to the contrary, that they are undergoing treatment rather than participating in research (10, 11) As such, patients might believe that their participation in clinical trials is a necessary next step in their care. Finally, investigators might deceptively present research and other investigative procedures as if they were therapeutic interventions

Another issue involves the effects of financial and other inducements on the voluntariness of prospective subjects' decisions to participate in clinical trials In a situation of general poverty combined with a high burden of disease, as exist in some parts of the Middle East; many prospective subjects might be unduly induced by any type of research proposal that holds out the possibility of any type of treatment.

The presence of investigators' potential financial conflicts of interest is another research ethics issue. Many investigators who conduct clinical trials are, or have been, beneficiaries of gifts or financial rewards from the pharmaceutical companies The financial ties include paid speaking engagements, stock equity, expensive gifts, attendance at sponsored scientific conferences, and paid consultancy work Investigators must voluntarily provide information about such potential conflicts that might undermine protections of research subjects

Finally, many trials are conducted without any arrangement for compensation in case of study related injury, disability or even death of human subjects Each research study should include mechanisms for compensating human subjects to cover all foreseeable and unforeseeable risks

Avoiding Exploitation

The equitable distribution of the benefits of research has been increasingly recognized as an important part of international research ethics Although the conduct of clinical trials can have immense implications for the economic development for resource-scarce countries, there has been heightened awareness of the potential for international health research to be exploitative of host country communities and population (12-14)

Exploitation has been described as an unfair distribution of the benefits of research in the context of international collaborative research The concern is that developing countries assume most of the risks of research while the developed countries receive most of the benefits.

Specifically, many are concerned that most of the private industry funding is devoted to research on the diseases that afflict the population of wealthy countries compared to those of resource-poor countries. Also, many privately funded research involves the testing of drugs and interventions that will be sold exclusively in the

wealthy countries. These developments will serve only to widen disparities in global health. Indeed, the history of international health research is tarnished by poor performance in the fair transfer of benefits to the communities in resource-poor countries that have participated in the clinical testing of novel drugs and vaccines (15).

At the core of this debate about exploitation in international health research is the question of what investigators and sponsors from wealthy countries owe to the subjects of clinical research conducted in resource-scarce countries. These issues can be summed up in the phrase "Who decides who owes what to whom?"

In response, there have been revisions and expansion of major international research ethics guidelines and a proliferation of commissioned analyses that have emphasized the critical role of procedural safeguards against the exploitation of host country population (16-19) Specifically, the research ethics guidelines have begun to assign foreign investigators and their sponsors the task of ensuring and realizing research related benefits for host country research subjects and their communities. For example, current international guidelines include provisions that require researchers from Western countries to negotiate with the host country collaborators, prior to the start of the research, about the conditions under which the research will be conducted, including what benefits are expected to accrue to the host communities. The guidelines also include provisions about the assurance of ongoing access to any intervention demonstrated to be effective through the course of the study. These assurances are commonly known as "post-trial obligations."

Recently, instead of "reasonable availability" of any drugs proven effective in the trials, a consensus has emerged that avoiding exploitation demands fair benefits rather than only reasonable access to successfully developed drugs (20) Fair benefits might include measures to enhance the public health infrastructure and research capabilities of host countries Essentially, research endeavors can become the driving force of health policy and medical services delivery in resource-poor countries.

However, the provisions of these services might induce the community to participate in the study when in fact it might not be in the community's interest to do so This ethical dilemma involving the tension between avoiding exploitation and avoiding undue inducement is not yet solved and remains an important concern

The international guidelines on their own, however, are insufficient to enhance the protections of research subjects and redirect research priorities towards diseases afflicting resource-poor communities. Many sponsors are requiring that research protocols undergo prior ethics review by an independent research ethics committee. For example, the Eastern Mediterranean Region of WHO now requires investigators to address issues involving informed consent and confidentiality, and inquire whether a research ethics committee had review their proposals (21).

However, the research ethics committees of developing countries - due mostly to poor funding and inadequately trained staff - might fall short of promoting high ethical standards for human subject research (18). Indeed, very few of the large universities in the Middle East have institutional research ethics committees, and even these committees have not yet formulated standard operating procedures and too often lack the expertise with which to evaluate protocols Another concern is that many investigators lack training in Good Clinical Practices, which are a set of standards for the design, conduct, performance, monitoring, analyses and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected (22). To prevent ethical abuses, the clinical research agenda of countries should not jump ahead of its system for ethical oversight

Enhancing Research Ethics Capacity

Several recent initiatives have been designed to strengthen the research ethics capacity of resource-poor countries. The Fogarty International Center of the National Institutes of Health provides grants to set up bioethics training programs for scholars from resource-poor countries (23) The ultimate goal of these grants is to enhance the bioethics review of research The Welcome Trust in the

United Kingdom also provides support to build ethics capacity in resource-poor countries that have well-established research centers. Funding is provided for project grants and for seminars and other capacity building initiatives (24). The WHO's Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) was launched in 2002 with a primary objective to "contribute to human subject protections globally by developing local capacity for ethical review of research involving human subjects and for developing policies on the ethics of heath research" (25).

Early this year, a collaborative endeavor between the European Union and several countries in Africa created the Networking for Ethics on Biomedical Research in Africa (NEBRA) that will help raise the role of ethics in medical research conducted in Africa (26). The program will enhance the understanding of ethical issues arising in individual African countries and to identify people already involved in reviewing the ethics of research.

Finally, the United Nations Educational, Scientific and Cultural Organization (UNESCO) is in the final stages of launching its Global Ethics Observatory (GEO), a collection of online databases and other resources aimed at strengthening research ethics in UN Member states. The databases will gather contact details of ethics experts and institutions, examples of laws and national guidelines, and information about ethics teaching programs. Egypt's Bibliotheca Alexandrina has established a regional center - the Arab Group for the Ethics of Science and Technology (ASEST) - that will complement the activities of GEO (27).

All of these educational initiatives can help increase the research ethics capacity of resource-poor countries, which can enhance the protection of research subjects and help ensure a fair exchange of benefits between resource-rich and -scarce countries. Such an exchange of benefits can help achieve global health.

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