Conflict of Interest as an Ethical Problem in Health Research in Developing Countries

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Health research involving human subjects, including clinical trials of drugs and medical devices, which may be of great financial value to their manufacturers, is extending rapidly in much of the developing world. Though no systematic count has been made of the number of experiments undertaken each year, nor of the number of human subjects enrolled in them, recent journalistic accounts report that major pharmaceutical firms have increased their pace of activity many-fold in the past decade.

Though health research in developing countries has been caricatured as the enormously wealthy Big Pharma preying upon the vulnerable masses of the third world, this increased scope and intensity of health research offers reasons to cheer.

Some of this research is directed to diseases primarily affecting people in developing countries. The well-known formula "90/10", a pithy statement of misplaced research priorities in which 90% of health research is directed at cures for maladies affecting those with only 10% of the global burden of disease, is just a guesstimate. But few would deny that it would be much easier to raise funds for research on male baldness than for tropical diseases that kill hundreds of millions of people, simply because the market is there. While the treatment of participants enrolled in experiments in developing countries deserves careful scrutiny, the greater problem for them and for their fellow citizens has been not victimization in research but abandonment through a *lack* of research.

It remains true, however, that much of the research done in developing countries is not expected, or even intended, to benefit the populations of the host country. High prices, or even moderate prices, may stand in the way of widespread use for the foreseeable future. Even so, the host country may benefit in many ways by having research conducted in its midst. Apart from any therapeutic gain to some or all participants, research sponsored by sponsors from developing countries bring the prospect of training, new facilities that are left behind when the research is done, and other forms of technology transfer.

The attraction of developing countries to sponsor research, particularly commercial firms, stems from several sources. Patients may be plentiful. A huge hospital such as Baragwanath, in Soweto, South Africa, sees hundreds of very sick patients a day in many categories, offering firms a crucial advantage to firms whose overriding goal is

speed to market. Indeed, it is often difficult to find patients in rich countries that are allowed to get that sick. Moreover, these patients are in many cases “treatment naïve”, which is to say that their bodies are less likely to have other drugs in circulation that could interfere with the intended experiment. Poor patients have fewer alternatives to the drugs and other treatments that may be offered as part of a clinical trial, so they are less likely to refuse to participate. Costs, including the cost of the hospitalization and payments to cooperating physicians, are generally much lower. Some claim that patients in developing countries are more likely to question the research carefully. In any case, regulation is in most cases much weaker than in developing countries

These advantages, however, are increasingly offset by the unwelcome prospect of moral controversy. A varied group of people in NGOs along with some journalists and academics – including reputable researches and at least one editor of a principal medical research journal – have in recent years been sharply critical of some sponsors and researchers involved in research on human subjects in developing countries. They have questioned whether participants really understand what they are getting into; whether patients in poor countries are denied the first-rate consideration and care that patients in wealthy countries can expect – evidence of a moral double standard, whether there is any significant benefit in some of this research for anyone but the sponsors and a few-off patients; and, generally speaking, whether patients in developing countries are not chosen precisely because they are relatively vulnerable and defenseless and therefore easier to exploit.

Whether these charges are accurate or not – and it varies, of course, case by case – the impression that a good deal of unethical research is being carried out in the third world by researchers in the employ of first-world sponsors is widespread and growing. One sign (and stimulus) of this concern was a six-part, exhaustively-researched series in *The Washington Post* in December 2000, alleging abuses on many continents by public and commercial sponsors alike. In view of these concerns, particular importance attaches to the fiduciary role of the patient’s physician, who may also be one of the research scientists. If the research does threaten harm without corresponding advantage to the research subject, or if the proposed research is exploitative, the physician may be the individual the patient must count on for protection.

The ethics of research involving human beings have always been focused on a conflict between interests, specifically the clinician’s dedication to the interest of the individual patient and the scientist’s pursuit of remedies for patients generally through the possible discovery of new therapies. The entire apparatus of ethical regulation and review in human subjects research has been devoted to managing potential conflicts between those roles, which are commonly filled by the same person or persons.

It has always been known that a third interest, that of the researcher him- or herself, is a factor as well. In the past, this was seen as a manageable element because the principal gain to the researcher was career advancement, and this would come through prowess as a scientist. Thus the physician’s personal interest and his or her interest as a researcher coincided.

But it has now become unavoidable to pay close attention to other, less exalted personal interests of researchers. Financial conflict of interest has intruded into the world of research ethics, and new mechanism and codes are being proposed to

address the problems. In the United States and some other countries, the rise of biotechnology as an industry and venture-capital favorite has revolutionized the relationship of biomedical scientists who do not work for pharmaceutical firms the profit motive. So initiative and comprehensive is this relationship that prominent biomedical scientist who do not have a financial relationship with a corporation, either as entrepreneur, stockholder, or paid adviser, are rarities. To be sure, these scientists insist that their financial interests do not intrude into the traditional balancing act of their clinical and scientific missions. But this assurance did not go down well with the public after the recent death of a patient in a University of Pennsylvania hospital following a gene therapy experiment, when it was revealed that the physician-investigator had a lot of money riding on the outcome.

In developing countries, significant participation in first-world companies as investors or executives is less common, but the ramping-up of the health research enterprise in developing countries has led sponsors of research, particularly pharmaceutical companies, to attract the participation of physician-scientists through financial inducements that present conflicts of interest that are potentially serious. The evidence for these practices is anecdotal; but all the anecdotes that reach me are consistent. Drug companies make payments to doctors in developing countries for enrolling patients in trials. The amount of the bounty that these companies offer varies by region and other circumstances, but per-head payments of over $1000 are not uncommon. By enrolling a single patient, a doctor can double, even quadruple, his or her monthly salary. Even if the bounty is somewhat lower than what the drug company would pay to an American doctor, its impact is bound to be far greater, for the obvious fact that the American doctor's substantial salary is likely to be his or her main source of income.

Should this be regarded as a bad thing, any could it possibly be branded a form of fraud or corruption? This practice has much to recommend it. Physicians deserve compensation for their effort, and in any case most of the trials would not take place without incentives to doctors to enroll their patients. In many, perhaps most developing countries, physician salaries are very low, and those who choose a research career over private practice may have wages that are lower that are lower still. These bounties help to sustain physicians in science. Patients can benefit from these payments, too: with so much riding on their participation, they can count on attention from their doctors that may be denied their fellow patients who are not enrolled in trials. Indeed, one of the standard complaints against these bounties is that it leads doctors to ignore non-enrolled patients. Those patients who *are* enrolled, however, enjoy the added attention.

Nevertheless, the hazards of these practices may warrant the attention of Transparency International. The term "fraud" may attach to those bounties if they are not disclosed to the patients (and though I have found no systematic study of disclosure, anecdotes suggest that disclosure is rare or nonexistent). One might resolve this problem by requiring disclosure (though do not expect this to happen anytime soon), but the possibility of corruption – corruption of the ethics, the moral mission, of the physician-scientist, and perhaps also his or her scientist judgment – remains. In the classic dilemmas of research ethics, the physician-scientist must somehow reconcile his or her two roles and missions. We do not speak of one interest "corrupting" the other since both are in the public interest. The pursuit of financial gain, however, is not. To be sure, it may, in deal circumstances, align with one of the more noble interests. The fee-for-services system of compensation, for example, was always defended on these grounds.

In the case of medical research in developing countries, paying doctors relatively huge sums to participate might align the developing-country physician with the scientific rigor of the sponsor who, after all, must ultimately satisfy the Food and Drug Administration or its counterparts in other countries.

But the hazards are obvious and cannot be easily dismissed. One need not treat John Le Carré's book, *The Constant Gardner* (about criminal conduct of clinical trials is an African country) as fact to appreciate the risks to subjects, particularly when no alternative sources of funds are available and when oversight and regulation are weak or nonexistent. The many accounts appearing in *The Washington Post* and other media of unethical research practices almost always involve one or more developing-country scientists acting on behalf of first-world sponsors for what is to them a large amount of money. If the trial goes well, the patients often benefit from their participation. But if the trial does not go well, if patients are enrolled in trials in which they do not belong from a clinical point of view, or are kept in, or kept on an experimental regimen solely to order to hasten the day on which the company can bring a drug to market, then the bounties paid to their doctor could win the allegiance of the doctors against the interest of their patients. The amount of money and other benefits that would be lost if the physician-scientist were to confront the sponsor might too great.

More subtly, the financial stake that the physician has in the research might affect his or her perception of events and outcomes and thud the management of the patient. Marcia Angell, when editor of *The New England Journal of Medicine*, pointed to considerable evidence of this phenomenon in her widely-noted editorial, "Is Academic Medicine For Sale?" (1999). Thigh it is difficult to quantify, and almost always stoutly denied by the scientists themselves, the effect on scientific and clinical judgment of this form of self-interest can be hazardous to the health of patients.

Moreover, the lure of big money can induce the physician to commit a bit of fraud against the sponsor. Anecdotes, in the *Washington Post* series and elsewhere, tell of phantom patients for whom bounties are claimed, with mysteriously similar charts; excessive zeal in recruiting patients, not all of whom could possibility have the specific profile required for enrollment according to the research protocol; and under-reporting of adverse events, apparently with the intent (however futile) of ingratiation the physician to the sponsor. One might also expect that consent procedures that threatened enrollment or continuation of the patient in the trial once underway would be under pressure, too, though again there are few reliable data.

Needless to say, this is not to single out physician-scientists in developing countries as morally deficient. Bounties are offered in the United States, too, and have some of the same ill effects (nor have they customarily been disclosed to patients). But the circumstances are different: bounties usually amount to less than the physician's salary, and regulation and oversight are likely to be much stronger. Were an American doctor offered $50,000 per patient and assured of immunity from regulation or ethical review, the temptations would be similar.

Other ways of funneling money to doctors in developing countries, again relying on anecdotes, present similar concerns and do border on fraud. For example, sometimes what is called "research" is in fact merely a marketing exercise, a way of introducing a drug or device to both doctor and patient, with the intention not of learning anything but

of promoting sales after the so-called experiment is over. This sham research also places a fig-leaf on payments to doctors for prescribing particular drugs or devices for their patients – not that direct payments are not also made, but in this case the money can be placed on the top of the table and given the noble name for research fees. The same can be said of providing the physician (and his or her spouse or companion) with travel expenses to a research conference in a pleasant resort or exiting big city, at which the participation expected of the physician consists of showing up to pick up to pay envelope. The consequence of this corruption of the clinical mission are felt throughout the developing world in the form of household bankruptcies (for overprescription of high-priced drugs) and foregone medical care.

But what is to be done? In the United States, where conflict-of-interest among physician scientists attracted considerable attention in the wake of the gene therapy case of Jese Gelsinger (Shalala 2000), those who set the rules are taking action. Donna Shalala, President Clinton's Secretary of Health and Human Services, called attention to the issue and initiated planning meetings among several US government agencies. The new regulations will build on thirty years' experience with institutionally-based peer ethical review of research, an oversight and regulatory enterprise that now consumes staggering sums of money (for example, Massachusetts General Hospital, one of Harvard's research institutions, spend $2 million dollars on its review committees per year, exclusive of committee members' salaries. The University of Wisconsin Medical School spends $700,000).

In all but a few developing countries, ethical review is a very recent tradition at best, and in virtually none of them there is adequate technical support. Tine is stolen from too-crowed teaching, patient care, and research duties, and staff support is typically nonexistent. Though a number of developing countries have issued thoughtful research ethics guidelines in recent years, conflict of interest among researchers has received scant attention, the prospect for adequate review and control of the risk factor in the near future is not bright. After all, the institution that employs the review committee is the same organization that would lose the income is the offer of research from the first-world sponsor made ethical review a condition of funding. They do this, of course, to satisfy the requirements of agencies in their own countries, such as the Food and Drug Administration. It is undoubtedly a good thing that drug companies are insisting on ethical review, and even providing the training needed. But can we expect them to put bounties, sham research, and the like at the top of the agenda?

Given that conflict of interest in research involving human subjects is a global problem – it is not only ubiquitous, but also in specific instances often involves collaboration between first-world sponsors and third-world physician-scientists and patients – it is fitting to see a global solution. What this solution would like is something we cannot know without more reliable data further study. But I offer a few initial suggestions here.

First, ethical research involving human subjects that takes place in developing countries must be strengthened throughout the world. This requires both short-term training for ethical review committee members and longer-term fellowship for scholars and research directors; technical support for review committees with limited access to the full range of specialized fields of knowledge; and perhaps financial support for staff and to compensate committee members for their time, perhaps itemizing the cost of ethical review in research budget for each protocol.

Second, the issue of conflict of interest among researchers in the developing world must be studied and documented, and discussion over measures to address the issue should be near the top of the agenda in s discussions of research ethics. The World Health Organization has joined with the National Institutes of Health, the Medical Research Councils of the UK and South Africa, and other sponsors of research in developing countries to launch the Global Forum of Bioethics in Research, an annual symposium in which these and other pressing issue can be debated and, one day, perhaps resolved.

Third, regulatory agencies in the first world should extend their oversight to practices by companies and other sponsors of research in their countries that provoke conflicts of interest in developing countries.

Finally, we might begin to think about international guidelines, or even a convention of some sort, that would set limits on the seduction and corruption of physicians and physician-scientist in developing countries – those all-important, and very vulnerable, links in the supply chain that connects companies with products for sale to sick people who can be recruited into experiments, or who can be induced to think that their health ad well-being depend on their buying these products.