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Universality and Its Limits: When Research Ethics Can Reflect Local Conditions

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Universality and its Limits: When Research Ethics Can Reflect Local Circumstances

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Studies in several developing countries for treatment to prevent HIV-transmission from mother to child generated considerable controversy in 1997. Critics of the studies argued that basic principles of research ethics were violated. According to the critics, researchers subjected women in developing countries to studies that would have been unethical in the United States (and other developed countries) and that the researchers were therefore engaged in unethical exploitation of citizens of the developing countries in which the studies were conducted.

While the critics agreed that unethical exploitation had occurred, they differed on the exact nature of the exploitation. Some observers condemned the researchers for employing a double standard — because the researchers were applying a standard of care that would have been unacceptable in their own country. In the view of these critics, researchers should have been comparing the experimental treatment to established therapy rather than to placebo, as would have been required in the United States or other developed countries.[1] Other critics objected on the ground that once the trials demonstrated the efficacy of the experimental therapy, the therapy would not become available in developing countries because of its high cost. In this view, a study in developing countries need not always conform to the standard of care in developed countries, but studies on residents of developing countries cannot be conducted solely for the benefit of residents of developed countries.[2]

The trials and their fallout raise important questions. Can researchers conduct studies in some countries that would be unethical in other countries? In other words, are there universal principles of research ethics that prevent researchers from avoiding moral constraints in one country by moving their studies to another country? And if trials can be conducted in some countries even though unacceptable in other countries, does the fact that a study would be unacceptable elsewhere place special limits on researchers conducting the study where it is acceptable?

I will argue that one can accept the idea of universal ethical standards for research and still permit different trials for different countries. It does not follow that, if a research study is unethical in the United States, it is also unethical in Kenya. Rather, one can accept the same principles of research ethics for Kenya and the United States and still conclude that those universal principles allow for different studies in different countries because of differences in local circumstances. I will also argue that concerns about exploitation should place constraints on researchers conducting studies with patients in developing countries, but I will conclude that these constraints need not be as strict as those suggested by existing guidelines or other commentators. I will use the AZT trials in several developing countries during the mid 1990s to illustrate my arguments.

The Controversial AZT Trials

In 1994, researchers reported the success of zidovudine therapy (AZT) to reduce HIV-transmission from mother to child.[3] In the studies, which were conducted in France and the United States, half of the pregnant women were given AZT for up to twenty-five weeks during pregnancy[4] as well as during labor and delivery, and their infants were given AZT for six weeks after birth. The other half of the women were given a placebo. The researchers reported a two-thirds reduction in HIV-transmission for the women and children who received AZT therapy.

Although the results were dramatic, the researchers could not affect treatment for all pregnant women. The treatment

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began when the women initiated prenatal care, and many pregnant women do not receive care from an obstetrician until they are ready to deliver. In addition, the treatment's costs have been estimated at $800 per patient, an amount unaffordable in most developing countries.[5]

In response to the study's limitations, other researchers conducted studies involving a less aggressive, less expensive course of AZT therapy to see if it would also reduce the risk of HIV-transmission from mother to child. The studies were conducted in developing countries, mostly in Africa, and pregnant women in nearly all of those studies were divided into two groups, one of which received the less aggressive therapy, the other of which received placebo.[6]

These studies were criticized initially because pregnant women in the placebo group were denied any therapy, even though a proven therapy to prevent HIV-transmission existed. According to the critics, an experimental treatment should be compared to established therapy when there is an established therapy. In this view, the less aggressive therapy should have been compared to standard AZT treatment rather than to placebo. If research subjects are instead given placebo, they are put at unnecessary risk for the disease being studied.[7] It is well-recognized that in the United States, a placebo control would not have been allowed. In other words, the critics said, researchers should not conduct studies in developing countries that would have been unethical in the United States.[8]

Defenders of the research replied that the women given placebo were not harmed by their participation in the studies. Because of their countries' poverty, the women would not have had access to AZT treatment outside of the study. By enrolling in the study, they had a 50 percent chance of getting a potentially effective treatment. Moreover, it was argued, a placebo arm to the study was necessary to find out whether the less aggressive course of therapy was effective and how effective it was. If, as expected (and as turned out), the less aggressive therapy was less effective than the more aggressive therapy, and the two forms of therapy were compared only with each other, we would not know if the less aggressive therapy was better than nothing.[9]

Still, even if a placebo control was permissible, other critics objected to the studies on the ground that the studies were validating experimental therapy that would become available primarily in developed countries. Even though the less aggressive course of therapy was much less expensive than the more aggressive course, it would still be unaffordable in most of the countries in which the AZT trials took place. Under such circumstances, the critics said, the research subjects were assuming the risks of research solely for the benefit of people living in developed countries, a situation that clearly constitutes exploitation.[10]

Different Research in Different Countries — A Double Standard?

Who was correct, the opponents or proponents of the study? To answer this question, I think it is helpful to imagine it is 1995, a year after researchers first reported the success of AZT in reducing HIV-transmission from mother to child. Imagine also that the following scenarios are about to occur.

Clinic physicians

A group of physicians from the U.S. decides to spend a year in a clinic in rural Kenya, delivering medical care to patients at the clinic. Medical students from the U.S. will rotate through the clinic during the year under the supervision of the visiting physicians. The physicians and students have a number of reasons for doing this. They think it is important to do some practice in a severely underserved community, they think the experience will sharpen their clinical skills, and they plan to spend some time in Kenya and neighboring countries as tourists. At the end of the year, the physicians will return to their U.S. practices, and the students will go on to practice in the U.S. The physicians and students will bring some equipment and medicines with them, but for the most part, they will rely on the resources of the clinic. That means that pregnant women receiving prenatal care at the clinic will not receive AZT to prevent the spread of HIV to their fetuses. The cost of the AZT treatment is well beyond what is affordable for the clinic.[11]

Physician entrepreneurs

A second group of physicians from the U.S. will establish a business in rural Kenya to process natural substances from the area into pharmaceuticals. In particular, the physicians expect to manufacture some drugs that will be effective agents against cancer, including cancers that are common in developing countries but very rare in developed countries. The company will pay appropriate royalties to the Kenyan government if any of the drugs are marketed. The physicians will hire workers from the local population, and they will pay them a good local wage, but one that is below the minimum wage in the U.S. The physicians will also provide health insurance that will cover the standard of care in the local community. That means that there will not be coverage for pregnant women to receive AZT to prevent HIV-transmission, again because such treatment is too expensive for that part of Kenya.

Research physicians

A third group of physicians from the U.S. comes to rural Kenya to conduct a research trial. The physicians are interested in seeing whether a less aggressive, less expensive

regimen of AZT treatment can also reduce HIV-infection in newborns born to HIV-infected women. The trial will have two arms: half the subjects will be randomized to receive the less intensive regimen of AZT to prevent transmission of HIV; the other half of the subjects will receive a placebo.

I take it that of the three scenarios I have described — the doctors and medical students practicing in a local clinic, the physicians establishing a drug company, and the doctors conducting the AZT trial — only the research scenario would be condemned as unethical, even though in all three examples, the U.S. physicians treat their Kenyan patients or employees differently than they would patients or employees in the U.S. because of differences in local circumstances. The physicians in the local clinic give different treatment because of differences in affordability between the U.S. and Kenya, and the physician-entrepreneurs offer lower wages and less generous health insurance because of differences in the standard of living between the U.S. and Kenya.[12]

Yet from the perspective of a pregnant Kenyan worried about transmitting HIV to her child, the research scenario is clearly superior to the other scenarios. Pregnant Kenyans are less likely to transmit HIV to their children under the research protocol than they are if they receive care in the clinic or if they work at the drug company.

The question then is: Why would we condemn the research scenario? If U.S. doctors treating patients, and U.S. companies hiring employees can operate according to local ethical standards,[13] why cannot U.S. medical researchers rely on local standards in meeting their ethical obligations?

In fact, we do not need to assume different ethical standards to justify the research study. We can employ a universal set of standards whose application may vary depending on local resources. The idea here is similar to the principle in medical malpractice law that a physician's obligations to patients can take into account the facilities available. A doctor practicing at a small rural hospital cannot be expected to provide the same care as a doctor practicing at a major academic medical center.[14] Thus, we would expect the U.S. researchers to follow the same human research rules overseas that they follow here (e.g., informed consent, reasonable risk-benefit ratio, minimization of risk). But if U.S. doctors treating Kenyans are not obligated to deliver the U.S. level of care but only care that is reasonable with Kenya's resources, researchers also should be able to tailor their protocols to Kenya's resources. In other words, letting researchers conduct studies in other countries that they could not conduct in their own country does not necessarily entail a double standard. It is a double standard if we define the standard in terms of which research trials can be performed. In this view, we would have a double standard if a particular study could be conducted in one country but not other. However, there is no double standard if we define the standard in terms of which ethical guidelines must be followed in designing a study's procedures. And the important standard is the ethical guidelines that must be employed.

Let me suggest another example that responds to the double standard argument. This example uses the ethical principle that research subjects can be compensated for their participation, but compensation should not be so great that it becomes coercive. Thus, we might allow research subjects to be paid a few hundred dollars but not tens of thousands of dollars. Now if we take a strict view of universal standards, we would have to have the same limits on compensation everywhere. If a certain payment would be unethical in Kenya, we would have to consider it unethical in the U.S. But we do not think that this is the consequence of universal standards. Just because a $50 or $100 payment in Kenya might be coercive, it would not be coercive in the U.S. We apply the same standard of no coercive payments, and that leads to cut-offs at different levels of payment around the world, because the standard of no coercive payments has to take into account local economic conditions.

In short, we need not condemn medical research in developing countries simply because a research protocol takes account of the economic resources of the host country and therefore has elements that would not be permitted in the U.S. or other countries with more wealth.[15]

Other objections to the AZT trials

Objections to the AZT trials went beyond the double standard argument. I will now consider other arguments that have been made against the AZT trials in developing countries in Africa and elsewhere.

The AZT trials in Africa were reprehensible in the way the Tuskegee study and other notorious research was reprehensible

These kinds of comparison are misguided. Tuskegee (the syphilis study of poor African-American men) was bad because the subjects were deceived from the outset of the study and because they were later deprived of a treatment that they should have received.[16] The AZT studies did not entail deception of the subjects, nor did they entail the withholding of care that the subjects were entitled to receive outside of the study. The pregnant women in the AZT trials were not made worse off by virtue of their participation in the trials.[17]

Note in this regard how the three-scenario comparison that I began with helps us with the analysis. I suggested that, if treating physicians do not have an obligation to provide the U.S. standard of care in developing countries, researchers would also not have that obligation. If we look at other studies that have been compared to the AZT trials, we see that the researchers deviated from obligations that treating physicians would have had. The Tuskegee case is a good example, treating doctors would have had an obligation to

be truthful and to provide penicillin (once penicillin became widely available).

Peter Lurie and Sidney Wolfe mention some other examples in an article in the *New England Journal of Medicine* that have the same problem as the example of the Tuskegee study. Lurie and Wolfe claim that, if the AZT trials were acceptable, it would also be permissible for researchers to inject live malaria parasites in HIV-positive subjects in China in order to study the effect on the progression of HIV-infection.[18] This argument is not persuasive because researchers injecting malaria parasites would be doing something that treating physicians could not do. Similarly, it does not follow from the AZT trials that researchers could assign malnourished aboriginals to receive either vitamin-fortified or standard bread.[19] It is true that the aboriginals were not made worse off by the trials, but I think we would say that, if treating physicians offer the aboriginals bread, they should offer vitamin-fortified rather than standard bread.

For the same reason that the Tuskegee and similar analogies are mistaken, so is it mistaken to argue that the AZT trials in developing countries were wrong because we do not let researchers treat poor people in this country differently than wealthy persons. We could not justify the AZT trials on poor persons in the U.S. by saying that the poor persons would not otherwise have received the aggressive regimen of AZT and therefore were not made worse off by their participation in the research trials. But the reason we say that the AZT trials would have been unethical here is because we believe that doctors in the U.S. have an ethical (and legal) obligation to give the same quality treatment to all persons in their community, regardless of their wealth (once treatment is commenced). We do not believe, on the other hand, that U.S. doctors have an obligation to give poor persons overseas the same care as wealthy (or poor) persons in the United States. In other words, while my scenario of the U.S. physicians practicing in a Kenyan clinic is ethically acceptable, it would not be acceptable if the physicians practiced in the same way in an inner city clinic in the U.S.[20]

Researchers have greater obligations to their subjects than do treating physicians to their patients

The short answer to this argument is that the researchers in the AZT trials did more for their subjects than treating physicians in the host countries would have done for the pregnant women as patients (as illustrated by my scenarios of the treating physicians and the research physicians). The researchers gave the pregnant women a 50 percent instead of 0 percent chance at a treatment that might have substantially reduced the risk of HIV-transmission.[21] The hypothetical treating physicians were not in a position to offer AZT treatment to any patients.

Moreover, we hold researchers to higher standards because research often entails the taking of special risks. If we are going to ask research subjects to assume a risk for the benefit of society, we owe them special duties. But in this case, the research subjects were given an opportunity to reduce their risk of HIV-transmission by participating in the study. In other words, there was no heightened risk that required special consideration.

In observing that the pregnant women might have benefited from their participation in the AZT trials, I am not succumbing to the "therapeutic illusion" of medical research. I recognize that research is designed to accumulate knowledge, not to benefit research subjects. Nevertheless, in many research trials, the subjects do have a reasonable expectation of benefit. Pregnant women in the AZT trials genuinely could think that they might reduce the risk of HIV-transmission to their children by participating in the trials.

Although the requirement of special standards for research was satisfied in the context of the AZT trials, it would impose greater limits for other studies in which experimental therapies are being tested. In other words, the fact that the pregnant women were clearly better off for their participation in the AZT trials is a feature of those studies that will not be present in other studies. Accordingly, the analysis will be different for other studies. I will indicate how this is so when I further consider the exploitation argument below.

The AZT trials employed a placebo control rather than a standard therapy control

In this view, the trials were unacceptable because experimental therapies for HIV should be compared to existing therapy, not to placebo.[22] According to The Declaration of Helsinki, new treatments "should be tested against ... the best current" treatments, with placebos reserved for studies in which no proven treatment exists.[23]

This argument fails as well. The best therapy available varies from country to country. For pregnant women in Kenya at the time of the AZT trials, there was no treatment to prevent transmission of HIV to their children. Thus, even though we also expect treating physicians to assure patients of the best current therapy, treating physicians need only provide those therapies that are reasonably available in their community. The treating physicians in my scenario of the local clinic in Kenya were obligated to provide the best therapy available in Kenya, not the best therapy available anywhere in the world. Similarly, physicians conducting research in Kenya should be obliged only to provide the best therapy available in Kenya.[24]

Moreover, as others have observed, a placebo control was important in the AZT trials.[25] If researchers had tested the standard therapy against the less aggressive treatment, and the less aggressive treatment provided less protection against HIV-transmission, we still would not know if the less aggressive treatment was better than placebo, or whether its advantages over placebo could justify its costs.

Although I would not criticize the AZT trials in Africa for including a placebo arm, I think the trials would have been better studies if they had included a third arm — we would have learned more about AZT treatment of HIV-infected women if the less aggressive treatment had been compared not only with placebo but also with standard therapy. That way we would have known how the less aggressive therapy compared to the more aggressive therapy as well as how the less aggressive therapy compared to the placebo.[26]

Note that there is a tension between an obligation to avoid placebo controls and an obligation to conduct research whose results will benefit people living in the country where the research is conducted (an obligation taken up in the next subsection). As I and others have argued, a placebo control was necessary to answer the question whether the less aggressive course of therapy was better, or sufficiently better, than no treatment, a critical question for people living in countries that could not afford the more expensive course of AZT.

The treatments being studied would not be affordable even at their much lower cost in the host countries and therefore should not have been studied in those countries

This argument accepts the use of a placebo arm in developing countries — even though forbidden in developed countries — as long as the therapy tested will be used in the host country. The requirement that the therapy be available in the host country after the study is over helps ensure that researchers do not exploit vulnerable citizens of developing countries. Some researchers, it is thought, are like the colonialists of old, raping poor countries for the benefit of their compatriots back home. According to the research guidelines of the Council for International Organizations of Medical Sciences (CIOMS), research conducted in a country must be responsive to that country's health needs.[27]

This is a complicated argument because it requires us to define exploitation, and people use the term in different ways. Some people would label a practice as exploitative only when the practice is immoral; other people would include a wider set of practices in their definition of exploitation and distinguish between acceptable and unacceptable exploitation.

Before I consider the definition of exploitation, it is worthwhile observing that most practices that we condemn as exploitative are practices that raise concerns about coercion or the taking advantage of someone's desperate situation. I do not think the AZT trials raised either of these concerns (assuming proper informed consent). We worry about using prisoners as research subjects because inmates may think participation is required to have a good relationship with prison authorities. We worry about letting people sell their kidneys because indigent persons may feel that they have no choice but to sell a kidney in order to feed or shelter their family. That is, we worry that their desperation will lead them to engage in action that is harmful to them. To be sure, one might argue that the subjects in the AZT trial participated because of their poverty, but the participation did not require them to act against their interests. We cannot condemn practices simply because poor people are more likely to engage in them than wealthy people. To do that, we would have to condemn much of capitalism.

Defining Exploitation

Returning now to the meaning of exploitation, I distinguish between fair and unfair exploitation rather than saying exploitation includes only unfair practices. Following Joel Feinberg, I will define exploitation as occurring when one person gains by using a characteristic of another person to his/her own advantage.[28] Exploitation, then, would include my raising money for my political campaign by taking advantage of a donor's generosity, as well as my obtaining my older brother's birthright by offering a bowl of porridge for the birthright when my brother is famished. While both are forms of exploitation, they differ in terms of their morality.

That takes us to the question: When is exploitation unfair? It is unfair if: (1) the other person does not give truly voluntary consent; (2) the other person is harmed; (3) the exploiter is profiting off the desperation of other persons (e.g., selling a worthless drug to the terminally ill who are adequately warned of the drug's uselessness); or (4) the exploiter's gain is disproportionate when compared with the exploited person's gain.[29]

Were the AZT trials exploitative?

If we are going to condemn the AZT trials as exploitative, it would have to be on the ground that the gain for the United States (the exploiter) is disproportionate when compared with the gain of Kenyans (the exploited person) (definition 4 above). In fact, Leonard Glantz, George Annas, Michael Grodin, and Wendy Mariner have argued that there is exploitation if research in a developing country will not be used to benefit residents of the developing country,[30] a principle consistent with the CIOMS guideline requiring that, when a therapy is developed, it must "be made reasonably available for the benefit of [the] population or community" in the host country.[31] If research results will be used only for the benefit of people living in the developed country, we should worry that the developed country's gain is disproportionate to the developing country's gain.

Whether this is so is a hard question. One could say that it is too strong a definition of unfair exploitation. In other settings, we do not consider it unfair when two people enter a contract under which different kinds of gain are realized. It is not unfair exploitation if workers at a Rolls Royce factory cannot afford to purchase a Rolls Royce. Using an example

from medicine (the second scenario at the beginning of this article), we do not think it is unethical to develop drugs from substances in developing countries — even if the drugs will be used primarily in developed countries — as long as there is fair compensation to the developing country in the form of royalties or other payments. Nor do we think it unethical if physicians go to Kenya and use the experience there to improve their clinical skills for patients in the U.S. (the first scenario at the beginning of this article).

Still we might say that research is different from business or clinical practice and that researchers have higher obligations than do employers or treating physicians. But even so, the principle enunciated by Glantz and the CIOMS guideline may go too far. With regard to the AZT trials, it is not clear that there was disproportionate gain. The research subjects got the chance to save their children from HIV-infection, a very important benefit. And all participants received access to good general medical care.

The example of the AZT trials suggests a distinction between trials in which the research subjects will clearly be better off by their participation and trials in which the subjects may end up being harmed by their participation. For an example of the latter kind of study, consider a trial of an experimental drug that may have valuable therapeutic effects but may also have serious toxicity. With this kind of study, the possibility of exploitation is much greater than with the AZT trials or other studies in which the advantages of participation clearly outweigh any risks. Accordingly, it is important to have stronger safeguards against exploitation for studies in which research subjects assume a real risk by virtue of their participation than for studies like the AZT trials in which the research subjects have much to gain at little risk to their health.

Appropriate safeguards to prevent exploitation

The question then is whether the stronger safeguards need be as strict as suggested by Glantz and the CIOMS guideline. Should we require that the intervention be made available after study in the host country? Should we also require, as would Glantz and CIOMS, that researchers establish in advance that the intervention will definitely be used in the host country?

One can object to either part of this strict position. Robert Crouch and John Arras, have criticized the second prong of the Glantz/CIOMS guidelines. They have argued that we might not expect funders of research to commit in advance to making available a treatment with hypothetical benefits and hypothetical costs. Rather, a firm commitment may not be achievable until the study's results begin to come in, and the treatment's success gives more reason, and generates more pressure, to make the therapy available in the host country.[32] Moreover, progress sometimes occurs in multiple steps. The experimental intervention might not make it back to the host country, but the results of the trial could easily lead to other trials with interventions that would make it back to the host country. If research demonstrates that a $50 therapy is almost as good as an $800 therapy, one can more readily justify a study of a $5 therapy.

While this objection to the second prong of the Glantz/CIOMS position has force, it seems insufficient to overcome that part of the position. If the intervention must be made available in the host country after the study, there are good reasons to require that the study's sponsor establish in advance that the intervention will in fact be made available. Given the examples of exploitation by researchers in the past and the serious harm caused to the research enterprise when the public becomes suspicious of the motives of researchers, we may want a strong rule to minimize the possibility of exploitation.

The response to the first part of the strict position of Glantz and CIOMS follows from my earlier point about people engaged in a mutual effort realizing different kinds of gain. Preventing exploitation does not demand that a treatment be made available in the country in which it is studied. Rather, it demands that the benefits to the host country be proportionate to the benefits realized by the country sponsoring the research. If the host country can benefit in ways other than using the studied treatment — by receiving appropriate royalties from the sale of the drug, for example — then no exploitation would result.

Moreover, it is possible to permit other kinds of benefit without compromising on the requirement that a research sponsor establish in advance that the benefit will definitely be provided (i.e., we can preserve the second prong of the Glantz/CIOMS position when we amend their first prong). Indeed, it may be easier to establish in advance the provision of appropriate royalties than to establish in advance that a drug being studied will be made available in the host country. A research sponsor may not be able to guarantee the proper functioning of all of the channels of drug distribution in a developing country, but it can guarantee the payment of a royalty on sales. In short, one can have a strong safeguard to prevent exploitation without requiring that a studied intervention be made available in the host country after the study.

It is not only feasible to allow different kinds of benefit, it may be desirable to do so. Denying the option of different kinds of benefit might wrongly tie the developing country's values to the values of the developed country. A wealthier country will likely place a higher value on treatments for disease than a poorer country that lacks clean water and other public health necessities. The developing country would do better to receive royalties or other payments that it could allocate to measures for preventing disease than to receive a drug for treating a disease that could have been prevented. Furthermore, by providing fixed payments rather than royalty payments, the study sponsors can ensure that a benefit is gained by the study subjects. If a developing country's benefit is to be realized solely through royalties, the country will

receive nothing if the experimental therapy does not make it to market.

Conclusion

In sum, we can accept the important principle that universal standards of ethics for human research (e.g., no exploitation) exist and also recognize that those principles apply differently when local circumstances vary. Studies that might be unethical in the U.S. may nevertheless be ethical in other countries, just as studies that are unethical in other countries may be ethical in the United States (e.g., a study in Kenya with compensation of $500).

When studies in developing countries take into account local circumstances, it is essential to employ strong safeguards that prevent exploitation. However, appropriately strong safeguards can be employed without requiring that a studied intervention be made available in the host country after the study is completed. Other kinds of benefit (e.g., royalties) can be provided to protect the host country from exploitation.

References

1. P. Lurie and S.M. Wolfe, "Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries," *N. Engl. J. Med.*, 337 (1997): 853–56, at 854–55.

2. R.A. Crouch and J.D. Arras, "AZT Trials and Tribulations," *Hastings Center Report*, 28, no. 6 (1998): 26–34, at 29; L.H. Glantz et al., "Research in Developing Countries: Taking Benefit Seriously," *Hastings Center Report*, 28, no. 6 (1998): 38–42, at 40–42.

3. E.M. Connor et al., "Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type I with Zidovudine Treatment," *N. Engl. J. Med.*, 331 (1994): 1173–80.

4. AZT treatment began when the women entered the study, which occurred between weeks fourteen and thirty-four of their pregnancies. *Id.* at 1174.

5. C. Levine, "Placebos and HIV: Lessons Learned," *Hastings Center Report*, 28, no. 6 (1998): 43–48, at 44. To be sure, there is some artificiality to the stated cost of drug therapy. Companies may be able to price far above actual costs and exact monopoly profits for drugs under patent protection. Furthermore, public pressure has been successful in lowering the market price of important drugs. Nevertheless, it is clear that citizens of developing countries cannot afford drug treatments to the same extent as citizens of developed countries.

6. Lurie and Wolfe, *supra* note 1, at 853–54.

7. *Id.* at 854–55.

8. K.J. Rothman and K.B. Michels, "Declaration of Helsinki Should Be Strengthened: FOR," *British Medical Journal*, 321 (2000): 442–45, at 443–44.

9. H. Varmus and D. Satcher, "Ethical Complexities of Conducting Research in Developing Countries," *N. Engl. J. Med.*, 337 (1997): 1003–05, at 1004–05; Crouch and Arras, *supra* note 2, at 27.

10. Glantz et al., *supra* note 2, at 40–41.

11. This example is based loosely on the Kenya Program of the Indiana University School of Medicine.

12. Some people might reject the view that a U.S. citizen's obligations to citizens and residents of the U.S. are greater than the citizen's obligations to people living in other countries (who are not citizens of the U.S.). However, as a matter of ethics and law, national borders matter. When Congress funds health care coverage for older persons, it acts ethically when it limits coverage to people living in the United States. Similarly, the constitutional rights of U.S. citizens and residents under U.S. law exceed those of noncitizens living in other countries. This distinction between local residents and people living in other countries reflects a number of considerations. First, ties of kinship matter. We recognize the interest of people in devoting more of their money and time to family members over strangers, to local nonprofit organizations over non-profits in other cities or states, to co-religionists over members of other religions, and to countrymen and women over people who live elsewhere. In addition, when people share citizenship or residency with each other, they share in a collection of rights and responsibilities. Nonresidents do not bear most of the responsibilities of community membership, and they therefore do not bear most of the rights of community membership.

13. Some people might find the drug company example unethical on grounds of exploitation, but I do not think we can condemn businesses simply because they bring a resource from a less developed country to a more developed country. It is not in the interest of developing countries if they are prevented from sending their fruits and vegetables, oil and gas, or precious minerals to other countries in exchange for goods that cannot be produced in their countries. The exploitation concern is discussed at length later in this article.

14. B.R. Furrow et al., *Health Law*, 2d ed. (St. Paul: West Group, 2000): at 265.

15. M. Baum, "Declaration of Helsinki Should Be Strengthened: AGAINST," *British Medical Journal*, 321 (2000): 444–45, at 445.

16. M. Angell, "The Ethics of Clinical Research in the Third World," *N. Engl. J. Med.*, 337 (1997): 847–49, at 847.

17. Some critics have questioned whether in fact the women gave true informed consent, and other critics have observed that many of the women suffered stigmatization when their HIV status became known. These objections are important, but they would apply to any research done in the same communities, regardless of whether a placebo control was used or whether the experimental therapy studied was destined for use in developing or developed countries.

18. Lurie and Wolfe, *supra* note 1, at 855.

19. *Id.* at 855.

20. Medical malpractice standards take into account local resources, but a physician practicing in an inner city clinic could not provide a lower level of care on account of the clinic's resources. Rather, if the patient needed care that could not be adequately provided in the clinic, the physician would transfer the patient to an appropriate facility.

21. In fact, the less aggressive, less expensive course of AZT treatment substantially reduces the risk of HIV-transmission from mother to infant, though not as effectively as the more aggressive, more expensive course of AZT. C. Grady, "Science in the Service of Healing," *Hastings Center Report*, 28, no. 6 (1998): 34–38, at 35–36.

22. H.T. Shapiro and E.M. Meslin, "Ethical Issues in the Design and Conduct of Clinical Trials in Developing Countries," *N. Engl. J. Med.*, 345 (2001): 139–42, at 140. See also National Bioethics Advisory Commission, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries*, ISBN

931022-13-5 (April 2001), *available at* <http://www.georgetown.edu/research/nrcbl/nbac/pubs.html> ("[r]esearchers and sponsors should design clinical trials that provide members of any control group with an established effective treatment, whether or not such treatment is available in the host country.").

23. World Medical Association, "Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects," *JAMA*, 284 (2000): 3043–45, ¶ 29, at 3045. In an October 2001 clarification, the World Medical Association indicated that placebo controls can be used even when proven therapy exists if (1) the placebo control is necessary to establish the safety or efficacy of an experimental therapy, or (2) the experimental therapy is designed for treatment of a "minor condition" and receiving the placebo will not increase the risk of "serious or irreversible harm." See World Medical Association, *Note of Clarification on Paragraph 29 of the WMA Declaration of Helsinki* (October 7, 2001), *at* <http://www.wma.net/e/policy/17-c_e.html#clarification> (last visited October 4, 2002).

24. R.J. Levine, "Some Recent Developments in the International Guidelines on the Ethics of Research Involving Human Subjects," *Annals of the New York Academy of Sciences*, 918 (2000): 170–78, at 174–76.

25. Varmus and Satcher, *supra* note 9, at 1004–05; Crouch and Arras, *supra* note 2, at 27.

26. Placebo controls — even when there is an established therapy — also have value for other kinds of studies. When testing an experimental therapy, one can determine whether it is effective with a smaller number of subjects if the experimental therapy is compared to a placebo rather than to established therapy. E.J. Emanuel and F.G. Miller, "The Ethics of Placebo-Controlled Trials — A Middle Ground," *N. Engl. J. Med*, 345 (2001): 915–19, at 916. For additional discussion of the justifications of placebo-controlled trials, see D. Orentlicher, "Placebo-Controlled Trials of New Drugs: Ethical Considerations," *Diabetes Care*, 24 (2001): 771–72.

27. See Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Guideline 10, *at* <http://cioms.ch/frame_guidelines_sept_2002.htm> (revised August 2002).

28. J. Feinberg, *The Moral Limits of the Criminal Law: Harmless Wrongdoing* (New York: Oxford University Press, 1988): 176–210.

29. *Id.* at 204–10.

30. Glantz et al., *supra* note 2, at 40–41.

31. Council for International Organizations of Medical Sciences, *supra* note 27.

32. Crouch and Arras, *supra* note 2, at 30–31.