“Let Them Get Infected! You Just Need To See A Difference!”

Race to the Ethical Bottom: Regulation of Biomedical Research in Developing Countries

“Always recognize that human individuals are ends in themselves; do not use them as a means to another end,” declared philosopher Immanuel Kant in his *Groundwork of the Metaphysic of Morals*. Human rights activists and physicians dedicated to social justice have often repeated this maxim in an effort to open the eyes and ears of policymakers to the perils of poorly regulated biomedical research projects. Yet abuses occur far too often as morally questionable clinical trials proceed without proper oversight and the lives of the poor are tossed into a lottery for the benefit of the rich and the bank accounts of global pharmaceutical corporations. As Western biomedical science has progressed, the double-blind randomized clinical trial has evolved into the gold standard for all drug research and development of novel therapies. For numerous reasons, these studies have increasingly relocated to the developing world in recent years and begun to utilize patient cohorts comprised of the international destitute sick. To date, the best means of ensuring that trials meet international ethical standards has been reliance on the World Medical Association’s Declaration of Helsinki, a thirty-five clause regulatory document drafted and periodically revised by a coalition of eighty-five national medical associations (Lurie 2005, 1119). In an alarming reversal of policy in October 2008, the United States Food and Drug Association officially discontinued its adherence to the guidelines laid out in the Declaration, instead substituting the International Conference on Harmonization’s Guideline for Good Clinical Practice (Kimmelman 2009, 13). In stark contrast to the Declaration of Helsinki, the Guideline for
Good Clinical Practice represents the voices of only three parties – the United States, the European Union, and Japan (Lurie 2005, 1119). Several key omissions on the part of the GGCP constitute a disturbing and misguided departure from the global consensus on ethical standards for international biomedical research, raising legitimate concerns about the rise of a new ethically relativistic and profit-driven biomedical neocolonialism. A critical examination of the historical contexts surrounding international clinical trials and the motives behind the FDA’s decision is warranted to determine what ramifications this new standard will have for development and for the welfare of the world’s destitute sick.

In order to construct an informed argument about the merit of existing regulations, it is necessary to understand the requirements that must be met for clinical research to be classified as ethical. According to bioethicist Ezekiel Emanuel, seven key precepts provide the framework for evaluating the ethical nature of a study. An acceptable trial must demonstrate the following:

“(1) Value – enhancement of health or knowledge must be derived from the research; (2) scientific validity – the research must be methodologically rigorous; (3) fair subject selection – scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion criteria for individual subjects; (4) favorable risk-benefit ratio – within the context of standardized clinical practice and the research protocol, risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for
society must outweigh the risks; (5) independent review – unaffiliated individuals must review the research and approve, amend, or terminate it; (6) informed consent – individuals should be informed about the research and provide their voluntary consent; and (7) respect for enrolled subjects – subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored” (Emanuel 2000, 2701).

Each requirement is inherently universal yet also adaptable to an extent based upon the political economic context of the research setting. Studies conducted in an international setting must necessarily focus especially on the conditions of fair subject selection, favorable risk-benefit ratio, and informed consent in order to successfully and equitably negotiate the challenges of cross-cultural translations. Translation in this case refers not only to linguistic barriers and exchanges but also to varying underlying socio-cultural structures. Indeed, the notion of a randomized clinical trial is itself a Western cultural construction. The complications that arise when attempting to reconcile contrasting understandings of fairness, randomness, and risk as well as the issues surrounding informed consent will be explored later. It is clear that any attempt to regulate cross-cultural research will result in one having many balls in the air at once.

The consequences of insufficient oversight for biomedical research are as well-documented as they are appalling. The twentieth century witnessed such atrocities as Nazi Germany’s human “experiments,” the infamous Tuskegee Syphilis Study, and the Willowbrook State School Hepatitis Study. Most students are familiar today with the
blatant disregard that Hitler’s scientists showed for human dignity during the Holocaust, but the latter two examples are dark marks on our own nation’s history. In 1932, the United States Public Health Service began a study on the natural history of syphilis in Tuskegee, Alabama. Four hundred infected poor African American sharecroppers were recruited as a cohort; each was led to believe that his disease would be treated. A permanent cure, penicillin, was discovered in 1947 and yet the study continued through 1972 as the inexpensive drug was withheld so that researchers might fulfill their initial curiosities about the disease’s spread and lengthy progression to death. The infamous project is a “shameful reminder of a not so distant past, when race and low socioeconomic status of human subjects made a host of ethical violations – concerning everything from informed consent to lack of treatment with standardized treatment regimens – acceptable in the quest for scientific truth” (Farmer 2004, 243). Contrasting with the cruel passivity of the Tuskegee investigators was the highly controversial mandatory inoculation of students at New York’s Willowbrook State School with live hepatitis A virus in the early 1960s. Physically disabled and mentally handicapped children were coerced into drinking a mixture containing infected human feces and subsequently treated with experimental globulin compounds (Shah 2006, 73).

In order to prevent such unequivocally unethical occurrences, the World Medical Association drafted the Declaration of Helsinki in 1964. Despite the comprehensiveness of the Declaration’s regulatory framework, many questionable studies have since managed to slip through the cracks. Two glaring examples of the repercussions of regulatory failure occurring in the last two decades include a randomized clinical trial which examined known and putative HIV risk factors in Uganda (Farmer 2004, 243) and
the failure to obtain informed consent for radically experimental treatment of a bacterial meningitis outbreak in Nigeria (Abdullahi v. Pfizer, Inc., 4). In the former instance, an American research committee tracked the unchecked spread of HIV between previously serodiscordant couples in Uganda to astutely conclude that “viral load is the chief predictor of the risk of heterosexual transmission of HIV” while calling for further research to “develop cost-effective prevention strategies to benefit everyone, especially those who participated in the research” (Quinn 2000, 927). It certainly does not require a doctorate in epidemiology to realize that preventative measures will do little for the seropositive spouses of study subjects who were not even informed that their partners harbored the virus, much less provided with any semblance of preventative measures, before it was too late (Farmer 2004, 243). In the Nigerian case, the American pharmaceutical company Pfizer took advantage of a bacterial meningitis epidemic in Kano, Nigeria to conduct a secretive clinical trial on their “new, untested, and unproven” antibiotic Trovan. Parents of infected children were not informed of the experimental nature of the treatment or of the fact that they could refuse it and seek free conventional treatment at the same location. As a result of the study, eleven children died and a number of others were paralyzed or blinded (Abdullahi v. Pfizer, Inc., 4). In each case, existing regulations proved insufficient and the deceived poor were essentially sacrificed upon the altar of biomedical progress. Not one day of jail time was served by any of the American investigators involved.

When such examples of abuse have come to light and inevitably sparked international debate, the investigators responsible have almost invariably adopted the same position as the “innocent bystander.” Nazi prisoners were going to be executed by
the army anyway, black farmers could never have afforded treatment for syphilis, handicapped students would have come into contact with infected feces on their own, Ugandan couples never have had access to birth control or public health education before, and the Nigerian patients would have just died from the next epidemic when there was no impromptu Pfizer clinic (Shah 2006, 77). These types of rationalizations are morally reprehensible and their “greater good” agenda rings hollow; yet it is precisely this sort of profiteering from the plights of the world’s poor that has led to the widely promoted globalization of clinical research. The examples from Uganda and Nigeria demonstrate the very real need for more international cooperation for research ethics.

Medical anthropologist and physician Jim Yong Kim refers to this continuing trend of exploitation of “the other” as a type of “global Tuskegee experiment” (Farmer 1999, 35). The negative externalities of biomedical progress are becoming increasingly concentrated among the world’s destitute sick. FDA-regulated investigator activity has spiked 15 percent per year since 2002 while the same indicator has decreased by 5.5 percent in the United States (Glickman 2009, 816). What are the driving forces behind this shift? Certainly it parallels the globalization of other sectors of society, but why has the exodus occurred so drastically over so short a time period? The truth is that the FDA’s abandonment of the Declaration of Helsinki is but the cherry on top – the document’s most important provisions have gone largely unenforced for some time. The debate over this issue centers itself around three main possibilities: the potential for procedural cost savings, a shortened timeline for testing, and the increasingly bureaucratic regulatory environment in industrialized nations compared to less burdensome ones in developing nations (Glickman 2009, 818).
A critical examination of each claim, however, will quickly reveal that everything boils down to the bottom line. Initial production costs can be drastically reduced by utilizing laborers willing to work for a significantly lower wage than counterparts in industrialized nations. It does not matter if the person in question is a seamstress in a clothing factory or a medical research study coordinator – if they are willing to work for one-tenth of the standard American fee then someone will most likely hire them.

Secondly, contracted timelines and less oversight of clinical trials for development research can massively downsize the cost of getting a new drug to market. Simply put, less waiting and fewer tests means more profit – in a world driven by the neoliberal free-market that means everything (Glickman 2009, 817).

This race for the biggest bottom line gives way to a race to the bottom of ethical standards, and in the current system there is not much that the losers can do about it. Essentially, the structural inequalities that define our world serve as the foundation for the growth of international biomedical research. During a controversial exchange that resulted in the resignation of numerous staff writers, the editor of the *New England Journal of Medicine* asserted: “The fact remains that many studies are done in the Third World that simply could not be done in the countries sponsoring the work. Clinical trials have become a big business, with many of the same imperatives. To survive, it is necessary to get the work done as quickly as possible, with a minimum of obstacles. When these considerations prevail, it seems as if we have not come very far from Tuskegee after all” (Angell 1997, 849). As long as it is possible to step over cumbersome regulations at home and make one’s own rules in an international setting, the race to the ethical bottom is likely to continue.
As standards plummet, several issues stand out as potentially capable of undermining even studies with truly ethical intentions. These include the threats of inadequate oversight, a marked decline in transparency, and the possibilities for abuse as outlined earlier. Foremost is the problem of securing appropriate oversight for trials and the interactions that lead up to them. Without strong legislation to serve as a guide, new studies in areas unfamiliar with ethical biomedical research are in danger of a number of translational pitfalls. As previously discussed, cross-cultural studies are by nature the intersection of fundamentally different approaches to an idea or a problem. As such, an American team seeking to conduct a randomized clinical trial in a non-Western developing country might encounter potential co-researchers and participants with no understanding of the placebo concept and perhaps a very different idea about what constitutes successful research.

A recent study in rural Tibet came across these stumbling blocks in their attempt to quantitatively compare the efficacy of a biomedical drug and a traditional Tibetan drug for the control of postpartum hemorrhaging. Most Tibetans believe, for example, that every substance in the universe has some level of medicinal value because it is comprised of some combination of the five elements that form our own bodies. It is thus impossible to provide a true placebo for such a study. In addition, the issue of informed consent posed a major ethical dilemma in that the Tibetan understandings of randomization, blinding, risk disclosure, and actual consent were fundamentally different from those of the American researchers. Most participants were not familiar with the idea of an equal chance between two outcomes, and the Western metaphor of “flipping a coin” had no cultural resonance. The necessity of blinding caused many patients to feel as though they
were being intentionally duped. To speak to an expectant mother about the possibility of bleeding to death is likely to cause an imbalance in her internal humors, thus making the very risk more likely by suggestion. Lastly, officially securing consent posed yet another problem because a number of participants were illiterate; one researcher’s suggestion of recording thumbprints failed because participants associated print-taking with the beginning of the reviled Cultural Revolution. Fortunately the team in question was comprised of both Americans and their Tibetan counterparts (both traditional Tibetan amchis and biomedically trained physicians) and they were thus able to construct culturally resonant concepts for each of the clinical trial’s requirements. In addition, they were able to create Tibet’s first official institutional review board by forming a coalition of health workers and researchers from a number of Tibetan institutions in the capital city of Lhasa (Adams 2005, 278-80). Had this particular study not been truly cross-cultural in the sense that it fully engaged all stakeholders, serious ethical issues would have arisen regarding miscommunications around consent.

Another serious consequence that will inevitably result from the lowering of ethical standards for global biomedical research is the loss of transparency. The Declaration of Helsinki mandates that research teams disclose the sponsor of their project’s funding and declare any conflicts of interest, publicly disclose the experimental design in the study registry, and agree to publish the trial’s results accurately even if they prove negative (Kimmelman 2009, 14). Unpublished information does not enter the collective scientific knowledge base and is thus a failure on all counts because no lessons can be learned from that which did not occur (Vastag 2000, 2985).
With so much riding on the strength of international regulatory networks, what should be the guiding principles steering research in developing countries? Three basic interrelated tenets emerge as the pillars of truly ethical policy. Cross-cultural clinical trials must not exploit vulnerable populations, must be limited to goals that are most responsive to the host country’s health needs, and must be bound by the same standards as similar studies in the developed world (Shapiro 2001, 139).

It is a reality that our world is defined by structural systems of injustice and political economic trends of inequality; all efforts must then be made to ensure that clinical trials intended to support development do not exploit those without a voice. Vulnerability encompasses all societal factors that reduce one’s entitlements to universal human rights such as education and health care as well as the ability to generally protect one’s own interest (Eckenwiler 2008, 765). Study cohorts should be a diverse cross-section of society, distributing the risk-benefit ratio as equitably as possible and avoiding the concentration of negative externalities among any single population: “Participants should not be selected because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied” (London 2008, 82). This stipulation requires that researchers and physicians “not only place the well-being of research subjects about the supposed benefits to science and society but also that they declare ‘I will not permit considerations of religion, nationality, race, party politics, or social standing to intervene between my duty and my patient’” (Farmer 2004, 247).

A growing chorus of voices in the research and human rights sectors is calling for much closer matching of study goals and host country needs. The primary purpose of
conducting biomedical research in developing countries, asserts Farmer, should be “to do a better job of bringing the fruits of science and public health to the poorest communities…” for host populations to share fairly in the benefits and not only in “the fallouts and placebos of our scientific and economic progress” (Farmer 2004, 250). The world’s poor have not been sitting passively by as the globe becomes more and more interconnected; indeed, people in developing countries are becoming more aware of the inequalities of the distribution of disease burdens. The “90/10 gap” is truly appalling: “Below 10 percent of the world’s health care expenditures are devoted to diseases that account for 90 percent of the global burden of disease” (Shapiro 2001, 141). This unacceptable dichotomy represents a regulatory failure to promote human rights and ensure fair benefits from research. It is a sharp rebuke to the neoliberal camp that endorses trials that “might aim to develop interventions that offer people in developing countries with particular diseases the best chance of a sustainable cure, and claims that such innovations will eventually reach them. When over 90 percent of unnecessary deaths in poor countries occur from causes for which effective treatments already exist, the slow pace at which the trickle-down approach proceeds is painfully evident” (London 2008, 84). The destitute sick have been silent long enough; they have earned a voice and it is long since time that the research community pays heed. A drastic resocialization of the primary motivations for clinical trials in developing countries is in order: “We must leave behind the terra firma of double-blinded, placebo-controlled studies, of cost-effectiveness, and of sustainability. Indeed, many of these concepts end up looking more like strategies for managing, rather than challenging, inequality” (Farmer 2005, 226).
Altering the motivations for clinical research alone will do little without a parallel readjustment of the accepted means. For the same reasons that the aims of biomedical clinical research studies warrant radical reformulation, so too do the standards by which those trials are conducted. Trials conducted in Uganda, Nigeria, or Tibet should not be held to lower ethical standards than trials conducted in France, Australia, or the United States.

One of the prime areas of contention around this assertion is the debate over the ethics of using placebo controls for studies in developing countries. Indeed, the most significant reason for the FDA’s decision to reject the Declaration of Helsinki is its wording regarding the restricted use of a placebo. It comes down to the question of whether it makes more sense to compare the drug under examination to a completely inert substance or to evaluate it alongside the most effective alternative. Those who promote the status quo and support the FDA in its recent actions cite “local standards of care,” attempting to argue that placebo use is justified in developing countries because the most effective alternative would not normally be available (Farmer 2004, 247). They claim that “denying treatment when treatment is not available to the general population (but may be available in some populations) is morally acceptable” (Resnik 1998, 302). This is an old argument, and it has long been accepted as the gold standard.

The World Medical Association’s recent steps back from that standard constitute a break with the reactionary and the parochial double standard that has been tolerated for too long. Many clinical trials conducted in the United States under the watchful manipulation of the FDA do not use placebos, instead opting for what is termed an active control. Essentially, an active-control research project is a trial that compares the study
drug to the best prophylactic, diagnostic, and therapeutic methods currently available. This appears more than logical and fair to patients in the United States; why then is it so objectionable to large numbers of researchers and bioethicists? “Indeed, in some divisions of the FDA, active-controlled trials are commonly used [in the United States] as the basis for drug approval. The field of oncology has for years eschewed pure placebo controls in trials of treatments of cancers for which effective therapy exists. Similarly, drugs for the treatment of pelvic inflammatory disease, bacterial pneumonia, and most other bacterial infections would never be tested against a placebo…. While these ethical concerns in industrialized nations, whatever they were, seemed to resonate with the sponsors, providing second-rate treatment to desperately ill infants in developing countries simply because they were poor apparently did not” (Lavery 2007, 161).

Once again, it boils down to the bottom line. In the capitalist society that we have constructed, it is all too easy to give in to the temptation the dollar when weighing the options surrounding an issue tied to development. When the driving concern is money, why would one want to bother trying to demonstrate that a drug is better than the best existing treatment when it is possible to profit simply by proving that it is better than nothing? The Ugandan HIV case study described earlier provides a sobering look at the real motivations behind the FDA’s refusal to accept the active-control as the new standard:

“A few HIV researchers noticed the potential conflict-of-interest early on in the business of HIV prevention research. Investigators testing new HIV prevention methods would have a
built-in incentive to slack off on providing other protective methods to their subjects. When a group of HIV researchers pressed their colleagues in a 1994 paper to ensure that their test subjects were all armed with the best protective measures available, including counseling, free condoms, and sterile needles, the response was tepid at best. ‘Why would you do that?’ a senior scientist grilled one of the authors. ‘You’d be cutting off your nose to spite your face! Let them get infected! You just need to see a difference!’

There is an inherent perversity in controlled clinical trials, which is that by relying on the contrast between two groups treated differently, one group must suffer worse outcomes than the other. In HIV prevention trials that means that one group must suffer more HIV infections than the other. It also means that uninfected people must expose themselves to the virus. Subjects must venture into the ring with the lion, some equipped with armor, the others bare fleshed. It doesn’t behoove researchers to hand out shields and swords, though that might save their subjects – then the researchers could never determine whether the armor worked. The more stripped-down the subjects are, the more viciously the lion tears into them, the easier it is for scientists to quickly discern the value of their preventive tools.” (Shah 2006, 83).
Profit margins aside, this analytic framework is innately illogical. By comparing a promising new drug to the best existing treatment on the market, one is automatically creating competition – the heartbeat of the capitalist economy. Surely a double-blind randomized clinical trial can be successfully completed without the extreme depravation of a control group to compare to the study group? Why not equip every participant to have a chance against the lion, and then evaluate which armor worked better rather than whether it worked at all? Assuming that the test drug in question did prove more effective than the most effective alternative, would it not be in a position to make its developers and study organizers quite rich – and much more rapidly than it might take to qualitatively compare the two choices via two placebo-controlled trials?

Indeed, there is good reason to be skeptical of those who cling to the status quo by supporting the FDA in its rejection of the Declaration of Helsinki. The document chosen as a replacement, the International ICH’s Guideline for Good Clinical Practice “is more open to the use of placebos and does not mention conflicts of interest, the need to publish results, or post-trial access to care. The decision would seem to encourage pharmaceutical companies to cut ethical corners when working abroad” (Normile 2008, 516). Of course, to say nothing of the transparency requirements, the Declaration’s article that extends researchers’ responsibilities to patients beyond the duration of their project would prove problematic in that it becomes a chiefly financial concern. Requiring that participants continue to be assured treatment with the best prophylactic, diagnostic, and therapeutic methods identified by the study is expensive and cuts into profit margins; it is therefore portrayed as ethically objectionable (Lurie 2005, 1118).
The FDA defended its decision by claiming that several of the Declaration’s most recent amendments “are not consistent with American law, not subject to an American veto, and could create a confusing situation” (Normile 2008, 516). Again, this logic is inherently flawed. The GGCP does not claim to be an ethical code but rather a description of existing procedures in specific nations – it is not an aspirational document (Goodyear 2009, 1559). Its authors did not intend it and the Declaration of Helsinki to be seen as mutually exclusive. In addition, how can the FDA’s switch to a separate document be justified as reducing confusion in cross-cultural clinical trials when the majority of the world will adhere to a different standard than the United States? As previously discussed, enough issues of translation and comparison already abound in international biomedical research without the United States imposing a new ethical pluralism.

The Declaration of Helsinki is far from perfect – no one is arguing otherwise. Yet it is the best existing method of ensuring that trials meet international ethical standards. Often referred to as “the cornerstone of research ethics,” the Declaration takes into account the voices of eighty-five countries, and it is revised periodically so that the global community can debate its purpose and efficacy (Goodyear 2008, 2128). The Guideline for Good Clinical Practice, however, is accountable only to the most developed countries in the world. Its authors intended it to contribute to regulatory harmonization, not to articulate global ethical responsibilities (Kimmelman 2009, 13). Ignoring the voices of the developing countries that will serve as hosts when dictating overarching policy constitutes ethical imperialism. By rejecting the Declaration of Helsinki, the FDA shows
that it cares more about facilitating research than about protecting the rights of the destitute sick who are recruited as participants in the projects (Goodyear 2009, 1560).

It falls to the new United States administration to responsibly reevaluate the nation’s stance on research ethics. Rather than discard the world’s best tool for ethical regulation and replace it with an entirely unsuited document that can be manipulated, the FDA should open a serious discourse with the member states of the World Medical Association before other countries begin to follow the United States’ lead by abandoning the Declaration of Helsinki. This is not an issue that should be compromised on – the FDA is in need of regulatory reeducation after the past eight years of failed neoliberal policy. Equality of access via emphasis on active-controlled trials and post-study responsibility to patients is the only option for the world’s destitute sick because: “The poor, as we’ve learned, demand it. As a teacher, I’ve also learned that students become frustrated when confronted by the enormity of the problems before us. It’s hard not to give up. And yet solutions are within our grasp if we have sufficient vision and will to demand something better for the poor, wherever they live. In constructing an alternative vision, we will all be acting unreasonably – that is, without the certainty of success. Nonetheless, we are condemned to act” (Farmer 1999, 36).
Bibliography


