Trials by Fire: The Case of Unethical Clinical Trials in the Countries of the South

Behzad Hassani

Introduction

The journey of a new medication from laboratory bench to bedside and to the pharmacy shelf is, although profitable and prolonged, often arduous and troublesome. Traditionally, drugs are tested on animals first and then, in a series of phases that may take several years, on human subjects. Issues surrounding the ethics of human clinical trials have always been the source of much controversy, although such trials are regulated and governed by watchdogs in the developed countries (eg. Food and Drug Administration in the USA). The story is somewhat different in the developing world.

During recent years, the pharmaceutical corporations and their patrons in the biomedical profession and the public sector have faced several obstacles regarding the recruitment of human subjects and passing their proposals by ethical review boards. The rising competitive pressure on the companies to develop drugs and market them faster has naturally caused them to shift focus from the countries of North to those of South. This shift of focus is one of the most egregious and least examined manifestations of the neo-liberal globalization movement. Differential access to healthcare, lack of political resolve and the politico-economic hegemony of giant pharmaceutical companies in developing countries have allowed unethical drug testing to become a common and unopposed occurrence in the South. The ability of researchers to conduct unethical drug trials in developing countries is symptomatic of a greater calamity—the deep and dividing inequality between the countries of North and South that prescribes a monetary value to human life. Furthermore, as the director of marketing for Johnson & Johnson mentioned, foreign patients with little exposure to medicines “offer a blank slate for experimentation” as their medical deprivation makes for a scientifically sound study. This in turn speeds the journey of new drugs to the marketplace of the developed world.

In this brief account, two cases of unethical drug trials conducted in the developing countries will be discussed. These examples relate to the disturbing issue of AIDS trials in the South focusing on the vertical mother-to-child HIV transmission. As these are merely a few drops in the vast Turbo-Capitalist Ocean, they allow, at most, for a narrow glimpse into the blight of trials by fire. Whether these archetypal studies have been motivated by wealth and scientific advancement or by humanitarian concerns, all have been in breach of ethical and moral principles. Furthermore, the anthropological concept of ethical imperialism (i.e. the imposition of Western bioethical standards upon foreign cultures) must be explored from a culturally interpretive as well as a critical politico-economic perspective. In addition, through a discussion of the recent changes made to international ethical guidelines, the very culturally-constructed dichotomy of public vs. private sectors, both equally guilty of this breach of moral conduct, will be contested. The interconnectedness of these two sectors will be examined.

Ethics of Drug Trials 101

Most international guidelines governing the ethics of medical research were developed after World War II to safeguard the participants from exploitation and atrocities such as those committed by Nazi doctors in concentration camps. The Nuremberg war crimes tribunal laid down a series of ethical standards guiding the practice of medical research. Subsequent ethical guidelines built upon the principles rooted in Nuremberg Code. The Belmont Report identified the three pillars of medical ethics: “respect for persons”, that is recognizing individuals as autonomous and voluntary decision-makers possessed of free will; “beneficence and non-maleficence” that is, ensuring the safety of the individuals by first causing no harm either through acts of commission or omission and by acting in the individual patient’s best interest, an axiomatic concept in medicine; and “distributive justice”, that is ensuring that the patients benefit from participating in the research and that care is equitably distributed among groups and individuals during and after the trials.

A critical extension of the principle of “respect for persons” and autonomy is the concept of informed consent. This ensures that the individual participating in the clinical trial is making the decision based on free will without coercion or outside influence, understands the risks involved, is aware of any potential benefits and their right to back out at any time. In the First World, it is vital that investigators obtain valid informed consent before patients take part in a trial. The repercussions for those who fail to uphold ethical principles in the North are stringent and can readily involve legal action. From an anthropological perspective, the above guidelines clearly reflect the individualistic ethos of Europe and North America, and thus constitute “ethnocentrism” when imposed upon other societies. Although, the pillars of beneficence, non-maleficence, and justice may be deemed intuitive to the healer-patient relationship universally, problems are to be found with respect to the principle of autonomy and informed consent. This will be briefly discussed in the section entitled “Ethical Imperialism”.
However, double-standards exist even with respect to the above principles when research is conducted in the Third World. We will see that there are two tiers in the medical research system: one that exists for the North, and one for the South. Note that the discussed trials are considered part of phase III, the final phase, as they implicate the greatest number of participants and assess the efficiency of the drug compared to a control group, either a placebo (a medically inactive substance) or current 'gold-standard' treatment regimens (p.65). These trials may be randomized (i.e. the experimental drug and control are assigned randomly to the subjects) and/or double-blinded (i.e. neither the physician nor the patients are aware of the identities of placebo and drug recipients) (p.70).

For Science
“In all your getting, get Understanding.”
Book of Proverbs, Chapter 4, Verse 7

AIDS trials in the developing world: Tuskegee Renewed
A series of articles in the year 2000 entitled the “Body Hunters”, published in the Washington Post, were among the first to blow the whistle, revealing several unethical research practices in developing countries. This commendable journalistic effort by the Washington Post exposed the breach of moral codes in the work of several investigators conducting AIDS studies in Thailand.3

Sponsored by the US Army, the experiments aimed to determine the natural course of vertical transmission of HIV from sero-positive mothers to infants through “monitoring”. This approach did not call for the provision of the effective antiretroviral drug AZT to any of the participants. The trial was approved by the National Institute of Health (NIH) before the widespread availability of AZT. A similar trial was being conducted simultaneously by researchers from Harvard University who felt that it would be unethical not to provide participants in the control group with AZT. Note that AZT had proven potent in diminishing the incidence of HIV vertical transmission in the US and France, and had been pronounced the standard treatment in the North prior to the Thai studies. The army researchers refused to allot some of their grant funding (a modest $1 million) to purchase AZT (cost of $15000). Not wanting to cooperate with the Harvard team (the Army believed that cooperating with the Harvard team would have implied “surrendering the site”), army investigators decided to wait for the Thai government to provide the medication. The Army argued that AZT was not deemed standard therapy in Thailand without Thai government’s approval. Needless to say, the provision of AZT would have clouded the scientific validity of the study as it would have interfered with the “natural” transmission of HIV. 37 babies born to the HIV positive mothers, who could have been spared in the duration of study, contracted the virus. Thai government approved AZT several months prior to the conclusion of the above study; however the provision of AZT was stalled through bureaucratic means, lest the scientific purity of the research be corrupted by the medication.9 In response to criticism from several ethic review boards, the team leader expressed his disappointment with the boards as “their deliberations seem often devoid of the larger view of advancing medical science for public good as opposed to the individual.”10

It appears that on the path to scientific glory, the prosperous North contributes genius, hypotheses, and Capital while the South provides vast numbers of chemically-uncorrupted patients. In this Global Village, we live in a climate of belief in which the safety of persons, particularly those of darker hues and lower socioeconomic status, is considered inferior to the health of the whiter and more prosperous population. The Western tradition of intellectual endeavor and information-gathering, in brief the realm of the intelligentsia, is believed to be superior to the traditional subsistence-driven labour (i.e. the “primitive endeavor”). The health of the South is deemed secondary to the advancement of science. With this bitter reality in mind, I ask the reader to compare the case discussed above with the infamous Tuskegee experiment below. Have we truly progressed?

The Tuskegee experiments were conducted by the US government on black farm workers in the US from 1932 to 1972.10 The investigators’ prerogative was to monitor the natural course of syphilis infection without the provision of treatment. Although Penicillin, still the most effective therapy for syphilis, became available in 1943, the investigators did not provide the drug to their patients after its introduction, and in fact actively dissuaded them from pursuing the treatment option for 30 years.10 This was done so that the treatment “would not cloud the scientific validity” of the study of “Untreated Syphilis in the Negro Male”. The Tuskegee experiments were stopped due to public outrage after front-page reports in the New York Times exposed this inherently racist, demoralizing, and dehumanizing medicine. In 1997, President Clinton offered formal apologies to the survivors of these experiments and called the studies “blight on our record.”10

The striking parallels between Tuskegee and the Thai study are disturbingly clear. The very unequal distribution of power in the doctor-patient interactions is facilitated by the lower socioeconomic status of participants of color, scientific egoism, and a medical orthodoxy with a racist past. This past is perpetuated in the present. Tuskegee may never be repeated in the USA again, yet this blight on North’s record continues. Tuskegee has been exported to the developing world.

For Humanity
Randomized Placebo-Controlled AZT Trials in the South
Another disturbing series of trials conducted in 1996 under the auspices of the National Institute of Health (NIH) and Centers for Disease Control (CDC) in several Asian and African countries sought to assess the efficacy of shorter courses of AZT in preventing mother-child transmission of HIV among 17000 HIV-positive women.3 A longer regimen of AZT had already been proven effective in the USA and France, and the researchers had decided to devise a shorter, simpler, and cheaper regimen that would be suitable for breast-feeding women in resource-poor countries. The endeavor was proclaimed a “humanitarian venture.”11 Of the two groups of female participants, one received AZT, but in a shorter course, for fewer weeks, and was administered doses less frequently than was the standard in the US regimen. The newborns would receive no AZT, unlike American infants who had received
AZT for six weeks after birth. The other group would receive a placebo implying that the children born to the sero-positive mothers of the placebo group would contract the virus. The CDC & NIH defended their methods by asserting that a placebo-controlled trial (PCT) offered the most resource-efficient and expeditious method of obtaining scientifically rigorous results, hence speeding the delivery of the regimen to the patients of the developing world. They further argued that the researchers were not required to provide the best medical care possible (i.e. the longer AZT regimen of the North) since such care was not the standard of the developing countries. The use of placebos, therefore, did not deny patients the care to which they would otherwise have access. Kottow argued against the double-standards by pointing out that even in the North, there are many ‘pockets’ of impoverished people with little or no access to health care. Even though these groups resemble populations of the South, researchers are required under ethical codes to offer the best possible medical care to them. The same must be applied to people of the South.

The pro-placebo arguments were further criticized by Drs. Lurie and Wolfe of Public Citizen, a US-based public watchdog (pp.853-856). They asserted that in the South, patients cannot benefit from the advanced regimens due to economic constraints imposed by the high prices set by the pharmaceutical companies. They further noted that such unavailability is certainly not because the Third World’s medical authorities have assessed the regimens to be ineffective and hence refused to approve them as standard of care. Since researchers often receive free samples of the drugs they are testing from the manufacturers, they are denying patients the chance to receive the care which is at their disposal. They further contended that equivalency trials, which utilize the best-known regimen compared against another plan, would provide data as valid, if not more accurate, than the PCT.

In fact, such an alternative was explored simultaneously in a study undertaken by Harvard University researchers who examined how different doses of AZT influenced transmission rates. Notice that the equivalency study received funding from the NIH only after a bitter battle was fought between Harvard scientists (who contended that a placebo-controlled trial was unethical when an effective treatment was available) and the NIH who emphasized the use of placebos for scientific accuracy. In essence, this alternative would pose the question “Is this treatment as good as, or nearly as good as, the accepted standard treatment?” compared to the placebo question “Is this treatment better than nothing?” I contend that it is unethical to even ask whether X is better than nothing when one knows that a Y exists that is very much better than nothing.

The proponents of PCT asserted that the longer AZT regimen could not be implemented in the developing world where women are often malnourished, anemic, and harboring infections other than HIV. They noted that the longer AZT regimen requires that newborns be bottle-fed, an obstacle in the South where breastfeeding is the norm. In fact, they accused their critics of “ethical imperialism” since they demanded that the ethical standards which evolved in the North be applied without flexibility to research universally. Varmus and Satcher, the heads of public institutes of NIH and CDC respectively, called the position taken by the critics “absurd” and sarcastically claimed that implementation of the equivalency studies would require making radical changes to the prenatal care programs in these countries: cleaning up the water supply, and stocking up on ample amounts of baby formula and food for the mothers. They further threatened that the drug donors in the pharmaceutical industry would not back these studies, let alone the continued post-trial treatment from which they stand to gain no profit.

I concur that the practicalities of providing the Northern regimen in the Southern countries with a poorly developed health infrastructure are daunting. For this very reason, I argue that the conduct of such trials in the countries of South cannot be proclaimed “humanitarian” or ethical if the conditions and goals of the studies are not adapted to the local health infrastructures of the communities. US scientists change these communities merely by setting up drug trials, as they temporarily introduce higher levels of care and thus are bound by the pillar of distributive justice to help the communities after the trials end. If the regimen proves effective, the investigators must ensure that the local governments take steps towards implementing the prevention program. Otherwise, the women who received placebo have been doubly harmed.

Needless to say, the beneficent North also benefits from these “humanitarian” trials. If the tested regimen is effective, the corporations reap financial benefits, and if the regimen is of little value, individuals in the North will not be subjected to the potential risks of the trials.

On the ethical front, I contend that one cannot morally conduct an HIV test on an expectant mother, fully disclose the positive status to the patient who has no access to proper care except for what the scientists may provide, and yet refuse to provide at least some care for the mother and the unborn baby. The women and their unborn children were harmed by not receiving the available treatment. This was a clear violation of the pillars of beneficence and non-maleficia. Yet I believe that the matter is further complicated by the fact that even the women who received the prophylactic treatment did not benefit directly - only their future offspring did. According to the pillar of distributive justice, the women themselves must also receive treatments for their disease. One wonders what will become of the children who are saved by AZT therapy. When their mothers succumb to AIDS, will they become part of the burgeoning population of AIDS orphans with limited survival prospects?

In the above case study, the gross inequity in resources, particularly concerning health care provision, which exists between the affluent industrialized nations and the developing countries, is once again apparent. The controversy has demonstrated the wanting prenatal care and high infant mortality rates of the South. It has revealed the markedly disparate rates of HIV-infected pregnant women in the North versus those in the South. Furthermore, it has highlighted the vulnerability of women in certain cultures, and the lack of choices available to them in terms of contraception,
protection from HIV infection, and infant feeding. On a more philosophical note, the debate has manifested the tension between the modernist ethics of science, grounded in an orthodox “mechanistic-reductionist paradigm” and an ethic based on a more “humanistic, post-modern paradigm.”13 The former is apparent in the PCT which strives to create order and predictability in the entropic world of complexity and uncertainty. Although the PCT may provide us with “hard unbiased” evidence,14 it also sacrifices the human concerns, needs, preferences, and relationships. In doing so, it demolishes the variables that compel humans to act as moral agents to one another. Such rigid scientific adherence to objectivity necessitates even more robust ethical safeguards in order to protect the vulnerable from exploitation.16 The post-modern ethic, on the other hand, allows for the human voice to be heard, and embraces the inherent uncertainty of science. I believe that adherence to scientific orthodoxy must not be used as justification to evade the duty of care, the core pillar of medicine. By evading this duty, the North sets dangerous precedents and paves the way to further negligence of “reverence for life” on a global scale.

A Note on Ethical Imperialism

As discussed above, the public and private conductors of clinical trials accused their critics of “Ethical Imperialism” for imposing Western ethical guidelines on subjects of diverse backgrounds. In truth, these guidelines reflect the cultural beliefs of the Western scholars who composed them, and the rigid application of such ethical views to diverse cultural settings without respecting the subtle differences would constitute ethical imperialism. Of particular significance is the challenge faced when implementing the pillar of respect for persons or autonomy, the embodiment of the Western individualistic ethos, in settings where personal choice is limited.17 For example, in some central African cultures the concept of personhood is defined by the dynamic system of social relationships, both of kinship and of community, and is constructed by one’s village, tribe, or social group.13 It may be necessary in such cases to obtain permission from community leaders or the patient’s spouse, in addition to patient’s own consent. This could give rise to the problem of coercion: a pregnant woman in an authoritarian male-dominated culture might feel obliged to consent when asked by a male leader or spouse. Coercion may also be economic in nature: in the South, where decent health care often does not exist, the subjects may feel that participation in a trial is their only opportunity to obtain treatment.17 Furthermore, there exists an asymmetry of knowledge and authority between the researchers and their subjects: in a survey of 64 parents whose children were involved in a trial, Hirth and Thong18 found that the majority believed that trials conducted in a hospital were of no or low risks, many felt that the strict procedure of informed consent was unnecessary as they would do what the doctor advised, and only a few were aware of their right to withdraw their child unconditionally from the trial at any time. Clearly, considering the current dynamics of doctor-patient relationship, consent given cannot be competent, informed or voluntary, especially in the developing world where diverse confounding factors abound. However, these obstacles must not be used as excuses to abandon ethical standards. On the contrary, the researchers must respect the core human dignity of their vulnerable subjects by placing more emphasis on the pillars of beneficence, non-maleficence, and distributive justice.13 Failing to do so would constitute exploitation and true unethical imperialism. I believe that there must be a core of human rights that we would wish to see honored universally, despite local variations in their superficial aspects. As Baker16 argues, “International bioethics can be rationally reconstructed as a negotiated moral order that respects culturally and individually defined areas of nonnegotiability.”

From Finland with Love: The Marriage of Public and Private Interests

The most widely accepted international ethical guideline for medical research is the regularly updated Helsinki Declaration. This was adopted in 1964, by the World Medical Association, a body representing physicians worldwide.19 In October 2000, the fifth revision of the declaration was released to address the controversial issues raised following the media coverage of the trials conducted in the South. The WMA recommendations included: “prohibiting the use of placebos in situations of local scarcity if the ‘best current method’ exists elsewhere; only conducting research in developing countries when that research is likely to benefit the local population and is culturally appropriate; provision of the best possible treatment to all participants; and finally, ensuring that the participants have fair access to post-trial treatment”. A debate, ignited by US-based pharmaceutical giants (backed by the FDA, NIH, and CDC) led to the addition of a “note of clarification” to the declaration.20 The footnote to paragraph 29 aimed to introduce ambiguity by attenuating the strong and strict wording of the 2000 revision. The convoluted amendment allowed for placebo-controlled trials, in light of the availability of proven therapy, “where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic and therapeutic method”.19

Having had such success with the footnote, pharmaceutical giants and their public patrons then targeted the distributive justice clause of paragraph 30. This clause ensures that at the conclusion of a study, all patients receive the best proven therapy identified by the study.

The newly suggested wording, born out of classical cost-benefit analysis, proposes that the doctors “should make every effort to ensure” patients receive any “available” treatment, but they are not obligated to provide the best proven therapy21 (p.2). In a statement, the working group behind the suggested amendments contended that “Neither sponsors nor researchers can take responsibility for deficiencies resulting from political mistakes and global economic circumstances”21 (p.2). On a positive note, for the time being, the wording of paragraph 30 has been left unaltered; however a note of “clarification” has been added, casting more shadow upon the message than light. The futile 2004 clarification “reaffirms its position that it is necessary during the study planning process to identify and describe in the study protocol, post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care...”.22 This contains similar elements of dilution of the paragraph 29’s amendment.
The cooperation between the pharmaceutical giants and public institutes of the North (WMA, NIH, and CDC) to modify ethical guidelines in order to pave the way to further exploitation of the South shatters the culturally constructed myth of the dichotomy between “private” and “public” that is enrenched in the Northern psyche. Often, we tend to demonize the “private” sector for its ‘cold-hearted capitalist’ agenda, yet we fail to address the wrongdoings of the state on the premise that it is rooted in the Utopian democratic principles of rule. Hence the state is incapable, in our mind, of violating the moral codes at the expense of the subjects it is meant to protect. McElhinny23 (p.128) argues that this linguistic dichotomy distorts our understanding of the deep interactions between the two ideological labels. Thus the interpenetration of the two spheres is obscured by the values and assumptions contained in the rhetoric. The marriage of “public” and “private” interests often brings marked consequences for the least privileged. In the context of this discussion, it paves the way to further exploitation of the South by the North.

Conclusions

Clinical research is vital if biomedicine is to continue providing us with new treatments. Turbo-Capitalism seems equally embedded in this endeavor, with the North producing and harvesting much of the world’s economic prosperity. The two spheres of private and public endeavor intersect in the case of drug trials. Big Pharma has a vested interest in creating new, profitable therapies. In addition, doctors and patients lobby for life-saving medication. Private and public researchers have been equally guilty of disregarding moral codes when conducting clinical trials in the South. Depending on the case, this has been due either to their eternal quest for speed and efficiency, to their unquenchable thirst for new knowledge, or, occasionally, to humanitarian incentives. Globalization, underpinned by a market “ethics”, often preferentially harms the worst off. However, a global ethics has the potential to remedy the balance and promote greater equity. Such an ethic must be underpinned by the principle of distributive justice on a global scale and act within the framework of fundamental human rights: the right to live with dignity, respect and health. Such a construct acknowledges cultural boundaries and distinctions, reverages the social “nonnegotiable”, and strives to build cross-cultural bridges upon the “negotiable”.

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References