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Human subject research, ethics and the developing world

F Moazam
Aga Khan University, farhat.moazam@aku.edu

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In the last few decades there has been an increasing interest in collaborative, multi-institutional research involving human subjects. Much of this is driven by an international community of dedicated scientists, clinicians and physician-researchers in their fight against disease. In the last few decades, the pharmaceutical industry has become a major source of funding for research. Specially those involving drug trials. At the same time the number of international research projects involving collaboration between host developing countries and sponsoring industrialized nations, is on the rise.

An increasing concern is being voiced recently regarding the need for ensuring ethical conduct in research particularly when human subjects are involved, much is being written on this matter in medical and biomedical literature and the issue is under discussion in many international organizations.

It is important for members of the healthcare profession in the third world to be aware of this ongoing debate and he cognizant of the benefits as well as a potential for misuse of human subject research. In this essay I plan to:

- Summarize the evolution of research ethics, as we know it today, that has occurred over the course of the last century.
- Briefly consider the increasing and in some ways detrimental role of the pharmaceutical industry in funding biomedical research.
- Present a few examples of ethically questionable, international research involving human subjects from developing countries.
- Comment on the seminal difference between a code of ethics derived from secular values and one that is rooted in religious beliefs.

Evolution of Research Ethics

Codes of conduct for members of the healing profession have existed for years. For physicians these date back to at least the time of Hippocrates, when the early Greeks considered piety and honesty as essential traits in any member of this profession. Following the decline of the Sassanid and Roman empires and in the years leading up to the 14th century, there was a flowering of a great Islamic civilization in Asia, Europe and Africa. This period has unfortunately been designated as the “Dark Ages” by Anglo-European writers who have tended to ignore the philosophical, mathematical and medical advances of this civilization, by shoring and advancing much of intellectual and philosophical traditions of the Hellenic period, it was in fact Muslim scholars that made the European Renaissance of the 16th century possible.

During the golden years of Islam, Arabic literature and progress in the medical science reached its zenith. In the Islamic world the healer held a special place. Writings that are extant from these years, elaborate in some detail on the “adab”. the moral and ethics conduct, of those in the healing professions. The Arabic world for physician, hakeem, denotes one who is full of knowledge and wisdom. The world is also one of the attributes of God. It was considered a religious obligation of physicians to be ethical, virtuous and willing to do everything in their power to aid the ill and the suffering. Writings of the medieval Muslim physician AL-Razi underscores this responsibility of physicians, while at the same time advising patients to follow “the orders” of physicians, to respect them, and consider them “better than their best friends”.

This admittedly unequal relationship between physicians and patients relied on mutual trust between the two parties and was based on a therapeutic paradigm. This arrangement worked well until the late 19th and early 20th centuries. Around this time, with the industrial revolution well underway, there was an explosion in scientific knowledge in Europe and North America. The advent of pharmacological...
agents such as antibiotics and rapid advances in medical technology did much to improve the lot of the sick. But the close, personal relationship between the healer and the patient began to conflate with impersonal, empirical medical research that began to be utilized for the advancement of general scientific knowledge and the benefit of future patients. The country family doctor began to give way gradually to the impersonal physician-scientist. The specialist was now more likely to be housed in distant, academic “institutions of excellence” in contrast to the general physician who practiced in a clinic or hospital around the corner.

Even in the early years of this transformation. Health-care professionals were aware of the implications of this paradigm shift on the welfare of individual patients. While medical research was still in its infancy. Claude Bernard made the following statement - The principle of medical and surgical mortality consists in never performing on man an experiment which might be harmful to him in any extent even though the result might be highly advantageous to science i.e. to health of others.

But the brave new world of science and research marched on, bringing with it innumerable and unquestionable benefits to mankind. In the early years, scientists and physicians often utilized themselves or their family members as research subjects. Jenner's experiments involving inoculation of his children with cowpox to study its effects on smallpox and Freud's experimentation on himself with cocaine as an analgesic. are just two of the examples that come to mind. But scientific curiosity and human struggle against disease demanded empirical data collected from large number of subjects.

Research methodology and its benefits received a tremendous boost in the industrialized world in the 20th century, particularly in the United States. Much of the medical and surgical progress and control of disease was undoubtedly made possible due to animal and human experimentation. It was only after world war II however. that the horror and immortality that could characterize human subject experimentation, first came to light. Nazi physicians were brought to trial in 1946 in the famous Nuremberg trials for having used human subjects For research without their consent. the objectives of this research included studying the effects on human when subjected to extreme heat, immersion in freezing water and following deliberate chemical and crush injuries.

The Nuremberg Code that was formulated in 1947 as a result of these trials was the first and most stringent pronouncement on the rights of research subjects. The first principle of the Code stated unequivocally that “the voluntary consent of the human subject is absolutely essential.” The Nuremberg trials are often considered a watershed in the history of human subject research. A new phraseology was added to the vocabulary of the scientific community. This was the right of an individual to not only be informed of the nature of the research, but also a right to refuse to consent to serve as a subject for research.

The Nuremberg Code which was formulated by judges rather than medical professionals had its limitations. With its stand on the requirement for voluntary consent from all human subjects, it essentially ruled out possibility of research involving children and incompetent patients. It also did not differentiate therapeutic from non-therapeutic research. In 1964 therefore, the World Medical Association (WMA) met in Helsinki, to formulate more detailed guidelines for ethical human subject research. The resultant Helsinki Declaration laid out 12 principles that must guide all human subject research. One of these reaffirmed the necessity for obtaining a voluntary and informed consent from all competent subjects. Furthermore, principle 5 stated that concerns for the interests of the subject must always prevail over the interests of science and society”. This in many ways. echoed the principle that Claude Bernard had expressed several years earlier.

Principle warned against informed consent being obtained from subjects “under duress”. It is relevant here to point out that blatant duress, as in prisoners or institutionalized individuals, is relatively easier to recognize. What is more important however, is to realize that duress can he far more subtle and can take the form of coercion that is far more difficult to recognize and sometimes even agree upon. An example of this is when powerless members of a community in an authoritarian, hierarchical society.
are called upon to enroll as human subjects for research.
The Nuremberg Code and the Helsinki Declaration, although addressing the issue of human subject research, did not speak directly to research in third world. In 1993, the Council of International Organization for Medical Science (CIOMS), in collaboration with WHO was the first to form a document entitled International Ethical Guidelines for Biomedical Research involving Human Subjects. These guidelines addressed the rights of the population of the third world directly. CIOMS was the first to suggest that there was now a "new" vulnerable group that must be recognized. For this group, its vulnerability was the direct result of socioeconomic factors related to a geographical location. In effect, this was a definition that applied to the population of the third world. The document devoted several sections of its guidelines specifically to ethical issues involving international research.
The 1980s saw a rapid increase in international, collaborative research involving human subjects. The Sponsoring countries were often those from the industrialized world, particularly the United States, that collaborated with researchers in the developing world, the "host" countries. Human subjects were generally drawn from the population of the latter. Although many reasons were responsible for this trend, some in particularly are noteworthy.
Infectious diseases in developing nations were taking a terrible toll on lives, and there was a genuine concern that measures must be found to address this calamity. HIV infection was developing into a pandemic, the likes of which had not been seen for centuries. Although it had a staggering hold on African countries, no country including affluent country of the world could consider itself immune from an infectious disease effecting another.
From 1960s onwards, the West began to experience a rise in civil rights movements, strong human and patient advocacy groups, I-minism and an informed, vocal press. There was widespread criticism of the medical profession in general and in particular in its handling of human subjects while conducting research. during this time, there was little, if any evidence of these phenomena occurring in the developing countries.
These radical changes in the industrialized world resulted in the introduction of increasingly stringent regulations for human subject research. This was specially the case in United States in the aftermath of exposure of several infamous research projects, including the Tuskegee Syphilis study and the Willowbrook experiments. Federal funding for human subject research now required conforming not only to federal and state regulations but also a review and approval by institutional review boards and ethics committees.
In contrast, third world countries, having just emerged from colonial rule and many still with authoritarian national governments, had non-existent research regulations in place. In addition to their impoverished and illiterate populations, issues of individual rights, civil liberties and a challenge to deeply rooted respect for medical authority, all on the rise in the West, were unfamiliar notions. It is therefore not surprising that under these circumstances, developing countries began to offer attractive sites for collaborative human subject research—research that could certainly be beneficial to the host countries, but would also be of tremendous use to the populations of affluent sponsoring countries.
The Role of the Pharmaceutical Industry
The role of pharmaceutical agencies in funding biomedical research began to expand rapidly in the 1980s as availability of grants from universities and government began to decrease. (Concomitantly, the share of the private sector in healthcare and medical research increased. Biomedical science and technology did not remain resistant for long to the global market concept, where the “bottom line” hinges on investment that lead to profits. And it was soon evident that drugs and technology could be good investments. One has only to peruse medical literature to realize that currently, substantial research involves drug trials funded by pharmaceuticals.
There is a growing perception that there is an emergence of “two worlds” on this globe. This may seem to be a simplistic presentation of a complex issue but nevertheless, it holds a large grain of truth By the
1990s. 77% of the world's population was living in the third world and 50% of them reside in countries where the annual per capita (1 NP was less than $270 (compared to $19,000 in the United States). Per capita energy utilization (Kilowatts/year) reveals a staggering discrepancy between these two worlds. The average for the industrial world is 3.2 (USA 9.0), whereas it stands at 0.28 for the developing world6. It is estimated that primary healthcare (water, sanitation, basic drugs etc.) for the whole world would cost $50 billion/year. This is equal to 2.3 of the money the world spends on cigarettes, 1/2 the amount spent on buying alcohol and merely 1/15 of the global military expenditure (David Morley - 1986).

The impact of pharmaceuticals on healthcare systems has been profound. In 1992, approximately 40% of the global expenditure on health research was provided by the pharmaceutical industry. In the USA, the drug market now accounts for 40% of the industry’s sales and 60% of its profits. A WHO Report from Geneva in 1996 states that over 90% of the annual global expenditure ($56 billion) on the health research and development in early 1990s, was directed towards disorders responsible for only 10% of the global burden of disease. The same report also states that “the multinational pharmaceutical industry operates like any other industry. It makes investment decisions to maximize future returns from the money invested. As such, it responds to economic demands rather than to statements on social or human needs” And it is a well known truism that whoever pays the piper will be in a position to call the tune.

Guidelines for conducting ethical research that are followed by researchers in developing and industrialized countries alike, primarily stem from the Helsinki Declaration and the CIOMS guidelines. These enunciate clearly that concern for interests of human subjects must prevail over interests of science and society. Secondly, in international, collaborative research, it is the responsibility of donor agencies and sponsoring and host countries to protect the vulnerable and their best interest. Thirdly, benefits from the research must accrue to those used as subjects.

International guidelines consider two processes to be key in ensuring that research is ethical in nature. The first of these is an informed and voluntary consent from subjects and the second is that approval of the research project by ethics committees of the sponsoring and host countries is essential. Both requirements stem from a Western ethos. And yet even in developed countries with high literacy rates and strong movements for individual rights, experience indicates that neither of the two processes have proven entirely successful in preventing abuse of research subjects. It is therefore not difficult to predict their lack of success in assuring ethical research where the subjects are powerless, impoverished and illiterate.

Healthcare and research occurs in an arena in which the incredible power of those with knowledge and skills interfaces with the vulnerability of others who are in need of this expertise. Consent forms and committee approvals can be obtained to abide by the letter of the law, but in the absence of a virtuous researcher or physician, will go just so far in protection against ethically questionable use of this power. Insufficient attention to the spirit that lies behind any well meaning guidelines lies at the root of much of the research that has been recently considered to be ethically troubling.

Example of ethically questionable Collaborative Research
In recent several instances of collaborative research have generated debate amongst medical researchers, ethicists and scientists as to their ethical soundness. Perhaps the most infamous of these are the drug trials conducted for HIV infections.

In 1994, results of the AIDS Clinical Trials Group (ACTG) Study 076 in USA and France revealed conclusively that vertical transmission of HIV from pregnant mothers to their neonates could be reduced by two thirds (25.3% to 8.3%) with an intense regimen of Zidovudine (AZT) drug therapy3. The trial was halted after the first interim analysis and this therapy was declared the standard of care for all HIV infected, pregnant women in these countries. The cost of each treatment was determined to be approximately $1000.

Six months later. Following a WHO meeting of international researchers and health officials in Geneva,
the CDC and NIH of the United States, embarked on collaborative studies on pregnant, HIV infected women in Africa and Thailand. The objective was to assess if a shorter and less expensive regimen of AWf would be effective in decreasing maternal to fetal transmission of the infection. The drug trials were structured to use a placebo arm so that the control group of subjects would get no treatment, while the other received a less intensive regimen of AZT. Such trials could not have been federally funded or undertaken in the host country as it would have been considered unethical to use a control group when a proven therapy already existed for the disease.

A controversy erupted around the studies in the USA in 19974-6. Those who defended these trials cited two main reasons for considering them as ethical. One of these was that an informed consent had been obtained from all subjects and the second that the trials were approved by the ethic committees of the host countries. Later that year, Howard French, a New York Times report7, interviewed some of the women who had consented to be subjects of these trials. His article revealed that none of them had understood the nature of the study, had no clarity about what a placebo trial meant and had agreed to serve as subjects believing that they would be helping their unborn babies.

Although there was vitriolic debate among supporters and critics of these studies, one thing was unquestionable. Neither the pharmaceutical industry participating in these trial, nor the researchers themselves, had made available to the communities who served as human subjects for the study. Furthermore, this regimen which was estimated to cost around $50-60, would have been well outside the reach of these subjects, although certainly not so for affluent countries in the global market for these drugs.

In another study in 1997, patients with HIV infection were deliberately inoculated with plasmodium vivax to produce symptomatic malaria. The objective was to study the effects on their immune systems. This was a collaborative research undertaken by two hospitals in China and the Heimlich Institute in Cincinnati8. As part of the protocol, subjects could not participate in any HIV therapy for the duration of the study and the follow-up period. Institutional Review Boards of the host country had approved the research as ethical, something that would have been highly unlikely if the study had been undertaken in the sponsoring country.

A hepatitis A vaccine trial was conducted in Thailand in 1991, sponsored by a multinational pharmaceutical agency. There was no provision built in the proposal that if the vaccine was found to be effective, it could be made available to the population that was being used as subjects for the study. An informed consent was stated to have been obtained from all subjects, but it was unclear whether they were told that the vaccine, if found to be successful, would not be available in Thailand. One must wonder exactly how informed these consents were and at the seriousness of the ethic committees in protecting the interests of the human subjects.

An ongoing study in Haiti involves collaboration between a local AIDS Clinic and Cornell University in New York. The objective of the research is to develop a vaccine by following couples longitudinally to assess the rate and nature of transmission of HIV to the uninfected partner, which in most cases happens to be the woman. Members of the Haitian ethics board that approved the study includes the husband of one of the researchers and the mother of the head of the research laboratory. Without question the membership of this board would have been rejected on ethical grounds in the country of the sponsoring university9.

In all these studies, the letter of the law, i.e., an informed consent and approval by ethics committees has been followed. Yet the studies have been criticized as ethically problematic.

Ethical guidelines - Secular vs Religious
Most healthcare professionals are well meaning and embark on research with a goal to find ways to conquer disease and help mankind. But the headlong speed of biomedical science is leaving far behind it the important issue of obligation towards the third world, safeguarding the interest of their populations and ensuring that the benefit from the research accrues to them. In the last, researchers
Collaborative research holds many tempting rewards for scientists. It provides opportunities for a move up the academic ladder, publications, fame, interaction with international researchers and sometimes, even financial gains. The increasingly dominant role of the pharmaceutical industry in funding research and its interest in competing in the global market for drugs and vaccines is progressively controlling the direction and the nature of medical research.

Responsible members of the international medical and scientific community have been concerned about the dangers to vulnerable individuals, both in developing as well as developed countries. To address this concern, the publication of an influential text entitled Principles of Biomedical Ethics by Beauchamp and Childress, drew on the philosophical traditions of the West to enunciate basic ethical principles that should guide biomedical science, including research. The principles they offer are well known to physicians all over the world and include autonomy, beneficence, non-maleficence and justice. These principles and their derivatives, fidelity and truth telling, form the framework within which the international ethics guidelines for human subject research have been constructed. The dominant moral and ethical values emanating from the West are based on an Anglo-American tradition, one that is philosophical, secular and right-based. They are grounded in a notion that individuals are autonomous agents, self-determinant and aware of their rights. In them is implicit that individuals reside in societies with legal systems that accept these principles and frame their responsibilities accordingly.

But the majority of human beings, residents of the “other world”, draw their moral values from very different traditions and cultural norms in which religious beliefs play an important role. In Pakistan, codes of behavior and consideration of what is right and wrong, are rooted in divine injunctions. They lay a much heavier emphasis on obligations and duties of an individual. When they do address the rights of an individual, it is within the context of relationships rather than as those of a free standing agent. A person is not seen as autonomous but rather as one enmeshed in relationships that include deep obligations towards family and community. And in the religion most followed in this country, Islam, the heaviest responsibility falls on the shoulders of those who are the most privileged, a category in which most healthcare professionals fall.

The principles lying at the root of the current international guidelines for ethical research were formulated in the rarified atmosphere of Geneva and Helsinki. They speak primarily in a language of the rights of the subject to be treated with respect. In contrast the long standing Muslim tradition of morality, the adab emphasizes the obligation and duty of health professionals to treating the vulnerable and those in need with respect. Although not necessarily exclusive to one another, there is a tremendous difference in the two approaches and in where one chooses to place the emphasis.

In recent years, the right-based approach to bioethics has been criticized by bioethicists in the Western world as being abstract and non-contextual. It has been pointed out that humans often exist in unequal relationships, such as those between physicians and patients and that relationships cannot be built primarily on the basis of rational contracts. Some of the clearest voices raising these issues have been those of women.

One of the earliest women known to have emphasized the importance of obligations towards the vulnerable was Rufaiadah al Aslamiya, daughter of a healer and priest in Arabia, who embraced Islam in the times of Prophet Muhammad (Islamic Medical International Conference - 1981). She was the first to organize Muslim women in taking care of those who were wounded in the battles of Uhud and Badr. It is reported that she was allowed to pitch her tent in the mosque in Medina to do so. Although Rufaiadah is generally regarded as having initiated the first “nursing school” (predating Florence Nightingale by a millenium) some Muslim writers have described her not only as an expert in Tib (medicine) but also in Jarha (surgery). She is credited with having developed a code of ethics, based not on the secular rights of the patients, but on the religious obligations of health professionals towards those who are in need.
Guidelines formulated in Geneva and Helsinki can undoubtedly play a role in educating researchers towards an ethical approach to research. But without a transfusion of the eastern ethos that speaks to the virtuous physician and researcher who goes beyond consent forms and committee approvals, they may never be robust enough to succeed in this objective. This is particularly true in the socioeconomic realities of developing countries.

Reference