The Standard of Care Debate: Can Research in Developing Countries Be Both Ethical and Responsive to Those Countries' Health Needs?

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To avoid exploitaiton of host communities, many commentators argue that subjects must receive the best methods available worldwide. Others worry that this requirement may block important research intended to improve health care, especially in developing countries.

To resolve this dilemma, we propose a framework for the conditions under which it is acceptable to provide subjects with less than the best methods. Specifically, institutional review boards should assume a default of requiring the "worldwide best" methods, meaning the best methods available anywhere in the world, in all cases.

However, institutional review boards should be willing to grant exceptions to this default for research studies that satisfy the following 4 conditions: (1) scientific necessity, (2) relevance for the host community, (3) sufficient host community benefit, and (4) subject and host community nonmaleficence. (*Am J Public Health.* 2004;94:923–928)

THE DISTRIBUTION OF HEALTH care around the world is marked by dramatic inequalities. Individuals in developed countries typically have access to safe water, new vaccines, and effective medications; individuals in developing countries often have access to little or no health care at all. These inequalities in health care have contributed to significant inequalities in health, with individuals who happen to live in the developing world experiencing far greater disease burdens and far shorter lives than individuals in the developed world. These inequalities have also led to a debate over what clinical investigators can do to improve health care in developing countries and thereby reduce health disparities between rich and poor.[1–6]

To protect host communities from exploitation, most commentators argue that efforts to improve health care in the developing world should never involve research that uses less than the "worldwide best"[7] methods, meaning the best methods available anywhere in the world.[8–15] Most notably, paragraph 29 of the Declaration of Helsinki states: "The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods."[7] Similarly, Shapiro and Meslin, chairman and executive director of the US National Bioethics Advisory Commission write: "In our view, an experimental intervention should normally be compared with an established, effective treatment . . . whether or not that treatment is available in the host [developing] country."[16(p140)]

A ban on research using less than the worldwide best methods would definitively address the potential for such research to exploit host communities. Yet, such a ban may also block important research designed to improve health care for the world's poor. Is it possible to address the potential for exploitation while allowing research that has the potential to benefit the host communities?

The debate over what standard of care should be required for individuals participating in research trials typically focuses on research conducted in developing countries by investigators from developed countries. This focus makes sense. Most clinical research is conducted by investigators from developed countries, and most communities lacking access to good health care are located in developing countries. Nonetheless, researchers from developing countries may also exploit host communities. And communities in developed countries sometimes lack access to the best methods available worldwide, increasing the potential that they may be exploited. A complete analysis, then, should address the potential for exploitation independent of the nationality of the investigators, or the geographic location of the study.

SCIENTIFIC NECESSITY

Some critics argue that research using less than the best methods available worldwide—medications, procedures, interventions, vaccines—is never scientifically necessary.[9,10,15] They conclude that requiring the best methods in all cases would allow investigators to obtain the same scientific information while providing greater benefits to subjects. This argument has focused on the controversial HIV vertical transmission trials.

So-called long-course treatment, also known as the 076 regimen, was—and remains—the best method for preventing transmission of HIV infection from mother to child. Unfortunately, the "early prenatal visits, intravenous infusion during labor, and cost" associated with long-course treatment make it neither affordable nor feasible in developing countries, where the burden of HIV disease is greatest.[17(p786)] To identify a method to help individuals in developing countries, investigators compared a less expensive, more easily administered "short course" of zidovudine (AZT) to what these individuals typically receive to prevent vertical trans-

mission—namely, no treatment at all. Criticism of these trials was widespread, with commentators arguing that the control arms could have used long-course AZT rather than no treatment, thus reducing the number of HIV-infected babies in the trials without undermining the scientific importance of the resulting data.[8–10,13]

Before the start of the short-course trials, data from South Africa showed wide variation in the HIV vertical transmission rate in untreated individuals over time, even at the same location.[18] These data provided compelling evidence, *ex ante*, that any assessment of short-course AZT needed an untreated control arm to determine whether the intervention was better than no treatment at all. This need for a no-treatment control arm was confirmed by the results of the trials themselves.

The transmission rates found in the trials—18.9% to 27.5% in the placebo arm[19–23] and 9.9% to 18% in the short-course arm—confirm that an equivalence trial

could well have shown a long-course transmission rate of 8%, and a short-course transmission rate of 17% (Table 1). Comparing this short-course transmission rate to the 076 placebo transmission rate of 25% would suggest that short-course treatment is better than placebo and possibly worth pursuing. Yet, the variability in the placebo transmission rate reveals that the placebo rate in an equivalence trial might have been 19%, suggesting that short-course treatment was not worth pursuing. The important point is that this result was a realistic possibility *at the outset,* implying that the trials needed a no-treatment arm to determine whether the short course was better than no treatment at all.

The literature, perhaps shaped by the debate over the HIV vertical transmission trials, has focused on what investigators may use as *controls* in clinical trials. Yet, a total ban on research using less than the best methods would also prevent investigators from assessing active agents that are

expected to be less effective than the worldwide best methods. This frequently overlooked implication of a total ban on less than the best methods is illustrated by the landmark nevirapine trials.

Approximately 75% of HIV vertical transmission occurs during or after delivery.[24] Thus, a treatment administered during delivery might offer a feasible, economical way to reduce HIV vertical transmission in developing countries, despite the fact that it would not affect the 25% of transmission that occurs during gestation.[25] This line of reasoning led investigators to nevirapine, a well-tolerated, low-cost, potent antiviral. A single 200-mg oral dose of nevirapine given during labor passes quickly through the placenta and has a long serum half-life.[26] Hence, a single dose of nevirapine given to the mother during labor, and to the infant within 72 hours of birth, might offer a feasible and affordable treatment for vertical HIV transmission in developing countries.

Because nevirapine does not offer protection against the approximately 25% of vertical transmission that occurs in utero, it was recognized at the time that it would be less effective than long-course AZT therapy. Hence, the requirement that trial participants receive the worldwide best methods implies that participants may not receive nevirapine alone, precluding assessment of nevirapine as a single agent. The human costs of this requirement are highlighted by the fact that trials conducted on nevirapine as a single agent have revolution-

ized perinatal HIV treatment in developing countries, potentially saving millions of lives.[27]

Determining whether a trial using less than the best methods is scientifically necessary requires clinical judgment based on the relevant probabilities: What are the chances the trial will answer an important question? What are the chances the same question can be answered by a trial using only the best methods? Because there is no infallible algorithm to answer these questions, institutional review boards will have to decide whether to allow less than the best methods on a case-by-case basis. To maximize subject benefit, institutional review boards should assume a default of requiring the best methods in all cases. From there, institutional review boards should allow research using less than the best methods only when scientifically necessary to answer an important question.

HOST COMMUNITY RELEVANCE

Provision of the best methods to everyone in the world would render incremental improvements in health care for developing countries otiose. To take just 1 example, approximately 10 million children die each year from diseases that could be prevented by aid amounting to less than 1% of the gross national product of developed countries.[28,29] Provision of such aid would save millions of lives and render unnecessary any research to assess whether less than the

TABLE 1—Outcomes of Short-Course AZT Vertical Transmission Trials: 1999–2000

Trial, Country, Year	Placebo Transmission Rate, %	Short-Course Transmission Rate, %	Long-Course Transmission Rate, %
076 Regimen, United States, 1999	25.5	NA	8.3
Placebo trial, Thailand, 1999	18.9	9.9	NA
Ivory Coast, 1999	24.9	15.7	NA
Ivory Coast, Burkina Faso, 1999	27.5	18.0	NA
Equivalence, Thailand, 2000	NA	10.5	6.5
Nevirapine, Uganda, 1999	25.1	13.1	NA

Note. AZT = zidovudine; NA = not available.

best methods may be partially effective in combating these diseases. Tragically, this aid has not been provided. In this context, research using less than the best methods sometimes represents the best hope for communities in developing countries to address their most significant health needs. When it does, when these trials address an important health need of communities in developing countries, the moral importance of helping the poor provides a strong argument in their favor.

SUFFICIENT HOST COMMUNITY BENEFIT

Even when scientifically necessary, and relevant to an important health concern of the host community, research using less than the best methods retains the potential to exploit host communities by failing to provide them with a fair level of benefits. The fairness of the benefits to the host community depends on the burdens and risks it bears and the extent to which others benefit from its participation in the trial.[30] In particular, as the host community assumes greater burdens, or others enjoy greater benefits from its participation, the institutional review board should insist that the host community receive correspondingly greater benefits to ensure a fair trial.

Beforehand, it may be unclear whether the tested method, even if proved effective, will be implemented in the host community. In such cases, the fact that the trial addresses an important

health concern may not in itself offer a fair level of benefits. Similarly, trials may produce so much benefit for others that the information provided to the host community does not represent a fair proportion of the overall benefits.[11] In these cases, the host community should receive additional benefits, such as development of clinics or training of nurses, to ensure that the overall benefits it receives are fair given the burdens it experiences and the benefits others receive from its participation.[30]

The need for a fair level of benefits highlights the fact that a ban on research using less than the worldwide best methods, although intended to *minimize* the potential for exploitation, may *increase* it in practice. To ensure that the host community receives sufficient benefits, investigators might focus their research on methods that the host communities can implement, if proved successful. Insisting that investigators use the worldwide best methods may force them to abandon these attempts to assess methods that can be implemented in the host communities, thereby increasing the chances for exploitation.

SUBJECT AND HOST COMMUNITY NONMALEFICENCE

The principle of nonmaleficence implies that research using less than the best methods should be allowed only when it will not make research subjects or the host community prospectively worse off.[31] To satisfy this

requirement, such research should not harm the existing health care system. For instance, research should not rely on nurses or laboratories that are needed to care for patients in the host community. Second, it is important to ensure that research using less than the worldwide best methods does not make subjects prospectively worse off than they would be in the absence of the trial. Provided there is clinical equipoise between the proposed new treatment and the local methods of care, individuals who enroll will receive either the methods they would have received otherwise, if any, or a method not known to be inferior to it.[32] When this condition is met, research participation can offer subjects an important benefit by providing access to medical interventions not otherwise available to them.

Satisfaction of these 4 conditions—scientific necessity, host country relevance, sufficient benefit, nonmaleficence—ensures that research using less than the worldwide best methods addresses an important health concern of the host community and offers the host community sufficient benefit without making subjects worse off. This potential to help the world's poor provides an important ethical argument in favor of allowing such research.

POSSIBLE OBJECTIONS

1. *These trials violate investigators' clinical obligations.* The US National Bioethics Advisory Commission and others argue that researchers gain moral obli-

gations to provide the best care possible when they enter into clinical relationships with research subjects.[31,33–35] This view implies that investigators should not conduct research using less than the best methods even when it satisfies the 4 conditions outlined: a potential for future benefit, no matter how great, cannot justify the violation of researchers' obligations to provide present subjects with the best methods. Although this argument seems compelling, it is not clear that it accurately reflects clinicians' obligations.

Clearly, investigators have clinical obligations that go beyond the scientific needs of particular research trials. Investigators cannot justify trials using less than the best methods simply by arguing that in the absence of the trial, subjects would receive nothing. For instance, an investigator working in the developing world cannot decide against providing her subjects with cardiopulmonary resuscitation at little or no cost simply on the grounds that, in her absence, they would not receive it. At the same time, investigators' clinical obligations do not seem to imply they must provide the worldwide best methods in all cases. It is widely agreed that investigators assessing whether aspirin reduces mortality from heart attacks in a developing country would not be required to provide subjects with coronary artery bypass surgery,[36] much less coronary intensive care in case of a myocardial infarction.[37] What implications does the fact that clinicians need not provide these worldwide best

methods have for the standard of care debate?

One's moral obligations depend in part on the costs associated with the available alternatives.[38–40] Whether I have a moral obligation to save a drowning child depends upon what is required, and what I must forgo. If I can save the child at little or no cost to myself or others, then I am obligated to do so. If saving the child would put me at great risk of death, or prevent me from saving several other children, I am not obligated to do so.

Physicians' obligations to their patients are similarly shaped by the relevant costs. This is obvious, although often implicit, in the context of standard medical care. To take an example relevant to developing countries, the Elizabeth Glaser Pediatric AIDS Foundation devoted a $100 million grant from the US Agency for International Development to blocking vertical transmission of HIV from mother to child in the developing world.[41] Long-course AZT therapy (the 076 regimen) is the worldwide best method for blocking vertical transmission of HIV from mother to child. Hence, the claim that clinicians are obligated to provide those for whom they care with the best methods implies that the clinicians working on this project are obligated to provide long-course AZT to block vertical transmission of HIV.

Assuming a cost of $250 per mother–child pair treated, provision of long-course AZT would translate into approximately 65 000 fewer HIV-infected children compared with the back-

ground infection rate without treatment. Conversely, devoting the same money to single-dose nevirapine, at $4 per mother–child pair, translates into approximately 270 000 fewer HIV-infected children compared with the background infection rate without treatment. That is, providing nevirapine rather than long-course AZT has the potential to save an additional 200 000 lives.

This difference supports the claim that the foundation made the ethically appropriate choice—supply nevirapine—even though its decision entails that the foundation's clinicians will fail to provide the worldwide best methods to block vertical transmission when they could have done so. This conclusion suggests that the provision of less than the best methods can be consistent with physicians' clinical obligations when providing the best methods would entail unacceptably high costs. Determining exactly how high the associated costs must be to justify providing less than the best methods will be difficult, and institutional review boards will have to use their judgment. Under the proposed 4 conditions, researchers may use less than the best methods only when their use is scientifically necessary to address an important health concern of the host community. Insisting that researchers provide all subjects with the best methods in such cases would entail a high cost, represented by the importance of the health concern that thereby goes unaddressed.

2. *These trials rely on a double standard.* Some commentators

argue that it is unethical to conduct research in the *developed* world using less than the best methods. Hence, allowing such trials in the *developing* world relies on a double standard: "Acceptance of a standard of care that does not conform to the standard in the sponsoring country results in a double standard in research. Such a double standard . . . permits research designs that are unacceptable in the sponsoring country."[8(p854)]

The fact that a particular trial design is allowed in one place but not another does not in itself constitute a double standard.[42] For there may be relevant differences—environmental, genetic, social, cultural differences—that render the same design acceptable in one place, but not the other. To take a straightforward example, no one would argue that approving research using bovine-derived drugs in the United States but not in India constitutes an ethical double standard.

Because patients in developed countries typically have access to the worldwide best methods, research using less than the best methods typically does not have sufficient social value to justify its risks. In contrast, such research may have sufficient social value in developing countries, where the existing standard of care is something less than the worldwide best. This suggests that research using less than the worldwide best methods can be ethically acceptable in developing countries, even though the very same research would be unethical in a developed country.

Furthermore, when a developed country makes a reasonable decision not to provide a worldwide best treatment on grounds of cost-effectiveness, it may be acceptable to conduct research in that country on less effective methods.[43] For instance, a new type of erythropoietin has been developed that is expected to be as effective as existing versions for postchemotherapy supportive care, and more easily administered. During the time this newer drug is on patent, it is likely to be very expensive, and a developed country may decide on cost-effectiveness grounds to provide its citizens with the older, less-convenient version. Assuming this decision is a reasonable one, it seems ethically acceptable to conduct trials in that country that compare proposed new treatments to the older version, rather than the worldwide best version.

3. *These trials are counterproductive.* Some critics argue that research using less than the best methods may be counterproductive, reducing pressure on host governments to reform, or pharmaceutical companies to provide treatments at an affordable price. "The issue of the affordability of drugs should be tackled by getting governments, pharmaceutical companies, donors, and other international agencies to cooperate in making drugs cheaper rather than by looking for other, probably inferior, regimens for people in less-developed countries."[44(p842)]

This possibility highlights the importance of assessing the ethical acceptability of research

using less than the best methods in light of *all* feasible alternatives. If an individual study, or even series of studies using less than the worldwide best methods would impair a realistic chance that the host country will receive state-of-the-art health care for the condition under study, such studies should be prohibited. However, when there are no realistic alternatives for the foreseeable future to address the health concern in question, use of less than the worldwide best methods may represent the best hope for the host communities. Here too, institutional review boards must use their judgment. What are the chances that the research use of less than the best methods will lead to the development of a feasible and economical treatment? What are the chances, in the absence of these trials, that the best methods will be provided for the condition in question?

SUMMARY

Critics rightly point out that research using less than the worldwide best methods has the potential to be scientifically unnecessary, counterproductive, exploitive, inconsistent with investigators' clinical obligations, and based on an ethical double standard. Fortunately, these possibilities, although important, are not inevitable. Investigators should be allowed to use less than the worldwide best methods only when doing so is ethically appropriate and has the potential to provide sufficient benefit for the host communities.

Specifically, institutional review boards should assume a default of requiring the best methods in all cases and approve research using less than the worldwide best methods only when it satisfies the following 4 conditions: (1) scientific necessity: investigators must use less than the worldwide best methods to answer the scientific question posed by the trial; (2) relevance for the host community: answering the scientific question posed by the trial will help address an important health need of the host community; (3) sufficient host community benefit: the trial will produce a fair level of benefit for the host community; and (4) subject and host community nonmaleficence: subjects and the host community will not be made prospectively worse off than they would be in the absence of the trial. ■

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Contributors

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