In recent years, the increasingly global nature of health research and the conduct of clinical trials involving human participants have highlighted a number of new ethical issues. This often happens when researchers or research sponsors from a developed country wish to conduct research in a developing country. The research in question might simply be one way of helping the host country address a public health problem, or it might reflect a research sponsor’s assessment that the foreign location is a more convenient or efficient—or less troublesome—site for conducting a particular clinical trial. In any case, as the pace and scope of international collaborative biomedical research have increased during the past decade, long-standing questions about the ethics of designing, conducting, and following up on clinical trials have reemerged. Some of these issues have begun to take center stage because of the concern that research conducted by scientists from more prosperous countries in poorer nations that are more affected by disease may, at times, be seen as imposing ethically inappropriate burdens on the host country and on those who participate in the research trials.\(^1\)

Argument from defenders of the trials are interrelated, but may be divided roughly into three categories. First, it is argued that significant differences in resources and health conditions between countries can alter the balance that must be struck between risks and benefits. In other words, a study may be acceptable in one country but not another because of differences in wealth or burdens of disease between the two. Second, the technical superiority of placebo-controlled methods is argued to have ethical implications. Faster answers are said to be possible with enrolment of fewer subjects. Finally, defenders attach importance to satisfaction of process requirements. For example, they highlight the support and participation of host country governments and the approval of ethics review committees in the host and sponsoring countries. Study subjects’ consent to participate is also highlighted, although critics have questioned whether this consent is truly “informed”.\(^2\)

There are good, bad and gray-zone reasons for conducting clinical trials in developing countries. What kind of reason is the rationale that a study methodology can be used that would be rejected, for ethical reasons, in developed countries? The answer is not as obvious as it seems. A textbook example of unethical research is the Tuskegee Study of Untreated Syphilis. In that study, which was sponsored by the U.S. Public Health Service and lasted from 1932 to 1972, 412 poor African-American men with untreated syphilis were followed and compared with 204 men free of the disease to determine the natural history of syphilis. Although there was no very good treatment available at the time the study began, the research continued even after penicillin became widely available and was known to be highly effective against syphilis. The study was not terminated until it came to the attention of a reporter and the outrage provoked by front-page stories in the Washington Star and New York Times embarrassed the Nixon administration into calling a halt to it. The ethical violations were multiple: Subjects did not provide informed consent (indeed, they were deliberately deceived); they were denied the best
known treatment; and the study was continued even after highly effective treatment became available. And what were the arguments in favor of the Tuskegee study? That these poor African-American men probably would not have been treated anyway, so the investigators were merely observing what would have happened if there was no study; and that the study was important. Ethical concern was even stood on its head when it was suggested that not only was the information valuable, but it was especially so for people like the subjects – an impoverished rural population with a very high rate of untreated syphilis. The only lament seemed to be that many of the subjects inadvertently received treatment by other doctors.  

This leads to the discussion of ongoing trials in the Third World of regimens to prevent the vertical transmission of human immunodeficiency virus (HIV) infection. All except one of the trials employ placebo-treated control groups, despite the fact that Zidovudine has already been clearly shown to cut the rate of vertical transmission greatly and is now recommended in the United States for all HIV-infected pregnant women. The justifications are reminiscent of those for the Tuskegee study: Women in the Third World would not receive antiretroviral treatment anyway, so the investigators are simply observing what would happen to the subjects’ infants if there were no study. And a placebo-controlled study is the fastest, most efficient way to obtain unambiguous information that will be of greatest value in the Third World. Thus, in response to protests from a lot of people to the secretary of Health and Human Services, the directors of the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) – the organizations sponsoring the studies – argued, “It is an unfortunate fact that the current standard of perinatal care for the HIV-infected pregnant women in the sites of the studies does not include any HIV prophylactic intervention at all,” and the inclusion of placebo controls “will result in the most rapid, accurate, and reliable answer to the question of the value of the intervention being studied compared to the local standard of care.”

There were reports of another clinical trial in Uganda of various regimens of prophylaxis against tuberculosis in HIV-infected adults, most of whom had positive tuberculin skin tests. This study, too, employed a placebo-treated control group. In the United States it would probably be impossible to carry out such a study, because of long-standing official recommendations that HIV-infected persons with positive tuberculin skin tests receive prophylaxis against tuberculosis. Whether this study was ethical depends on the strength of the preexisting evidence. Only if there was genuine doubt about the benefits of prophylaxis would a placebo group be ethically justified. Although, an argument can be made that a placebo-controlled trial was ethically justifiable because it was still uncertain whether prophylaxis would work, it should not be argued that it was ethical because no prophylaxis is the “local standard of care” in the sub-Saharan Africa. Only when there is no known effective treatment is it ethical to compare a potential new treatment with a placebo. Investigators are responsible for all subjects enrolled in the trial, not just some of them, and the goals of the research are always secondary to the well-being of the participants. Those requirements are made clear in the Declaration of Helsinki of the World Health Organization (WHO), which is widely regarded as providing the fundamental guiding principles of research involving human subjects. It states, “In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject,” and “In any medical study, every patient – including
those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method."³

In July of 2002, Pfizer was to stand trial for their experiment on Nigerian children with meningitis. In a class-action suit filed, thirty Nigerian families say the company violated the Nuremberg – Code by forcing an unapproved, risky experiment on unsuspecting subjects who suffered brain damage, loss of hearing, paralysis and death as a result. The quest for rapid results sent Pfizer scientists jetting to Nigeria in late March 1996. Pfizer scientists had been industriously collecting data on its experimental broad-spectrum antibiotic Trovan when one of the worst epidemics of meningococcal meningitis broke out in Nigeria. The scourge presented a golden opportunity to test their hot new drug, which they suspected could effectively treat meningitis in oral form, bypassing the painful injections their competitors' drugs required. In Nigeria, where the contagion infected more than 100,000, the company could test Trovan on hundreds of patients in a matter of weeks.⁴ The Nigerian government was happy to cooperate, arranging for the company's accommodation and silencing criticism from local physicians, according to court documents. The FDA granted permission to export the experimental medicine the very same day it was requested. And a Nigerian hospital ethics committee sanctioned the study design, as required by Helsinki, the company claims. Not so, confessed two Nigerian doctors to the Post in January 2001. "There was no ethical committee at the time of the trial, none met, and no approval was properly given for the trial," said one. The "approval" document was cobbled together long after the experiment concluded and was then backdated, the other doctor said. And Pfizer's study design was dangerously risky, critics say. One of Pfizer's own scientists, Dr. Juan Walterspiel, warned management that the study methods were "improper and unsafe" before and after the study was conducted, acts of integrity that led to his swift dismissal.⁴

The company, in a heady mix of haste and arrogance, planned to give 100 deathly ill Nigerian children experimental Trovan either orally or by injection, and compare their outcomes to 100 others given shots of competitor Roche's FDA-approved Rocephin. But an oral form of Trovan, though convenient, was too risky to test on dangerously sick poor kids, Walterspiel complained. "Some of the children were in critical condition and most of them malnourished, which made oral absorption even more unpredictable," Walterspiel wrote to Pfizer officials in a December 18, 1997, letter. According to Nigerian families' class-action suit against the company, Pfizer then forced sick children into its study, failing to inform them either of the experimental nature of the drug they'd be subjected to or the availability of WHO-approved meningitis treatment from nearby Doctors without Borders team. Not a single Helsinki-required informed-consent form was signed, the company admits. No witnesses signed statements attesting to the "verbal consent" Pfizer claims to have obtained either, the company admits on its website. "These people had no idea they were part of any clinical trial," says Elaine Kusel, an attorney representing the Nigerian families suing Pfizer.⁴

It wasn't the first Third World trial involving lack of consent. One analysis of South African patients who had participated in a study of HIV transmission found that almost 90 percent felt forced into the trial. Thirteen percent of researchers said they weren't sure if their study
participants were aware that they were in a research project. "Informed consent is a joke," a clinical investigator who worked in developing countries commented. Pfizer scientists took other liberties as well. When some children resisted the painful Rocephin shots, Pfizer scientists slashed the dose to one-third the FDA-approved levels. This unapproved, reckless deviation from the study protocol endangered lives. Pfizer disputes the claim.

The extent of the damage from Trovan and the low dose of Rocephin remain unclear. Pfizer claims it lost just 6 percent of its patients in both the Trovan and Rocephin groups, proving that oral and injected Trovan worked as well as Rocephin. But the company didn't adequately track the long-term recovery of its patients. Initial fatality rates may have been relatively low, but with only one follow-up visit (the FDA recommended two in 1998), nobody knows how many children ended up deaf, brain-damaged or dead—whether from meningitis, experimental Trovan or a low dose of Rocephin. The FDA’s approval of Trovan for no less than fourteen adult indications netted Pfizer more than $160 million until reports of liver damage led the FDA to pull the plug in 1999.

Let’s look at another example. Two children suffered serious allergic reactions after being used as guinea pigs by the California-based company Ventria Bioscience in Lima, Peru. The children were part of a clinical trial of a genetically modified (GM) rice serum containing two synthetic human proteins lactoferrin and lysozyme normally found in human milk and other bodily fluids, not yet approved for testing in the US or anywhere else in the world. The company was hoping to sell the GM rice as a “nutraceutical” presumably on grounds that it provided extra nutrition. Nevertheless, it was unlikely to gain approval for a clinical trial in the US; so, like other companies, it decided to target Third World countries where regulations are lax. The trials in Lima were carried out at the Institute for Child Health and at the Nutrition Research Institute. Ventria had experimented on 140 children from the age of 5 months to 3 years suffering from diarrhea. It is doubtful whether informed consent was obtained. One child is now so ill that according to his mother, he is allergic to many foods such as fruit and chocolate. A US pediatrician Jim Diamond suspects that the reason that the children in the control group were given a less effective glucose solution was to make the positive effect of the transgenic rice appear more dramatic: 5.21 days to recovery in controls as opposed to 3.67 days with GM rice serum. Ventria wasted no time in announcing the results. Professor Flora Gonzales, who specializes in genetics, fears that the tests could have unpleasant long-term consequences. She believes that children given the GM rice serum could suffer degenerative diseases like Alzheimer’s because of damage incurred by the altered proteins.

Not only have unethical drugs trials been pushed onto developing countries, but also so has pharm crop production itself. GM pharm crops such as rice, maize, tomato and tobacco crops started in California, but were rapidly moved on to other states such as Hawaii, and now France. The government in Bangladesh has just announced that its National Biotechnology Policy aims to introduce GM rice production into the country by 2010.

So, what is the FDA doing? How is the agency handling the situation? Well, let’s first look at what the Nuremberg Code says. This code was developed in the aftermath of atrocious human experiments during World War II, and provides guidance for protecting human experimental subjects from injury, disability or death. Its main principle is the necessity to obtain voluntary informed consent from the patient. The latter day US Government, however, offers powerful incentives to pharmaceutical companies to test on children. These companies, that voluntarily
test drugs on children, are given a “pediatric exclusivity provision.” This adds six months of patent protection or market exclusivity to their product which means more profits. The FDA also imposed a “pediatric rule” that require companies to test on children under certain circumstances. The rule includes the likelihood that the drug tested could be used on a substantial number of children and in different pediatric age groups, leading to high volume sales. The trials in Peru of a remedy for diarrhea appear to fulfill the criteria of this rule; as do the trials of an unapproved antibiotic for meningitis in Nigeria. The FDA is also implicated in a controversial story involving drugs giant Bayer Corporation, brought to light by the New York Times. It is alleged that Factor VIII, a drug for treating mostly child hemophiliac patients was contaminated with the HIV virus during the 1980s. When American hemophiliacs contracted HIV after using the injected, blood-clotting drug made from unheated blood concentrates, the FDA recommended that Bayer dump their surplus on Japan, Malaysia, Singapore, Indonesia and Argentina. That way the company could still reap profits from sales, despite it being pulled from the US market. In Hong Kong and Taiwan alone it is estimated that over one hundred hemophiliac patients, including a two-year old child, contracted HIV after using the tainted medicine. New stocks of the drug were made using heat-treated blood concentrates (which kills the virus) for the American market while the remainder of the old stock went off to France and Spain. Two French officials were later imprisoned for approving the use of the contaminated, unheated Factor VIII. The FDA was neither subject to investigation nor indictment and wanted the problem “quietly solved without alerting Congress, the medical community and the public.” Bayer maintains that it behaved responsibly and ethically.5

Conveniently, many of the FDA's ponderous regulations stop at the border. For example, the FDA's requirement that companies prove that their experimental drugs are safe on animals before starting tests on humans doesn't apply for tests conducted outside the United States. Experiments on Americans must undergo painstaking, lengthy reviews by government-regulated "institutional review boards" (IRBs). But if you go to some countries and say you want the IRB to review this, they say, “What is an IRB?” The FDA simply requires that foreign trials conform to the World Medical Association's Declaration of Helsinki that critics call rudimentary, nonbinding and ambiguous. Scientists routinely ignore Helsinki directives to publish negative results and make study designs public, and they relate Helsinki-required ethics committees in developing countries to rubber stamps.4

So, are the FDA and the Pharmaceutical industries exclusively responsible for the unethical practices in clinical research? Let’s look at some facts. In a hospital in Morocco, cancer patients must wait 2 or 3 days for a bed to open up. In Guatemalan health center, two stressed clinicians juggle all of the more than 400 new cases of leukemia each year. In some places in India, 60-70% of cancer patients are turned away from hospitals because of lack of medical resources.6 Further, in these countries, regulatory laws and monitoring also are minimal/weak and corruption is high, which makes them ideal for clinical trials. Government bureaucracy overwhelms clinical research in the United States, scientists complain, but in developing countries there is tremendous government cooperation. The governments of China, India and Taiwan are bending over backward to get these companies to conduct research and manufacture there. They are giving tax breaks and building facilities. In Taiwan, many hospitals have switched overall record-keeping to English, so if Western companies want to do a clinical trial there, they will have no problem.4 The BBC screened a documentary on April 27, 2006 called “Drug Trials: The Dark Side” that
showed the woeful lack of informed consent by Indian patients, many of whom were taken off their existing medication to take part in drug trials commissioned by US companies. The patients were under the impression that their usual drug was no longer available and the new drug was merely a continuation of their treatment. Typically, the patients interviewed by the BBC reporter Paul Kenyon were in awe of their doctors, and because of ill health and poverty, were willing to agree to anything they were asked to do. Most consent forms were written in English, which many patients could not read, let alone understand, and some were able to give only a thumbprint as their consent to the clinical trial. One patient who agreed to take part in the placebo part of the trial did so because he believed that if his doctor was administering the pill, then it must somehow do him good. None of the patients received any money for their involvement, and when the trials finish, there is no guarantee that their treatment will continue, or that the drug will be available to the wider population as a whole.\(^5\)

There is no question that research and development is becoming an international enterprise; according to a 2005 report from the Pharmaceutical Research and Manufacturers of America (PhRMA), in 2004, the pharmaceutical industry spent about $8.2 billion on research and development outside the United States. One major motivation for looking abroad is the lowered cost. Trials in countries such as China and India can cost about one-half to one-third that of running a trial in developed country. Furthermore, such trials can save time- which could translate into saving money. Clinical studies in developed countries must compete with trials from other companies or institutions for trial participants in Europe and North America, so it may take a considerable amount of time to gather enough participants for a study. Also, some diseases do not have a high enough incidence rate within the US to support a large-scale clinical trial. Some types of cancer, such as stomach cancer, occur at much higher rates in developing countries than developed countries as the United States. Also, it is argued that learning about the etiology and development of different kinds of cancers in different populations and in different environments may help researchers more thoroughly understand and then treat the disease.\(^6\) Some researchers within the academic research community disagree on whether it is ethical to give patients in developing countries treatments that are considered “second-class therapy” in developed countries – a practice considered unethical in developed countries. Some agree that such studies are ethical; even if the outcomes are not comparable to those in developed countries, lives are still saved if the outcomes are better than the baseline outcomes for that country. It took developed nations more than 60 years to go from treating the first childhood cancer patients to where we are now. For low-income countries, it has taken less than 10 years for the same change.\(^6\) On the other hand, what is not told publicly is that there is a lack of formal training and education, especially in conducting clinical trials, among researchers from developing countries. Only about one-third of oncologists in low-income countries have had “real research training.” There is also a shortage of other properly trained personnel needed for good clinical trials – nurses, lab technicians, data managers, clinical pharmacists, and biostatistics.\(^6\)

Almost all the top names in the pharmaceutical world have zeroed-in on India, setting up clinical trial facilities in major cities, especially Hyderabad and Ahmedabad. Global consultancy McKinsey & Co estimates that by 2010, global Pharma majors would spend around $1-1.5 billion just for drug trials in the country. So, these days, Dr Vishwanath Reddy, a pharmaceutical consultant based in Hyderabad, is getting a steady stream of visitors. He says he gets at least
one business call a week from a foreign company eager to set up clinical trials facility in India. The biggest advantages many look at are India’s huge population of more than one billion, and cheaper costs. Pharma giants are also magnetized by India due to the fact that the country offers nearly 700,000 specialty hospital beds, 221 medical colleges and skilled English-speaking medical personnel. Moreover, trials for a standard drug in the United States can cost about $150 million. A similar drug could be tested in India at a 60 percent reduction of that whopping cost. By 2010 it is estimated that some two million people in India will be taking part in clinical trials.

Over the past decade, the drug industry has quietly exported its clinical testing overseas, where oversight is slim and patients plentiful. According to a largely unnoticed Health and Human Services (HHS) report, the number of foreign investigators seeking FDA approvals increased sixteen-fold between 1990 and 1999. The actual numbers are probably much higher - companies aren’t required to alert the FDA before taking their research overseas, nor does the FDA track research by location after approving new drugs. Globalizing clinical research solves the pharmaceutical paradox that while the average American brings home more than ten prescriptions a year, just one in 350 is willing to play guinea pig for new drug testing. An abundance of poor, undertreated and doctor-trusting patients in Eastern Europe, Latin America and Southeast Asia renders the quick, positive results corporate sponsors need to get new drugs approved fast. According to one review, a whopping 99 percent of controlled trials published in China bestowed positive results upon the treatment under investigation. Wyeth Pharmaceuticals currently focuses about 20% of its research and development studies in countries outside the developed countries of Europe and North America. However, within the next 2 years, the company plans to shift this percentage to up to 40%. GlaxoSmithKline also intends to boost its drug trials conducted in countries outside the United States and Europe to 50% in the next 2 years, up from 29%.

Watchdogs like Public Citizen’s Health Research Group vociferously criticize unethical study designs but can do little to police study conduct, which both the FDA and the drug industry view as secret, "proprietary" information. Ethics documents issued by international associations such as the World Medical Association and the WHO/UNESCO’s Council for International Organizations of Medical Sciences, as important as they are, are alarmingly toothless. Pharma companies themselves have attempted a voluntary "harmonization" of clinical research standards abroad to meet FDA standards but, not surprisingly, such efforts are frighteningly nascent in many developing countries. Such voluntary endeavors, while crucial, are hardly sufficient to protect the would-be guinea pigs of the world sacrificed on the altar of Big Pharma profit. One of the most important components of conducting clinical trials in developing countries is the spirit of the proverb, “first do no harm.” In that regard, some humanitarian organizations such as Oxfam question whether ethical standards that are stringently enforced in developed countries can be maintained in developing areas that often have weaker regulations and methods of enforcement.

There are serious breaches of ethics and protocol in clinical trials, especially those conducted in Third World countries. There is a need for global regulation in clinical research, so that drugs
and trials not approved in one country may not be tested or used in another. Lets hope that the WHO Registry of Clinical Trials will ensure that all clinical trials are at the very least registered with the World Health Organization, and that a minimal set of data about the trial is readily available, should questions of safety and emergency care of trial subjects arise. Getting trial managers in low-resource settings to adhere to a standard protocol and treat each patient in the same way is a good starting point for many trials in low-income countries. Before any trials can be run, researchers must carefully consider the community and culture they will be working in; otherwise, they may run the risk of ethical quandaries, alienated participants, bad publicity, and poor results. The IRB reviews, FDA approvals and the like that protect patients at home need to be not only universal but mandatory. In the process of receiving medical assistance, outsourcing revenue and promotion of medical research, we should follow “bioethics” and not play havoc with poor, uneducated and otherwise helpless people.

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