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Clinical Trials in Developing Countries:

A Review of the Moral Issues

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Abstract

Several ethicists have raised criticisms of various placebo-controlled clinical trials conducted in developing countries between 1995 and 1998. This essay reviews and rejects the arguments that these trials violated basic canons of medical ethics, or constituted exploitation by scientists in advanced countries of subjects in developing countries. A uniform international standard for the evaluation of such trials is proposed, replacing the old standard of voluntary and informed consent with a more focused standard of uncoerced and undeceived consent.

Key Words: Clinical trials, developing countries, moral issues, ethics.

THE SEPTEMBER 18, 1997 ISSUE of *The New England Journal of Medicine* exploded like a bombshell over the medical ethics community. Not since Harry Beecher's assault in 1966 on the ethics of clinical research scientists (1) had such accusations been hurled about on those cream-colored pages. The subject in question was the conduct of fifteen clinical trials in developing countries (2–5), trials that typically included a placebo arm. Critics charged that patients in placebo arms had been denied needed medical treatment, contrary to medical ethics and to international conventions governing such studies. The article presented the spectre of Western scientists looking for quick publication and Western drug companies looking for quick profits, of exploitation of weak governments and impoverished people by the strong and heartless. The most disturbing charges were pressed vis-à-vis trials for new

therapies to block transmission of HIV from mother to child. Expectant mothers in active trial arms got azidothymidine (AZT); expectant mothers in placebo arms got nothing. Had the trials been conducted with two active arms, it was charged, hundreds of cases of infant HIV infection could have been prevented. For physicians to permit such events seemed to violate elementary canons of human morality.

The "Sounding Board" case for the prosecution was made by Drs. Lurie and Wolfe from the Public Interest Health Research Group (6); the ethics of the trials was defended (two weeks later) by Drs. Varmus and Satcher from the NIH and the CDC (7). *The New England Journal of Medicine* itself, which might have been expected to maintain some neutrality between the warring camps, assigned an editorial to Associate Editor Marcia Angell, who weighed in heavily on the side of Lurie and Wolfe (8). Angell compared the controversial trials to the Tuskegee syphilis study (9, 10), suggesting that researchers conducting the trials were engaged in acts of racist condescension (11).

The controversy subsided somewhat in 1998, when most of the AZT studies ended, with hasty proclamation of successful results (12). Through 1999, further controversy

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simmered over revisions in international guidelines (Déclaration of Helsinki) governing such trials. Supporters of the trials, which were *prima facie* inconsistent with the Helsinki guidelines (13), wanted the rules weakened (14); opponents of the trials naturally wanted them tightened (15). The felicitous discovery in 1999 of an effective, practical, and inexpensive drug for the prevention of maternal transmission of HIV (16) provided a final vindication or condemnation of the 1997 studies, depending on one's point of view.

Though these studies are completed, the philosophical issues raised during the controversy remain unresolved. They may bedevil future campaigns against medical problems in developing countries. It is my purpose to consider the general form of the objections raised against the AZT trials and to subject them to the philosophical analysis that this cooler moment makes possible.

The Question of Equipoise

Dr. Angell's editorial (8) begins, "... an essential ethical condition for a randomized clinical trial comparing two treatments is that there be no good reason for thinking one is better than the other." She goes on to argue that since the efficacy of "long course" treatment with AZT in reducing maternal transmission of HIV was known (17), a short course of AZT could be presumed to be more effective than placebo. Thus, in the AZT studies in question, which typically compared a short course of AZT against placebo, one of the trial treatments was "known to be better" than the other, contrary to Angell's moral requirement.

The moral rule of epistemological indifference or "equipoise" in clinical trials was introduced into medical ethics by the late Prof. Benjamin Freedman in 1987 (18). It has often been invoked, but rarely examined. To begin with, the rule refers only to treatment studies and not to basic science (e.g., physiology) studies, where the rule cannot apply. So if researchers are doing a mixed study which is part treatment and part basic science, it is possible that the rule may not apply there either.

Let us assume that we are looking at a pure treatment study, one that compares established drug A with experimental drug B for condition c. It may be known that, for the average patient, drug A is a more effective treatment than drug B for condition c. However, drug A may have certain side effects that make it

dangerous for a certain subgroup. It is important to know, then, how much less effective drug B is than drug A, in order to get a fix on whether drug B is recommendable, all things considered, for members of the subgroup, who on safety grounds should not be randomized into the trial. Here the rule of equipoise is justifiably broken.

Consider the case in which drug A is known to be more effective than drug B, but drug B is considerably cheaper than drug A. In a society with limited resources, we can assume that there is a fixed budget for dealing with condition c. The question for such a society, and this is a moral question as much as an economic one, is whether a fixed number of dollars will save more lives, or more years of life, or more quality years, if put into drug A or put into drug B. We cannot answer this unless we know precisely how much less effective drug B is than drug A. We have here social equipoise between two strategies for dealing with a health problem, but we do not have medical equipoise for the subjects in the study comparing drugs A and B.

Next consider a trial of behavior modification to reduce HIV infection. Suppose that there is a vaginal gel with known antiviral efficacy and there are condoms of known efficacy in preventing transmission, and that a woman stands a better chance of not becoming infected if she imposes condoms on her partner than if she uses the gel alone. Suppose, furthermore, that it is not known what fraction of the men, in the natural setting, can be persuaded to use condoms, and what fraction of the women can be persuaded to use the gel. In order to know which strategy is best for reducing HIV infection, how dollars for supplies and time for educational efforts are to be invested, we must run a test of condoms-versus-gel versus condoms-plus-gel, contrary to the rule of equipoise.

In an ideal world there will always be enough money for the medically superior treatment, always enough time for the educational efforts that will persuade everyone to use it. Even in a less-than-ideal world that is a bit better than this one, wise political leaders will transfer funds allocated to the purchase of tanks and landmines to the prevention of TB, AIDS, and malaria. But this is not an option for clinical researchers, unless they happen to be running a country along with a clinic. Morally, they must make their best guess about available resources, and proceed with that as a given. In

underdeveloped countries, where health budgets may average one dollar per year per capita, it is crucial to know, when a treatment is effective but expensive, whether one tenth of the drug will have one tenth the effect, or one hundredth, or one half. One cannot know this without testing sub-optimal regimens.

Finally, note that the rule of equipoise says that a treatment trial is immoral when I give B rather than A, when I know that A is better than B. But whatever ethical principles make it immoral for me to give B rather than A if I know that A is better, would make it somewhat immoral for me to give B rather than A if I sincerely believe that A is better, since our choices are governed by our beliefs. It follows that a clinical trial would be immoral if the researcher sincerely believes that one treatment is more effective than another (on the basis of anecdotal evidence, scientific logic, clinical experience, or whatever). It is my impression that most researchers conduct trials sincerely believing their pet drug will work. A consistent application of the rule of equipoise would eliminate from science all researchers who happen to be optimists.

The Victims on Placebo

Before there was ever a controversy about trials in developing countries, there were controversies about the use of placebos and sub-optimal regimens in clinical studies (19). Beecher, in 1959, noted that the use of placebos was contrary to the Nuremberg Code, strictly construed (20). Most clinical researchers are also physicians, and the presence of persons on placebo in a trial tugs at the duty, or at least the impulse, to treat. Various gimmicks in trial designs containing placebos have been proposed to reconcile therapeutic compassion with scientific objectivity (21, 22), but none has caught on. Researchers/physicians can console themselves with the thought that, in a double-blind placebo-controlled trial, they do not know, in face-to-face situations, whether a given subject is going without treatment. But this form of ignorance is not bliss.

The 1996 version of the Declaration of Helsinki (23) stipulates that in the case of therapeutic research, "every patient, including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic method." It follows that only two sorts of trials are morally permissible: (a) if there is a disease for which there is no therapy,

then one can run treatment B against placebo; and (b) if there is a disease for which treatment A is standard, then one can run treatments A plus B against treatment A alone. But few diseases have no therapy, and in many trials one cannot give subjects both treatments A and B because of interactions between A and B.

The majority of trials, of scientific necessity, will pit A versus B or B versus placebo. In the case of the AZT trials, the design favored by the researchers was the "short course" of AZT versus placebo (Design S); the design favored by the critics was the "long course" of AZT versus the "short course" of AZT (Design L). The troubling argument against Design S was that some infected mothers placed in the placebo arm transmitted HIV to their infant children, and that some of these transmissions could have been prevented had these mothers received AZT. But if this is a moral criticism of design S, it is equally a moral criticism of design L. If you have one trial arm with expectant mothers receiving the short course and one trial with expectant mothers receiving the long course of AZT, then you know that there will be some HIV transmissions in the short course arm that would have been prevented if those very subjects had received the long course. The only method in which you have no preventable transmissions of HIV is to give everyone the long course, and if you do that, you have no trial at all.

Design S and Design L both involved procedures such that, if researchers had behaved differently, there would have been fewer infants infected with HIV. But it is also true that if critics of the trials had donated all their personal savings toward the purchase of AZT, which could be distributed in war-torn countries by Médecins sans Frontières, fewer infants in the world would be infected with HIV. Likewise, fewer infants would be suffering in developing countries if I had donated \$200 to CARE today rather than spending that sum (as I did) on a complete set of Haydn symphonies on CD. If we criticize the researchers who conducted these trials for not doing everything they could to prevent vertical transmission of HIV, the same criticism can be laid at our own doorsteps. There are some ethicists, Peter Singer most prominently, who have argued that morality demands that some large fraction of the incomes of persons in developed countries be transferred to persons in poorer countries, where each dollar can do

more good (24). Few have agreed with Singer that an action is morally acceptable only if it reduces human suffering more than every other alternative act. The world is full of crimes, but buying Haydn symphonies does not seem to be one of them.

The permissibility of placebo arms in studies is related to the permissibility of conducting natural history studies of medical problems (25). Suppose that an enterprising epidemiologist applies for a grant to determine precisely the natural transmission rate of HIV from mother to infant in selected African villages across a wide stretch of territory. Suppose that the study involves only HIV testing and questionnaires, that the epidemiologist is not trained or equipped to treat HIV infection, and that the peripatetic nature of the work precludes treatment of cases in villages left behind. Isn't it morally permissible to fund such a study? Why not?

Consider now a treatment study of maternal HIV transmission with two active arms. Since everyone gets treatment, the critics are silent, or at least happier than they would be if there were a placebo arm. Suppose everyone agrees that there are no moral problems with the study, at least as regards trial design.

The natural history study is morally permissible. The "active only" study is morally permissible. But what is a double-blind, placebo-controlled trial but a natural history study combined with an active treatment study? If it is morally permissible to run the two studies side by side, is it not equally permissible to run the two studies with a common pool of subjects, randomized into one or the other? If it is morally permissible to enter subjects into "study A or study B," how can it be morally wrong to enter subjects into "study arm A or study arm B?"

The "Standard of Care" Principle

Those who defended the AZT trials occasionally appealed to what has become known as the "Standard of Care" principle: that a clinical trial which meets all other moral standards is morally permissible if and only if it does not deprive subjects of any medical care they would have received if there had been no trial (26).

In the case of the AZT studies, subjects in placebo arms did not receive AZT. But if there had been no trial (so the argument goes), these subjects, given social conditions, would not have received AZT anyway. By contrast,

subjects in the Tuskegee syphilis study were deprived of penicillin that they would have received (so the argument goes) had there been no trial. In Tuskegee, the "standard of care" requirement was not met.

It is immediately obvious that the Standard of Care principle is entangled in hazy counterfactuals and foggy empirical claims. A subject in the Ivory Coast AZT trial, had there been no study, might have gotten access, in some way or other, to therapeutic AZT. On the other hand, a subject in the Tuskegee study might never have gotten penicillin even if there had been no study, because of poverty, ignorance, or bad luck. There is a delicate dance here between the concepts "could" and "would" (27). The Ivory Coast subjects could have gotten AZT (the stuff existed) had there been no trial, but what they actually would have gotten had there been no trial is anyone's guess. The Tuskegee subjects could have gotten penicillin (the stuff existed), but what they would have gotten had there been no study is also anyone's guess. It is difficult to set up the Standard of Care principle so that it slices cleanly between the AZT studies and the Tuskegee study, our paradigm case of American research evil.

Notice that in our struggles with the dizzying problem of "what would have happened if things had been different," our ability to predict improves as the difference between the actual world and the hypothetical "different" world diminishes. Thus, opponents of the trials argue that if you have a subject in the placebo arm of a trial, you can predict what would happen if she had not been in the placebo arm: she would have been in the active arm and would have gotten AZT. But here one is not comparing a world in which there is a trial with a world in which there is no trial, and that is the proper comparison to make when you pass moral judgment on the trial. It seems that when we have the right comparison, we can make no judgment, and when we can make a judgment, we have the wrong comparison. This is not a good basis for making policy (28).

Instead of the Standard of Care principle, we should consider here the more general moral principle that we should do no harm, where "doing harm" is defined as "performing some act A which leaves the individual worse off than he or she would have been if A had not been done." Note that, with this wording, the Harm principle is violated not only if I injure someone, but also if I prevent someone from

getting a benefit which she would have otherwise received. So in the case of the Tuskegee study, the researchers harmed their subjects if they prevented them from getting penicillin. Likewise, they harmed their subjects if they prevented them from obtaining information about the existence of penicillin. Did the researchers in the AZT studies harm their subjects in analogous ways? No one has charged that they intercepted benefits that were on the way to subjects, or that they injured them in the course of the research. So even if the Standard of Care argument is mistaken, the researchers still cannot be blamed for causing harm.

The Duty to Benefit

The AZT researchers did not harm their subjects. But it might be argued that they did not help them either, violating some moral principle to help those in need. But what exactly is this principle?

Certainly the principle cannot be that the researcher must help each subject as much as he or she could. This would require the researcher to assist the subject with all her problems, medical, financial, emotional, and social. It would require researchers to devote their entire personal fortunes and all their free time to the benefit of their subjects. This is asking too much; imposing this requirement would end all research.

Even at the medical level, it is not clear what is required by way of benefit. The criticized trials included studies of TB treatment among HIV-infected persons as well as the much discussed studies in prevention of vertical transmission of HIV. The critics argue that researchers conducting maternal transmission studies should have done more than they did to stop maternal transmission in their subjects. They also argue that the researchers conducting TB studies should have done more to stop TB in their subjects. But they do not argue that people doing TB studies should do more to treat maternal transmission, or that people doing maternal transmission studies should do more to treat TB.

These attitudes lead to implausible results. Suppose that there are four clinical studies running, D and E in x-town, F and G in y-town. In study D (HIV and maternal transmission), researchers treat half of the subjects for maternal transmission (the other half are on placebo) and provide all of the subjects, by way

of ancillary care, with prophylactic treatment for TB. In study E (HIV and TB prevention), researchers provide half of the subjects with prophylaxis for TB (the other half are on placebo) and all of the subjects, by way of ancillary care, with AZT for maternal transmission problems. According to the critics, D and E are immoral, because of the placebo arms. In study F (HIV and maternal transmission), all the subjects get treatment for maternal transmission, but no one gets ancillary prophylaxis for TB. In study G (HIV and TB prevention), all the subjects get prophylaxis for TB, but no one gets ancillary treatment for maternal transmission. According to the critics, F and G are morally exemplary, because there are no placebo arms. But the health care delivered to subjects in x-town is superior to the health care delivered subjects in y-town; 75% of the subjects in x-town get prophylaxis for TB and treatment for maternal transmission, while only 50% of subjects in y-town receive such care.

Morality demands that the fortunate help the unfortunate, but it leaves some leeway as to when, where, and how we give this help. Perhaps one of the occasions when people are not required to be in the helping mode is when they are engaged in clinical research that leaves them blind as to who needs help. But before we reach the conclusion that clinical researchers are uncharitable brutes exploiting convenient loopholes in the moral law, consider this. Every person entering into one of the disputed AZT studies obtained a benefit from doing so — a 50% chance of obtaining AZT. This is a real benefit because it is worth real money. (In a therapeutic setting with limited quantities of AZT, people would pay real dollars or real dinars for a lottery ticket providing a 50% chance of getting AZT.) Of course, if a person loses out in the AZT lottery, the lottery ticket becomes worthless, and likewise if a person is randomized to a placebo arm of an AZT trial, her 50% chance of getting AZT evaporates. But the fact that a benefit evaporates does not mean that it was not provided. To say that these clinical researchers provided no benefit to subjects on placebo would be like saying that a physician who initiates a therapy with a 50% chance of saving a patient's life has done nothing to help the patient, if in the end the patient dies.

It might be objected that all this philosophical talk about probabilities and benefits loses sight of the human tragedy at the

heart of the problem. Here is a pregnant woman with HIV. I am, a physician with a supply of AZT. If the woman gets AZT, this may prevent the birth of an HIV-infected child. This is a medical emergency: swift action is needed to prevent irreversible harm. But I don't give the woman AZT. I'm doing a study; my goal in life is to hit a confidence level of 95%. Have I lost my soul to science? If I encounter a drowning woman, don't I have an obligation to throw her a line, rather than study the drowning process?

There are, we rush to note, mitigating circumstances. If I don't give the woman AZT, she may well have a non-infected child; the odds are two-to-one that the baby will be fine. On the other hand, if I give the woman AZT, she may have an infected child anyway. All that AZT does is to reduce the odds. But if all I can possibly do is reduce the odds of harm, is it not morally open to me to select the means by which the odds are reduced? If I have a quantity of a drug which will reduce the chance of death in one person by 50%, am I not morally free to divide the dose in half, if by so doing I can reduce the chance of death in two people by 25%? And if all I can do now is reduce the chance that a woman will give birth to an infected child, is it not open to me to select a procedure which will reduce the chance of infection in a larger group of women, including women who will benefit when the trial is over? What moral principle says that this woman in immediate need has a right to help, but those women in future need have no such right?

These considerations are particularly relevant to the Helsinki-inspired suggestion that all subjects, or some subjects, in these trials should have received the standard Western long course of AZT, in which therapy is inaugurated as early as the 14th week of pregnancy. Since most women in the countries in question do not seek medical assistance until late in pregnancy, a trial involving the long course of AZT, with its daunting recruitment and compliance problems, would have been more time-consuming. A quick result demonstrating the efficacy of the short course at low cost clears the deck for the budgetary allocations and foreign aid appeals that may prevent more infections in the long run. The pregnant, infected woman in front of you is an emergency. The group, all of whom are pregnant, infected women, is also an emergency. This is not a choice between emergency and research. It is a choice between emergencies.

Voluntary and Informed Consent

The physician engaged in a research study seeks the good not of individual subjects, but the larger constituency of afflicted persons. Of course the individual subjects have rights, secured and expressed in the consent process. But there have been persistent assertions in the media that the consent process failed to legitimize the AZT studies because the consent given by subjects was not voluntary and not informed (29).

The argument that the consent for these studies was not voluntary hinges primarily on the consideration that subjects in the study were desperate. "At the time they explained this to me I asked myself the simple question of whether I had any choice. As long as there was a possibility to save my daughter, I had to try," said one subject in the Ivory Coast trial (29). That the subjects in these studies were often desperate is beyond doubt. Their desperate condition necessitates special moral protection. It is, for example, a principle of both law and morals that persons cannot be held to contracts made from desperation. It would follow, then, that these subjects could not be held to any agreements made upon entering into the studies, a consideration guaranteed in any event by the rule of research ethics that every subject is free to withdraw without penalty at any time. Nor could researchers legitimately charge subjects for participation, but this too is forbidden by the existing canons of research ethics.

The crucial moral point is not whether desperation is present, but whether the presence of desperation signifies an absence of consent. If desperation invalidates consent, then every last-ditch cancer study, every study of refractory epilepsy, indeed, every study of a serious medical problem for which there is no treatment, would be immoral. This conclusion holds for studies in advanced countries as much as in developing ones. The sick are desperate in every country. Among the ethicists, there is no consensus that desperation invalidates consent. There is only agreement that coercion invalidates consent, and that is a different matter (30). Researchers coerce their subjects if they threaten them with harm for not participating. Thus it is possible for subjects to be desperate but not coerced, as well as coerced but not desperate. The mother from the Ivory Coast reports desperation, not coercion. I do not mean to suggest that bad external

conditions are irrelevant to consent. Being in prison invalidates consent, even when threats are not made, and consent to a study of a disease would be invalid for subjects who were surreptitiously infected with that disease by the researchers. But these are not the sorts of situations surrounding these trials of AZT.

The question of whether or not consent to a given study is "informed" is a problem worldwide. The bottom line must be that subjects understand that their participation is voluntary, that they are participating in a research study, and that participation in a research study is not the same thing as getting the best possible medical treatment (especially for studies that involve randomization into placebo or sub-optimal treatment). There is every reason to believe that some research subjects do not grasp the difference between treatment and research. What I refuse to concede is that this problem is more acute in developing countries than in developed ones. Most accusations of racism in this debate have been bogus, but it is indeed racist to imply that Americans and Europeans have the intelligence to comprehend consent forms but that Asians, Africans, and Latin Americans do not.

A particular moral problem arises when an effort has been made to inform a subject, the subject remains uncomprehending, and participation is beneficial for the subject. An expectant mother in the Ivory Coast trial, handed a positive result for HIV, agrees on the spot to participate in a placebo-controlled trial (29) "because of the medical care they are promising me." This looks like uninformed consent. But if the woman is excluded from the trial, she loses her only chance of getting AZT. Can we suppose that if the woman had comprehended the notion of placebo and the possibility of non-treatment, she still would have participated in the trial? Rationality favors it, but on the other hand she might have thought it too much trouble in return for a mere 50% chance of getting AZT.

Conundrums like this prompt me to suggest that the moral standard for valid consent should not be the presence of information but the absence of deceit. If a research subject has false beliefs about the study, but these false beliefs have not been induced by the researchers (if, indeed, the researchers have made a reasonable effort to uproot these false beliefs), then the consent can still be valid because it is undeceived. If the researchers in the Ivory Coast study said things that induced a

woman to believe that she would surely receive AZT, then her consent, resulting from this deception, was invalid. But if the Ivory Coast researchers tried to explain the notion of placebo and the woman persisted in believing that she would definitely get AZT, the consent is valid because it is undeceived, provided all other ethical requirements are met. In fact, some effort was made to explain the notion of placebo to this woman (29). Likewise, the efforts of researchers in Thailand to translate and explain the word "placebo" to their subjects show a thoughtful and concerted effort to inform (31). No one anywhere perpetrated a campaign of deception, in the high Tuskegee style.

I suggest that the old requirement that consent should be voluntary and informed be replaced by a new requirement that consent should be uncoerced and undeceived. This is not a weakening of moral standards, but a focused attempt to capture what morally matters in the consent process. Coercion in research is morally wrong; deception in research is morally wrong. The consent process must rule them out. But the inability of subjects to comprehend the details of consent forms is not so much a moral issue as a fact of life. Likewise, the desperation of the sick is a fact of life. If we insist on scientifically literate, happy and undesperate subjects, we will only encourage contempt for the consent process, since such subjects will not be found and research will proceed anyway. For the ethicists and researchers who view the search for informed consent as a clumsy charade, contempt is what the process deserves. But for persons like myself, who defend trials with sub-optimal regimens, the consent process is essential: how can sub-optimal trial arms be legitimate unless subjects consent to their presence? The correct resolution of these dilemmas is not to junk consent (32) or to stop research, but to find the morally relevant form of consent and insist upon it.

Exploitation and Justice

Though all the trials in question proceeded with the consent and support of relevant national public health officials (33), in a number of cases the studies assumed a potentially disturbing form: white researchers/black subjects. The track record of white people among black populations is not good; locals have a right to fear the worst. The

argument that these AZT trials "could not have been done in a Western country" gave the impression that white researchers were trolling worldwide for exploitable participants, pouncing on subjects where the regulatory forces were weakest. If so, the AZT trials would be morally comparable to the efforts of multinational corporations to find and exploit developing countries with weak environmental regulations or lax occupational safety requirements.

But the AZT trials could not be done in the West because they were tests of therapies not needed in the West. Comparative regulatory strength was not the issue. There is a generally accepted principle of international research ethics that trials in a country should focus on medical problems in that country (34). Since the problem of finding a short course treatment for maternal transmission of HIV was a problem specific to developing countries, the trials proceeded in appropriate locations with appropriate subjects.

So far, the majority of AIDS therapy trials have been in developed countries, with the majority of AIDS patients being in developing countries. The sacrifices of subjects in the AIDS trials in developed countries have been considerable, and the knowledge gained from Western trials benefits persons with AIDS in developing countries. Now it has been a guiding principle of research ethics for more than thirty years that the burdens of research should be equitably distributed among those populations that stand to benefit from the research (35). I will not suggest that populations at risk in developing countries have exploited the Western research subjects who have been overdosed or undertreated or otherwise suffered so that AIDS research could go forward. But I do think that the sacrifices of Western research subjects for more than two decades serve as a sufficient rebuttal to the misplaced charges of exploitation thrown at the sponsors of trials in developing countries in the mid-1990s. At worst, the sponsors of these trials could be called opportunistic: they saw an opportunity for research and they seized it. But this opportunism is not a special feature of research in poor countries. In medical research at large, every disease is an opportunity for grants, for work, and for a cure.

Ethics Charges and Research Progress

If I were a young clinician observing the charges of racism and exploitation thrown

about in this controversy, I would be inclined to steer away from work on world public health problems rather than negotiate the ethics minefield laid down by contemporary moralists. No one is going to call you a moral monster if you devote yourself to acne problems in American kids. If I were director of research for a multinational drug company, I would learn from this controversy that it is better for the corporate image, and surely more profitable, to develop copycat versions of Viagra® than to take on malaria, TB, AIDS, giardiasis, shigellosis or any of the other diseases of the poor that make up the greater part of human suffering. There is indeed an ethics problem in this area: the misallocation of research funds away from the primary scourges of human life (36). But the charges leveled at the AZT trials can only make this problem worse.

The psychological impact of an ethics accusation is considerable, and only those who have lived through one know the stress of the experience. Those who conducted these trials have been through mental hell. Nevertheless, research goes forward and progress is made. The recent announcement of the effectiveness of oral miltefosine is a signal advance in treating visceral leishmaniasis, which afflicts 500,000 victims in developing countries each year (37). In the current climate, I can only hope that the researchers who brought in this result have their consent forms in order.

References

1. Beecher HK. Ethics and clinical research. *N Engl J Med* 1966; 274:1354-1360.
2. Whale CC, Johnson JL, Okwera A, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with human immunodeficiency virus. *N Engl J Med* 1997; 337:801-808.
3. Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand. A randomized trial. *Lancet* 1999; 353:773-780.
4. Wiktor SZ, Ekpini E, Karon JM, et al. Short course oral zidovudine for prevention of mother to child transmission of HIV-1 in Abidjan, Côte d'Ivoire: A randomized trial. *Lancet* 1999; 353:781-785.
5. Dabis F, Msellati P, Meda N, et al. 6 month efficacy, tolerance, and acceptability of a short regime of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Côte d'Ivoire and Burkina Faso: A double-blind, placebo-controlled multicentre trial. *Lancet* 1999; 353:786-792.
6. Lurie P, Wolfe SM. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *N Engl J Med* 1997; 337:853-856.
7. Varmus H, Satcher D. Ethical complexities of conducting research in developing countries. *N Engl J Med* 1997; 337:1003-1005.

8. Angell M. The ethics of clinical research in the Third World [editorial]. *N Engl J Med* 1997; 337:847-849.
9. Jones JH. *Bad blood: The Tuskegee syphilis experiment*. New York: Free Press; 1981.
10. Brandt AM. Racism and research: The case of the Tuskegee syphilis study. *Hastings Cen Rep* 1978; 8:21-29.
11. Fairchild A, Bayer R. Uses and abuses of Tuskegee. *Science* 1999; 284:919-921.
12. Stolberg SG. Placebo use suspended in overseas AIDS trials. *N Y Times* 19 Feb 1998 A:16.
13. Angell M. AIDS studies violate Helsinki rights accord. *N Y Times* 24 Sep 1997 A:26.
14. Levine R. The need to revise the Declaration of Helsinki. *N Engl J Med* 1999; 341:531-534.
15. Brennan T. Proposed revisions to the Declaration of Helsinki — will they weaken the ethical principles underlying human research? *N Engl J Med* 1999; 341:527-531.
16. Altman L. New means found for reducing HIV passed to child. *N Y Times* 15 Jul 1999 A:1. [The initial excitement over the effectiveness of nevirapine was tempered somewhat in 1999 by the discovery that the drug quickly generates resistant strains of HIV. See: One more reason to worry. *Sci News* 2000; 157:109.]
17. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Engl J Med* 1994; 331:1173-1180.
18. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987; 317:141-145.
19. Cohen J. AIDS trials ethics questioned. *Science* 1997; 276:520-523.
20. Beecher HK. *Experimentation in man*. Springfield (IL): Charles C. Thomas; 1959.
21. Marquis D. How to resolve an ethical dilemma concerning randomized clinical trials. *N Engl J Med* 1999; 341:691-693.
22. Chalmers TC. The ethics of randomization as a decision making technique and the problem of informed consent. Report of the 14th conference of cardiovascular training grant program doctors; 1967 Jun 3-4; Bethesda, MD: National Heart Institute; 1967. pp. 87-93.
23. World Medical Association. Declaration of Helsinki as amended by the 48th World Medical Assembly, Somerset West, Republic of South Africa, October 1996, at II.6.
24. Singer P. Famine, affluence, and morality. *Philosophy & Public Affairs*; Spring 1972; 1:229-243.
25. Defining a "natural history study" is difficult. Often the observations are so manipulative that "nature" disappears. See Rothman D. Were Tuskegee and Willowbrook 'studies in nature'? *Hastings Cent Rep* 1982; 12(2):5-7.
26. For a critical account of appeals to this principle, see Lurie P, Wolfe S. Letter to Dr. Delon Human. Public Citizen Health Research Group Publication 1477. Washington, DC: March 1999.
27. Jackson F, editor. *Conditionals*. Oxford readings in philosophy. New York: Oxford University Press; 1991.
28. Lewis D. *Counterfactuals*. Cambridge (MA): Harvard University Press; 1973.
29. French HW. AIDS research in Africa: Juggling risks and hopes. *N Y Times* 9 Oct 1997 A:1, A:14.
30. Wertheimer A. *Coercion*. Princeton (NJ): Princeton University Press; 1990.
31. Limpakarnjanarat K, Chuachoowong R, Bhadrachom C, et al. Informed consent for a clinical trial in Thailand [letter]. *N Engl J Med* 1998; 339:1332.
32. Truog RD, Robinson W, Randolph A, Morris A. Is informed consent always necessary for randomized clinical trials? *N Engl J Med* 1999; 340:804-807.
33. Saba J, Ammann A. A cultural divide on AIDS research. *N Y Times* 20 Sep 1997 A:15.
34. Levine RJ. International codes and guidelines for research ethics: A critical appraisal. In: Vanderpool HY, editor. *The ethics of research involving human subjects: Facing the 21st century*. Frederick (MD): University Publishing Group; 1996. pp. 235-259.
35. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report*. Washington (DC): DHEW; 1979 18 Apr. Publication Nos.: (05) 78-0013 and (05) 75-0014.
36. Silverstein K. Millions for Viagra, pennies for diseases of the poor. *The Nation*. 19 Jul 1999, 13-19.
37. Jha TK, Sundar S, Thakur CP, et al. Miltefosine, an oral agent, for the treatment of Indian visceral leishmaniasis. *N Engl J Med* 1999; 341:1795-1800.