OPINION

Clinical Trials of Drugs and Vaccines Among the Desperately Poor in Poor Nations: Ethical Challenges and Ethical Solutions

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Clinical research has been expanding into poor nations in recent years. In doing research in such settings, the response to challenges arising due to the vulnerability and resultant potential exploitation of very poor subject populations is heightened awareness of the need for adequate local oversight and regulation. More regulation, however, often is difficult to implement and may not be practical. The provision of benefit at the conclusion of clinical trials in poor nations or for poor people is a better response to the moral challenge of exploitation.

A recent report from the US Department of Health and Human Services[1] noted that roughly 80% of drug approvals in fiscal 2008 were based at least in part on data from outside the United States. Eight percent of drug approvals contained only foreign data. The American experience is not unique. There has been a steady shift of clinical research from the developed world to the developing world.[2] Sometimes research outside the US is conducted to find products for diseases that affect both the rich and the poor. Sometimes research is undertaken to find vaccines or drugs to treat diseases that occur only among the poor in the developing world. And sometimes research is directed toward finding beneficial treatments for those in rich nations who can pay for the successful products of research without attention to access for those too poor to afford the same treatments.[3]

A variety of problems are encountered when carrying out research in poor nations and among poor populations, ranging from the overall poor health of the subject population being studied to difficulties in collecting accurate data. Nevertheless, the lower cost and ease of recruitment of subjects outside the United States has led to a well-documented shift over the past two decades toward involving new regions of the globe such as Eastern Europe, Latin America, and Asia as study locations and poor persons outside the developed world as subjects.[1–3]

The expansion of research involving poorer persons raises several ethical challenges,[3] in particular, the avoidance of exploitation. Exploitation means taking unfair advantage of people to serve your own ends and goals. In clinical research, exploitation involves asking others to bear risk while benefits accrue to persons not exposed to those risks. Exploitation is a particularly offensive ethical act in clinical research in that the rich and advantaged gain at the expense of those who are neither.

The danger of exploitation confronts any entity, public or private, profit or not-for-profit, that undertakes research in poor nations or among the poor in nations that are undergoing rapid economic development. The extremely poor often lack basic social goods such as medicines, food, water, and education—deficits that can compromise their ability to understand the nature of medical research. Absence of basic necessities creates environments that are in themselves limited in opportunities and therefore potentially coercive with respect to the choice by a person or group to participate in research. Such circumstances can lead the desperately poor to grasp at any opportunity seen as possibly beneficial.

Basic medicine is often unavailable in very poor nations. Where it is available, it may not be properly dispensed and is often not taken in the recommended manner.[4] Given these realities, poor persons may simply not understand the concept of research. Their plight may lead them to view the appearance of any novel medicine offered by someone in a white coat as beneficial, if not miraculous.

The government of a poor nation may be uncertain as to whether a therapy being offered to its people in a time of epidemic or crisis is experimental or proven. A country may feel so imperiled by the prospect of a pandemic that it will seek unproven drugs, devices, or vaccines and present these to its citizens as therapies, as happened during the recent H1N1 pandemic.[5]

Choosing to participate in research when one is starving, living in a box, or drinking badly polluted water may seem

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doi:10.1038/clpt.2010.208

to the very poor an option with no acceptable alternatives. Research participation entails exposure to doctors, nurses, clean environments, and possibly clean food and water. The difficulty that potential subjects might have in understanding the nature of research consent, peer review of research implementation by independent local committees, and efforts to minimize conflicts of interest represents the three core principles of research ethics, all of which may prove very difficult to implement. These protections evolved in part in response to past situations in which researchers in wealthy nations took advantage of the powerlessness, illiteracy, or desperation of others and exploited them to advance biomedical research.[6] However, there are serious limitations to their implementation in poor nations.

Core research norms such as obtaining the informed consent of the individual may be difficult to implement in cultural contexts where decisions are ultimately made by local leaders, religious figures, or husbands on behalf of wives and daughters.[7] Local resources for providing oversight to research may be weak, corrupt, or both. The ability to collect information about adverse events can be difficult, and control over the quality of data can be spotty.[3,7,8] Although the debate over the implementation of these protections in clinical trials involving the very poor continues to evolve,[3,6–8] the key to preventing exploitation may not be forthcoming. There are limits to the applicability of research ethics norms created in developed-world settings to poor nations and their poorest residents.[9]

In trying to minimize exploitation, it may be just as important to develop and implement policies delineating what will be given to those involved in research and their countrymen at the conclusion of clinical research as it is to battle over the nuances of research ethics requirements that cannot in fact be implemented or monitored in any practical sense. The challenge that research sponsors face in trying to avoid the charge of exploitation is showing that research subjects who are very poor have not simply been exposed to risk but have benefited from their participation in research.

There are those who argue that being a subject in a clinical trial is in itself an advantage to the very poor.[8] They may receive access to some forms of health care either in the control arm of the study or simply as a condition of monitoring their response to novel agents; they may be told about health problems of which they were not aware; the experimental agents used may provide benefit; and there may be benefit in having food, water, and a safe environment to experience—albeit intermittently.

It is true that participation in trials can bring these benefits, but the determination as to whether benefit has been delivered must be made on a case-by-case, trial-by-trial basis. In some trials, the standard of care given is for all intents and purposes not beneficial. In others, subjects are seen by investigators who cannot provide them with very much in the way of ancillary health-care benefit. Moreover, the short duration of the study in some trials undermines any possibility of true benefit for subjects.

Although there may be benefits from participating in a trial, research for the most part involves not knowing whether the entity being tested has benefit or what the risks of exposure might be. The duty of researchers seeking to avoid exploitation would therefore seem to involve a commitment not simply to try to follow good practices in research ethics, which present well-known difficulties, but also to either make subjects better off at the end of a trial or improve the lot of all persons in a poor nation where a trial is carried out.[9]

There is no simple formula for deciding how much benefit ought to be given to subjects by, for example, providing them access for a substantial period of time to agents proven effective against diseases they may have. The determination of benefit must take into account whether prevention or treatment is involved, the practicality of delivering the agent proven beneficial, the risk of providing proven agents in places with few resources and little health infrastructure, and the determination by the subjects themselves of what they would value in terms of benefit. It may well be that a road or a water-treatment plant or a clinic will go much further in terms of benefit than attempting to provide a stockpile of medicine over a period of many years in environments where there is no water, road, or doctor.

The provision of benefit at the conclusion of clinical trials in poor nations or among poor people is an antidote to exploitation. What is currently lacking is the commitment to do so in ways that truly provide benefit consistent with the values of the subjects in trials and some means to monitor such commitments. It is long past time to remedy both deficits.

CONFLICT OF INTEREST
The author declared no conflict of interest.

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