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Research

The Ethics of Research in Lower Income Countries: Double Standards Are Not the Problem

David S. Wendler

ABSTRACT

Discussion of the ethics of clinical trials in lower income countries has been dominated by concern over double standards. Most prominently, clinical trials of interventions that are less effective than the worldwide best treatment methods typically are not permitted in higher income countries. Commentators conclude that permitting such trials in lower income countries involves an ethical double standard. Despite significant attention to this concern, and its influence over prominent guidelines for research in lower income countries, there has been little analysis of what constitutes an ethical double standard in clinical research. The present article attempts to address this gap in the literature. This analysis finds that ethical double standards involve a kind of disrespect, and yields a three-step decision procedure for evaluating when trials of less than the worldwide best methods raise this concern. Application of this procedure reveals that permitting these trials in lower income countries rarely involves an ethical double standard. Instead, the real challenge is determining when clinical trials of interventions that are less effective than the worldwide best represent a permissible and effective response to differences in access to healthcare between higher income and lower income countries. To protect research subjects, without blocking clinical trials that have the potential to improve health in lower income countries, research review committees and other stakeholders should focus on this issue, not on ethical double standards.

Clinical trials of interventions and medications that are less effective than the best interventions and medications that are available worldwide (hereafter referred to as the worldwide best methods) raise important ethical concerns and have been the subject of significant debate, especially when the clinical trials are funded by entities in higher income countries and are conducted in lower income countries.[1] Proponents argue that trials to assess less than the worldwide best methods have the potential to improve health in lower income countries and, thereby, reduce health disparities between lower income and higher income countries.[2] Critics respond that such trials are not permitted in higher income countries. They conclude that the trials are unethical,[3] and they should not be permitted in lower income countries either.[4]

Despite the importance of this debate, and the fact that it is now entering its third decade, there is still no analysis in the literature of what constitutes an ethical double standard in clinical research. As a result, it is unclear which trials should be permitted and which trials should be prohibited. The present article attempts to address this gap in the

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literature by providing an analysis of ethical double standards and using it to identify those factors that are relevant to assessing when permitting a trial using less than worldwide best methods involves an ethical double standard. This analysis yields a three-step decision procedure, which suggests that clinical trials in lower income countries rarely raise concern over ethical double standards. This analysis further suggests that disagreement over the appropriateness of clinical trials that use less than worldwide best methods traces to a related but distinct issue. It traces to disagreement over whether permitting these trials represents a permissible and effective response to differences in access to healthcare between higher income and lower income countries.

Evaluation of this distinct concern requires stakeholders to answer three questions that are obscured by a focus on ethical double standards. First, is conducting the trial consistent with the obligations of those involved? As we shall see, the answer to this question frequently depends on who is sponsoring the study. Second, will permitting the trial be counterproductive in the sense of leading to worse healthcare in the long run for the affected communities? Third, will permitting the trial increase the potential for abusive research? To protect research subjects without blocking appropriate studies that have the potential to reduce health disparities between higher income and lower income countries, research review committees, guidelines, and other stakeholders should focus on these questions, not on ethical double standards.

BACKGROUND

The ethics of clinical trials that use less than the worldwide best methods gained attention in 1997.[5] At the time, the 076 regimen (also known as "long-course" azidothymidine/zidovudine—AZT) was known to be effective at reducing vertical transmission of human immunodeficiency virus (HIV) from mother to child.[6] However, there was concern that this regimen might not be feasible and affordable in lower income countries, leading investigators to a series of trials that compared a truncated version of the 076 regimen (so-called "short-course" AZT) to placebo.[7]

Proponents argued that testing a potentially feasible and affordable regimen offered significant potential benefits to mothers and infants in lower income countries who otherwise had little to no access to effective interventions. Nonetheless, this study design would not have been permitted in higher income countries, where pregnant women had access to the 076 regimen. Critics concluded that permitting these trials in lower income countries, but not in higher income countries, involved an ethical double standard.[8] Twenty years later, this charge continues to influence discussion of the ethics of clinical trials in lower income countries. Most prominently, the revision process that led to the current version of the *World Medical Association Declaration of Helsinki* (hereafter, the *Declaration of Helsinki*) included significant debate over when trials using less than the best methods should be permitted in lower income countries.[9] An expert conference, convened by the World Medical Association in Sao Paulo, Brazil, in 2011, to settle this debate, led to a preliminary proposal to allow these trials in limited circumstances (disclaimer: I was a participant at this conference).[10] This proposal was later dropped in response to objections that permitting trials of less than the best methods in lower income countries involves an ethical double standard. The *Declaration of Helsinki* thus directs physicians and other stakeholders to conduct trials using less than the best methods only when the research subjects are not exposed to any "additional risks of serious or irreversible harm as a result of not receiving the best proven intervention."[11] The *CIOMS* (Council of the International Organizations of Medical Sciences) *International Ethical Guidelines for Health Related Research Involving Humans* (hereafter, the *CIOMS Guidelines*) similarly allow use of less than the best methods only when "delaying or withholding the established effective intervention will result in no more than a minor increase above minimal risk to the participant."[12]

These requirements block essentially all clinical trials on interventions and medications that are less effective than the worldwide best, including trials that have the potential to reduce health disparities between higher income and lower income countries. To evaluate whether this prohibition is justified, it will be helpful to consider an example that is unrelated to the HIV trials.

LESS THAN THE WORLDWIDE BEST CHEMOTHERAPY

Stem cell transplantation is the worldwide best treatment for many leukemia patients.[13] Stem cell transplantation also costs several hundred thousand dollars per patient, far beyond the means of many lower income countries. With this in mind, imagine that an investigator develops an experimental combination of medications that were used to treat leu-

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kemia in higher income countries before the advent of stem cell transplantation. While this combination almost certainly will not be as effective as transplantation, it may be more effective than the treatments currently available for most leukemia patients in lower income countries. Moreover, because the drugs are no longer on patent, the combination would be affordable.

Because the proposed chemotherapy combination is likely to be more effective than the treatments that are currently available to individuals in lower income countries, these individuals would be better off enrolling in the chemotherapy trial than pursing the standard care that is available to them. At the same time, these individuals would face a higher risk of death in the chemotherapy study than they would face if they received transplantation. Clinical trials to evaluate this experimental combination thus would violate the *Declaration of Helsinki*'s requirement to use less than the best methods only when subjects do not face any additional risks of serious harm compared to the risks they would face with the best intervention. These clinical trials would also violate the *CIOMS Guidelines*, which allow trials of less than the best methods only when the trials pose no more than a minor increase over minimal risk compared to the worldwide best treatments. Should the chemotherapy trial be prohibited, despite its potential to benefit participants, on the grounds that permitting it would involve an ethical double standard?

ETHICAL DOUBLE STANDARDS

The potential for ethical double standards arises when individuals (or groups) are treated differently. Of course, differential treatment is often permissible, sometimes even obligatory. Imposing a fine on one individual, but not another, does not constitute an ethical double standard when the two have behaved differently in relevant ways. Similarly, with respect to clinical trials, it can be ethically appropriate to permit a trial in one place or population but prohibit it in another. For example, it would be permissible to conduct a study involving a bovine-derived drug in the United States, but to prohibit such a trial in Hindu communities in India. The difference in the permissibility of the trial would be justified by the differences in the fundamental values of the two populations.[14] Put differently, differential treatment at the level of a specific trial is the result of a uniform application of the principle that clinical trials should be conducted in ways that respect the fundamental values of the host communities.

As this example highlights, differential treatment raises the potential for ethical double standards only when some individuals are treated less well, despite their being similar in relevant respects. And one might argue that unjustified differential treatment involves an ethical double standard in all such cases, including when differential treatment traces to purely random behavior on the part of the agent in question. For example, one might regard as an ethical double standard randomly fining some individuals but not others. Granting this theoretical possibility, ethical double standards are especially troubling when some individuals are treated less well because they are regarded as inferior or less deserving. Fining one individual but not another is especially troubling when the differential treatment traces to the fact that the fined individual belongs to a socially disparaged group. This analysis suggests that ethical double standards involve unjustified worse treatment that represents a particular kind of disrespect, namely, treating some individuals (or groups) worse because they are regarded as inferior or less deserving than other, similarly situated individuals (or groups).

Appeals to ethical double standards are used to condemn certain behaviors by pointing out that an agent behaved inconsistently across relevantly similar cases. This is distinct from a claim that the treatment of the disparaged group, considered in isolation, violates an ethical constraint on the agent's behavior. Imagine, for example, that the agent in the previous example is not permitted to fine anyone. In that case, one can condemn the agent's behavior by pointing out that the agent is not permitted to issue fines. This criticism does not cite differential treatment, hence, it does not involve an appeal to ethical double standards.

Similarly, one might condemn clinical trials in lower income countries that use less than the best methods, not by an appeal to ethical double standards, but by arguing that researchers have an obligation to provide the best methods to their subjects. Consider the following passage in the *CIOMS Guidelines*: "In general, studies must be designed to generate sound scientific information without delaying or withholding established effective interventions from participants. Researchers and sponsors may deviate from this default rule when withholding such interventions is methodologically necessary and exposes participants to no more than a minor increase above minimal risk."[15] If researchers do have a general obligation to provide research participants with the best available methods, all studies that use less than the best methods would be

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unethical. In that case, one could condemn these trials without citing the inconsistency of prohibiting the trials in higher income countries. This inconsistency might add to the ethical concern, but it would not represent the primary problem with these trials, namely, that they are inconsistent with the investigators' obligations.

"Appropriate respect" is typically regarded as a behavioral side constraint, in the sense that disrespect is not permitted, even when the consequences are otherwise acceptable. To see this, imagine I teach clinical investigators that they should treat research participants in lower income countries with disrespect, but only when some good may come of it, and when doing so does not pose serious risks. This would be odd. Respect for research participants is mandatory in all cases; it is not something that can be justified when it benefits others and the risks are low. Notice, however, that the *Declaration of Helsinki* and the *CIOMS Guidelines* allow trials that use less than the best methods when the risks to subjects are sufficiently low. This approach would be odd in the same way if such trials involved an ethical double standard. In that case, the guidelines for appropriate behavior on the part of researchers would be claiming that disrespect of individuals in lower income countries can be acceptable when the risks to them are not too great. The assumption that these guidelines do not condone disrespect, even when it poses low risks, suggests that opposition to these trials may not trace to concern over ethical double standards. We will pursue, and, I shall argue, ultimately confirm this suggestion.

DECISION PROCEDURE

I have argued that ethical double standards represent a particular kind of disrespect, one in which some individuals are treated worse because they are considered to be inferior or less deserving than other, similarly situated individuals. On this analysis, whether permitting a trial of less than the best methods in a lower income country involves an ethical double standard depends on three questions. Taken together, they provide a decision procedure that research review committees (and other stakeholders) can use to evaluate the potential for ethical double standards (see figure 1).

First, are there ethically relevant differences between conducting the trial in lower income versus higher income countries? Second, does one or more of the ethically relevant differences support differential treatment? Third, do the ethically relevant differences together justify permitting the trial in lower income but not in higher income countries? If the answer to any of these questions is "no," permitting the trial raises concern over an ethical double standard. In addition, as I have argued above, the potential for an ethical double standard is especially concerning when it is based on the view, or seems to convey the view, that individuals in lower income countries do not deserve the worldwide best methods. To illustrate this approach, we shall consider how it applies to the proposed combination chemotherapy study described earlier.

Step 1

Stem cell transplantation is feasible and affordable in higher income countries, but not in lower income countries. Hence, the study of a low-cost chemotherapy combination therapy has potential value for lower income countries, but not for higher income countries. Furthermore, research subjects in lower income countries would not receive stem cell transplantation if the low-cost trial was not conducted. Thus, enrollment in the trial does not make the participants worse-off than they would be, absent the trial. This suggests that there are ethically relevant differences between conducting the trial in lower income versus higher income countries.

Step 2

The assessment of the chemotherapy combination therapy has significant potential value for lower income countries, but not for higher income countries. This provides a strong reason to permit the trial in lower income countries, but not in higher income countries. Specifically, value for the host community or population is widely endorsed as an important ethical consideration that argues in favor of permitting a trial.

Step 3

Because some ethical considerations support a trial does not establish that it should be permitted in lower income countries. We still need to determine whether there are any other ethically relevant considerations that conflict with differential treatment. In theory, this question can be difficult to answer, because it can be difficult to determine whether one has taken into account all of the relevant ethical considerations. In addition, the justification for the trial is that individuals in lower income countries are worse-off in the sense of not having access to the worldwide best methods. This raises concern that conduct of the trial is based on the belief that individuals in these countries do not merit the best methods. Explicitly permitting such trials may be

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perceived as unseemly, because they may be seen as calling attention to the fact that individuals in lower income countries are worse-off than those in higher income countries.

One way to address these concerns in practice is to consider whether it would be acceptable, if similar circumstances obtained, to conduct the proposed study in a higher income country.[16] This approach offers a way to assess whether ethically relevant considerations are being inadvertently ignored. By removing the potentially disparaged characteristic of being from a lower income country, this approach offers a way to help ensure that permitting a trial does not reflect the belief that those in lower income countries are less deserving.

WOULD THE TRIAL BE ACCEPTABLE IN HIGHER INCOME COUNTRIES?

Imagine that some leukemia patients in a higher income country do not have health insurance and cannot afford stem cell transplantation. To make the cases parallel, imagine that the population's poverty and lack of access to effective healthcare is due, in part, to historical discrimination and injustice.

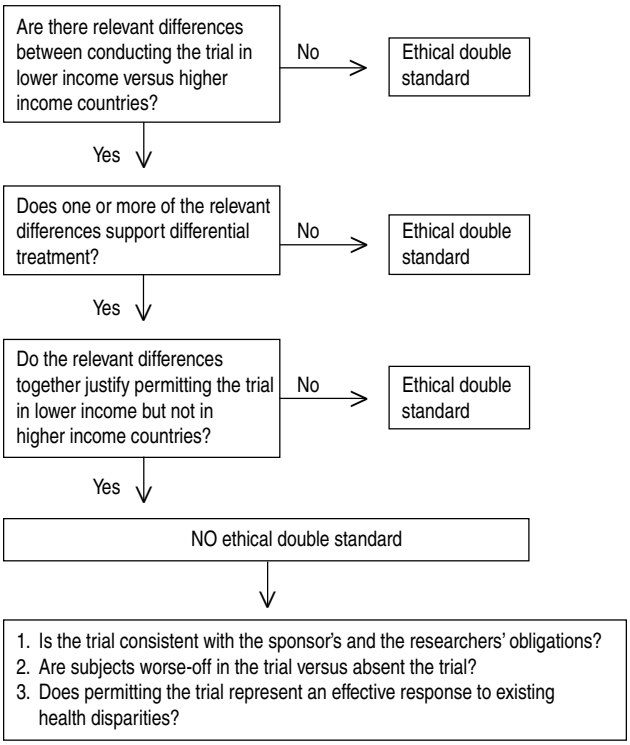

FIGURE 1. When does permitting a trial of less than the best methods in a lower income country, but not in higher income countries, constitute an ethical double standard?

Finally, imagine that the company that controls the treatments used in stem cell transplantation declines, without justification, to offer the treatments to members of the population at a price they can afford.

In this setting, it seems unethical for this company to conduct a trial of the low-cost chemotherapy combination therapy. Arguably, the company should offer the best treatment methods at a cost that these individuals can afford (or the government should provide stem cell transplantation to patients who need it). This conclusion highlights an important point. Because circumstances might justify a study of less than the best methods does not imply that such trials are acceptable no matter who conducts them: one also needs to assess whether the proposed sponsor has an obligation to provide the population in question with the best treatment methods.

Now imagine that this situation continues for years, despite concerted efforts by a nonprofit organization to force the company or government to provide the best treatment. Recognizing the enduring nature of the situation, and that many patients who need treatment are not receiving it, the nonprofit proposes to test the experimental combination therapy. In this case, the trial does not involve an ethical double standard, because there is an ethically relevant difference between this population and most leukemia patients in the U.S., namely, access to stem cell transplantation. The nonprofit clearly is not saying that the affected population does not deserve the best treatment methods for leukemia. In other words, the differential treatment is not an instance of disrespect. Instead, the nonprofit continues to regard the current circumstances as ethically inappropriate. Its goal is to help the population by the means available.

ETHICAL DOUBLE STANDARDS ARE NOT THE ISSUE

In the hypothetical case above, potential participants had no access to transplantation. This lack of access represents an important ethical difference that supports conducting a trial of the low-cost chemotherapy combination therapy in this population, but not in others. In addition, the fact that the population did not have access to transplantation implies that enrollment in the trial was consistent with their prospective interests, in the sense that the risk/benefit profile of enrolling in the study was at least as favorable as the available alternatives. Of course, enrollment in the trial may turn out, on balance, to be harmful to one or more of the participants. None-

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theless, enrolling in the trial was prospectively in the participants' interests. This suggests that trials of less-effective interventions should be permitted only when subjects who enroll will not be made prospectively worse-off than they would have been, absent the trial. The low-cost chemotherapy example thus suggests that allowing trials of less than the best methods does not constitute an ethical double standard when there are differences in access to effective treatments that might be at least partially addressed by the trial, and enrollment does not make participants prospectively worse-off.[17]

Trials of less-effective interventions typically are not of value for higher income populations who already have access to the worldwide best interventions. Instead, the value of the trial involves the possibility of providing disadvantaged populations with some effective treatment and at least reducing health disparities. Furthermore, if the population does not have access to the worldwide best methods, provision of less-effective methods often will satisfy the condition of not making subjects prospectively worse-off. It follows that the design of many, perhaps most, trials of less than the best methods in lower income countries do not raise concern over the potential for ethical double standards. Whether these trials are permissible then depends on whether those involved have an obligation to provide host communities with the worldwide best methods. When the investigators and the funders do not have an obligation to provide the best treatment methods, the trials can be ethically appropriate.

This conclusion is not based on claims that critics question or reject. It is based on the claim that whether a study is relevant to the health needs of a host community and whether enrollment makes subjects prospectively worse-off are important ethical considerations. Almost all commentators and guidelines, including those skeptical of clinical trials using less than the best methods, endorse these claims. For example, the *CIOMS Guidelines*, which preclude most trials of less than the best methods, state that clinical trials in low-resource settings must be "responsive to the health needs or priorities of the communities or populations where the research will be conducted."[18] Similarly, in an article questioning the appropriateness of the HIV vertical transmission trials, Glantz and colleagues argue that "research is, by definition, designed to create generalizable knowledge, and is only legitimate in a developing country if its purpose is to create generalizable knowledge that will benefit the citizens of that country."[19] One more example: Shapiro and Meslin, who led a U.S. bioethics commission that assessed the ethics of research in lower income countries, argue that clinical trials sponsored by higher income countries and conducted in lower income countries should provide participants who have life-threatening illnesses with the best care available anywhere in the world. They also claim that these trials "should be limited to those that are responsive to the host country's health needs. If the intervention being tested is not likely to be affordable in the host country or if the healthcare infrastructure cannot support its proper distribution and use, it is unethical to ask persons in that country to participate in the research."[20]

Even opponents to conducting such research in lower income countries regard the relevance of the research to the host community as ethically vital to clinical trials. This provides further evidence that their opposition to trials using less than the best methods does not trace to the potential for ethical double standards. It does not trace to the claim that there are no ethically relevant differences between the host communities and higher income countries that can justify permitting the trials in the former but not in the latter. To the contrary, these commentators and guidelines stipulate that clinical trials must be responsive to the host communities' health needs and priorities. What then explains the intense and enduring disagreement? Why do commentators insist on provision of the worldwide best methods to research participants in lower income countries if this very stipulation renders many trials inconsistent with their own ethical principles?

THE ACTUAL POINTS OF DEBATE

As noted previously, some commentators claim that researchers have a general obligation to provide all research participants with the best treatment methods that are available anywhere. While this claim would provide clear and strong opposition to trials of less than the best treatment methods, without any appeal to ethical double standards, it is implausible. Even clinicians from higher income countries who work in lower income countries do not have an obligation to provide the best treatment methods to all of their patients. Unless one thinks that researchers have greater obligations in this regard than clinicians do, it follows that researchers do not have a general obligation to provide research participants with the worldwide best methods.

This conclusion needs to be distinguished from the claim that certain parties may have obligations to provide research participants with the best available treatment methods. In the previous example, it

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was suggested that the company that controls the treatment might have been obligated to provide stem cell transplantation to all patients who need it. If that is the case, the company that controls the treatment should not be permitted to conduct a trial of a lesser intervention. The first challenge in evaluating the ethical acceptability of trials that use less than the best methods, then, is determining whether permitting these trials is consistent with the obligations of the specific funders and/or researchers.

Second, research studies of less than the best methods can be justified when they offer important benefit to the host population. To make sure that this condition is satisfied, research review committees should not merely consider whether the trial represents an advance on the *status quo*; they should also consider the long-term consequences of allowing the trial. In some cases, permitting trials that assess second-best interventions may reduce pressure to eliminate the underlying disparities altogether.[21] In the example above, could the nonprofit have used its resources to pressure the government to provide stem cell transplantation to leukemia patients? Or might it have been able to pressure the company that controls the treatment to lower its prices to the point that the best treatment is affordable to the patients? The answers to these questions will depend on each case and circumstances. Hence, rather than adopting a blanket approach and blocking all trials of less than the worldwide best interventions, research review committees and other stakeholders should permit such trials only after determining that the existing circumstances are unlikely to be remedied in the foreseeable future.

To consider a specific example, one critic of trials in lower income countries that use less than the best methods argues that the trials are based on the assumption that the circumstances of the subjects may be problematic, but require "no outside effort to improve care and protection beyond what is locally available." The author goes on to argue that these trials display "indifference to harm and neglect, ignoring the deprivations they confront and failing to exercise the social virtues of palliating destitution of their research subjects."[22] The author is right to be concerned with the extent to which such trials are appropriately responding to the needs of local populations. When the trials are not responding appropriately, or when there is an available alternative response that would benefit local populations more, the trials should not be permitted.

Third, insisting that all research studies use the best treatment methods offers important protection for research subjects. It essentially ensures that subjects will not be made worse-off by enrolling in research studies. This suggests that permitting trials that involve less than the best treatment methods in lower income countries may increase the chances that unacceptable trials are approved as well. To take an analogous case, the requirement that research subjects must provide their own informed consent to participate in research—that is, are decisionally capable adults—offers important protection to participants. But this requirement also has the potential to block valuable research that will benefit those who cannot consent for themselves, such as research needed to improve healthcare for children. Recognizing this dilemma, most regulations permit research that involves children, but also adopt additional requirements to block abusive studies. The regulations establish a default of enrolling individuals who can consent, and allow research that involves children only when: enrolling children is necessary, the study is valuable, and the risks are acceptable. Research review committees should similarly adopt a default of requiring clinical trials to use the worldwide best interventions. Nonetheless, they should permit trials of less than the best methods when the funders/sponsors/investigators do not have an obligation to provide the best treatment methods, the trials offer important value for the host community, and enrollment will not make the research subjects prospectively worse-off.

SUMMARY

Intense disagreement over when it can be appropriate to conduct clinical trials of less than the worldwide best methods in lower income countries is now entering its third decade. Critics argue that these studies are unethical on the grounds that permitting them involves an ethical double standard. This article argues that studies of less than the worldwide best methods in lower income countries rarely raise concerns over ethical double standards. This conclusion suggests that stakeholders should focus instead on three questions that are obscured by a focus on ethical double standards. First, is conducting the trial in question consistent with the obligations of those involved? Second, will permitting the trial be counterproductive in the sense of leading to worse healthcare in the long run for the affected communities? Third, will permitting the trial increase the potential for abusive research? This approach offers the potential to protect research participants without unnecessarily blocking clinical trials that benefit them and their communities and, thereby, reduce existing disparities in health be-

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tween higher income and lower income communities and countries.

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