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## The Ambiguity and the Exigency: Clarifying ‘Standard of Care’ Arguments in International Research

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### ABSTRACT

This paper examines the concept of a ‘standard of care’ as it has been used in recent arguments over the ethics of international human-subjects research. It argues that this concept is ambiguous along two different axes, with the result that there are at least four possible standard of care arguments that have not always been clearly distinguished. As a result, it has been difficult to assess the implications of opposing standard of care arguments, to recognize important differences in their supporting rationales, and even to locate the crux of the disagreement in some instances. The goal of the present discussion, therefore, is to disambiguate the concept of a ‘standard of care’ and to highlight the areas of genuine disagreement among different standards. In the end it is argued that one standard of care argument in particular is more complex than either its proponents or its critics may have recognized and that understanding this possibility opens up a potentially promising avenue of inquiry that remains to be carefully explored.

*Key words:* clinical trials, Declaration of Helsinki, international research standards

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### I. INTRODUCTION

For some time now, the medical and bioethics communities have been struggling with a number of difficult and sometimes divisive issues concerning the ethics of international research. Many of these issues were raised in the recent controversy over the decision to use placebo control groups in clinical trials designed to test the efficacy of a short-course of zidovudine (AZT) for the prevention of maternal-infant HIV infection in sixteen countries in sub-Saharan Africa, Southeast Asia, and the Caribbean. The studies, sponsored by the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC), became the topic of a heated debate when a pair of articles published in the *New England Journal of Medicine* (Angell, 1997; Lurie and Wolf, 1997) charged

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that the use of a placebo control group made them unethical. Even though subsequent studies involving placebos were either suspended or modified after the completion of a CDC-sponsored study in Thailand, the controversy has continued and the ethical and scientific debate has intensified. Now, however, the dispute surrounding some of these issues could have far-reaching implications for the whole of international human subjects research. Plans are underway to revise key guidelines governing the ethical conduct of international medical research, and several of the most controversial issues at the heart of the short-course AZT trials are playing a central role in the debate over some of the proposed revisions.

Rather than attempting a wholesale appraisal of the diverse and complex array of issues involved in this debate, the present paper will focus instead on one prominent, and highly controversial, issue. From the outset of the controversy over the short-course AZT studies, both proponents and critics of the placebo-controlled design supported their positions with what I will call the ‘standard of care’ argument. Critics argued that the placebo driven trial design was unethical, at least in part, because it failed to provide the current standard of care to all members of the clinical trial. In support of their position they pointed to article II.3 of the Declaration of Helsinki which states that “In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method.” They also pointed to the fact that in technologically developed countries such as France and the U.S., the standard treatment used for preventing the transmission of HIV from seropositive pregnant women to their infant children, known as the AIDS Clinical Trials Group (ACTG) regimen 076, had been shown to cut maternal-infant HIV transmission rates by more than half (Connon *et al.*, 1994; Sperling *et al.*, 1996). To adopt a standard of care for developing nations that falls below the standard of care in the sponsoring countries, it was argued, was to adopt an unacceptable double standard in international research.

Proponents of the placebo design countered by pointing out that the 076 protocol was unavailable in the countries that would host the short-course trials because, at \$800 per dose, it far outstripped the \$10 average per-capita health budgets of the developing countries in which the trials had been proposed. As a result, they argued, the standard of care that governs the citizens of those countries is no treatment at all. Because they believed that the local standard of care was the most relevant, they concluded that the placebo design was not unethical. Now, current proposals would amend the Declaration of Helsinki so as to reflect this view. Instead of requiring that subjects receive the “best proven diagnostic and therapeutic method,” one

proposed revision would require only that subjects “not be denied access to the best proven diagnostic, prophylactic, or therapeutic method that would otherwise be available to him or her” (cited in Brennan, 1999, p. 529).

In what follows, I will argue that this debate has been complicated by some unrecognized ambiguities in the notion of a standard of care. In particular, I will argue that this concept is ambiguous along two different axes, with the result that there are at least four possible standard of care arguments that must be clearly distinguished. Without a clear map of the normative terrain it has been difficult to assess the implications of opposing standard of care arguments, to recognize important differences in their supporting rationales, and even to locate the crux of the disagreement in some instances. The goal of this discussion, therefore, is to disambiguate the concept of a standard of care and to make the areas of genuine disagreement among different standards salient. This kind of conceptual cartography is fundamentally important for assessing the relevance and validity of the arguments in question and I will argue that it highlights important ways in which one of these arguments in particular may be more complex than it originally appears.

Because the goal of this paper is to provide a careful examination of the concept of a standard of care and the normative arguments that it supports, it does not attempt to provide an overall evaluation of the short-course AZT studies. As a result, it also will not present an overall evaluation of the importance of standard of care arguments relative to these broader concerns. This is important because it may be the case that there are other issues raised by these trials that carry sufficient moral weight to trump the standard of care argument. Before we can know whether this is so, however, we need to carry out the necessary conceptual and ethical analysis of the standard of care arguments that will enable this larger conversation to proceed more carefully, and hopefully, more fruitfully as well.

## II. WHAT IS (ARE) THE STANDARD OF CARE ARGUMENT(S)?

In order to tease out some important ambiguities in the concept of a standard of care, it will be helpful to look carefully at one prominent way in which the debate over the standard of care has been framed. Consider the following claims:

When Helsinki calls for the “best proven therapeutic method” does it mean [A] the best therapy available anywhere in the world? Or does it mean [B] the standard that prevails in the country in which the trial is

conducted? Helsinki is not clear about this. But I think that [1] a careful analysis of this document and its history suggests that the best proven therapy standard was intended primarily as a standard of medical practice. A consideration of that conclusion yields a second conclusion: that [2] the best proven therapy standard must necessarily mean the standard that prevails in the country in which the clinical trial is carried out (Levine, R.J., 1998, p. 6; letters and numbers added).

In part, interpretations A and B differ over what I will call the question of the *relevant reference point*. Emphasizing this disagreement makes it appear as though the dispute hinges on the question of whose medical practice constitutes the relevant medical practice. Interpretation A holds that the relevant standard of care is the one determined by the best therapeutic methods available anywhere in the world. Call this the *global* reference point. Interpretation B holds that the relevant standard of care is determined by the standard that prevails in the country in which the trial is conducted. Call this the *local* reference point. So understood, the sides of this debate are divided into proponents of a local standard of care and critics who champion a global standard of care.

Framing the debate as a question of the relevant reference point, however, effectively obscures a more fundamental and largely unarticulated source of disagreement. To see this, consider a crucial assumption that lies behind the following argument.<sup>1</sup> It is sometimes claimed that (1) because the content of the standard of care is fixed by the local reference point and (2) because the prevailing treatment for preventing maternal-infant HIV transmission in the countries where the short-course AZT trials were conducted was no treatment at all, that (3) the use of a placebo does not fall below the established standard of care. It is important to see, however, that in order for (3) to follow from (1) and (2), we have to do more than simply adopt the local reference point for the standard of care. For the argument to be valid it must also employ what I will call a *de facto* interpretation of the concept of the standard of care. Let me explain.

Let's grant the claim that the standard of care is intended to be a standard of medical practice. The above argument tacitly assumes a *de facto* interpretation of the standard of care according to which the standards of medical practice for a community are set by the actual medical practices of that community. It is only under this interpretation that the use of a placebo does not fall below the standard of care in countries where there is no effective treatment for maternal-infant transmission of HIV. For the sake of clarity, the argument from the *local de facto* interpretation of the standard of care can be stated as follows:

- (A)
1. It is unethical to conduct a clinical trial in which some subjects receive a level of care that falls below the established standard of care.
  2. The established standard of care is to be determined by the local *de facto* practices of the host community.
  3. In the countries where the short-course AZT trials were conducted the local *de facto* clinical practice for preventing maternal-infant HIV transmission was no treatment at all.
  4. The use of a placebo control group in these countries does not fall below the established standard of care.
  5. Therefore, the use of a placebo control group is not unethical on the ground that it fails to provide the established standard of care.

If we assume that the crux of the debate hinges on the question of the relevant reference point then we must also assume that critics of this argument accept the *de facto* interpretation but opt instead for a more global reference point. So understood, they would be making a *global de facto* argument: <sup>2</sup>

- (B)
1. It is unethical to conduct a clinical trial in which some subjects receive a level of care that falls below the established standard of care.
  2. The established standard of care is to be determined by the broader *de facto* practices of the sponsoring nations.
  3. The *de facto* clinical practice for preventing maternal-infant HIV transmission in the countries of the developed world sponsoring the short-course AZT trials is the 076 protocol.
  4. The use of a placebo control group in the countries where short-course AZT trials were proposed falls below the established standard in the developed world.
  5. Therefore, the use of a placebo control group is unethical on the ground that it fails to provide the established standard of care.

This may represent a common way of framing the debate over the standard of care, but it obscures the fact that the *de facto* interpretation of the standard is itself highly contentious. As a result, it fails to capture a more fundamental area of disagreement. If we return to the language of the Declaration of Helsinki, for example, we see that it speaks of providing the best *proven* diagnostic and therapeutic interventions. This seems to indicate that the idea of a standard of care is what I will call a *de jure* standard in that it is set, not by what physicians in some locality actually

do, but by the judgment of experts in the medical community as to which diagnostic and therapeutic practices have proven most effective against the illness in question. This is the interpretation embraced by Marcia Angell when she argues that the investigators conducting a trial “would be guilty of knowingly giving inferior treatment to some participants of the trial,” unless subjects in the control group “receive the best known treatment” (Angell, 1997, p. 847). For critics like Angell, the question of the relevant reference point is irrelevant because adopting the *de jure* interpretation of the standard of care allows them to argue that a placebo control is unjustified even relative to the local point of reference. To see how this might be so, consider the argument from the *local de jure* standard of care:

- (C) 1. It is unethical to conduct a clinical trial in which some subjects receive a level of care that falls below the established standard of care.
2. The established standard of care is to be determined by the judgment of medical experts in the host community as to which diagnostic and therapeutic interventions have been proven most effective.
3. Medical experts in the relevant host communities know the 076 protocol has been shown to cut the maternal-infant HIV transmission rate by more than half in developed nations such as the United States.
4. The use of a placebo control group in the developing countries where the short-course AZT trials were proposed falls below the established standard in those very countries.
5. Therefore, the use of a placebo control group is unethical on the ground that it fails to provide the established standard of care.

A global version of this argument can be constructed by substituting the following for premise C2:<sup>3</sup>

- (D) 2. The established standard of care is to be determined by the judgment of medical experts in some larger medical community as to which diagnostic and therapeutic interventions have been proven most effective.

Below, I will suggest that this argument is more complex than even its proponents may realize and that its implications have yet to be clearly explored. For the moment, however, I simply want to note that the choice of reference points does not affect the conclusion of the argument. As a result, it looks like the real crux of the dispute may hinge, not on the

question of the relevant reference point, but on the way we interpret the standard of medical practice that is embodied in the standard of care: is it a *de facto* or a *de jure* standard?

When the crux of the argument is understood this way, it becomes absolutely essential not to confuse the argument from the global *de facto* standard (B) with the argument from the local *de jure* standard (C). In part, this is because arguments (B) and (C) themselves differ over the question of the relevant reference point. As a result, objections that tell against the use of a global reference point may carry weight against argument (B) and not militate against – and may even support – argument (C). Furthermore, given that these arguments embody different conceptions of the standard of care, each of which has a substantially different supporting rationale, we must not assume that they will have the same implications for the conduct of international research. In the following section I will suggest that a failure to differentiate arguments (B) and (C) may have led to the acceptance of a false dilemma: either we accept the local *de facto* standard of care or we accept a higher standard that rules out altogether the international research that could be most important for populations of the developing world.<sup>4</sup> In order to appreciate this, however, and to evaluate the merits of the local *de facto* and local *de jure* arguments, it will be necessary to look more carefully at the differences between the *de facto* and *de jure* interpretations of the standard of care.

### III. THE LOCAL *DE FACTO* STANDARD OF CARE

One fairly simple reason that we might be inclined to accept the local *de facto* standard of care is that it appears to be more reasonable than the global *de facto* standard. Consider, for instance, some of the problems with the latter argument (B). On its face it appears to place arbitrary restrictions on important international research. Critics can easily question why the practices of some wealthy, technologically developed groups with sophisticated and well-entrenched healthcare infrastructures should also govern people who live under conditions of extreme fiscal scarcity, without a robust healthcare infrastructure, under different cultural and social conditions. Isn't this arbitrary? Might it not be ethical, rather than social or cultural, imperialism?

In contrast, proponents of the narrow *de facto* argument (A) argue that it will foster the research that will ultimately lead to the kinds of interventions that will best address the healthcare concerns of developing populations. The local *status quo* frames the appropriate clinical question and enables us to design a study that will demonstrate the effectiveness of an

intervention when compared to the current treatment situation (in the case of the short-course trials, nothing) (Levine, R. J., 1998, p. 7). This difference in the treatment situation is what makes it permissible to conduct a placebo-controlled trial in a developing country when it could not be conducted ethically in the U.S. Furthermore, it is argued, the use of a placebo does not deny subjects of developing countries care that they would otherwise receive, since they aren't currently receiving any beneficial care, and it does not inflict new or additional health burdens on research subjects (Grady, 1998, p. 36; Salim and Abdool, 1998, p. 565; Francis, 1998, p. 837; see also Levine, C., 1998, p. 46). In fact, it is likely that in many cases research subjects would receive a net benefit from participating in this kind of research since they would probably receive routine health care, otherwise unavailable, as a part of the clinical trial.<sup>5</sup>

When the alternative is the global *de facto* argument (B), we may be inclined to support the local *de facto* argument (A) simply out of the desire to help developing countries conduct the research that will answer the healthcare questions that best address their substantial and urgent healthcare needs. This way of thinking, however, may also keep us from recognizing the substantial shortcomings of the local *de facto* standard of care. For many, the most appealing aspect of this standard of care is the fact that it allows us to design clinical trials that will answer the right experimental questions. In the case of the short-course AZT trials, for instance, the relevant question was not how a short-course of AZT compared to the 076 regimen but how much better it would be than nothing. Unfortunately, however, it is precisely because the *status quo* is what sets research into motion that it cannot also function as an independent test of the moral acceptability of a clinical trial. Let me be clear about what this means. The research questions that are relevant to a particular community are, to a large degree, a function of the needs of the people in that community relative to the level of healthcare they actually receive. It is also true that acceptable clinical trials should produce results that will be relevant to a community's healthcare needs. But it doesn't follow from this that all research that would be relevant to a community's healthcare needs is morally acceptable research. Relevance, elegance, efficiency, these are all virtues that morally acceptable trials should possess. But not all relevant, elegant, and efficient trials are morally acceptable.<sup>6</sup>

It is important to recognize, therefore, that the local *de facto* standard of care does not receive independent support from the claim that subjects who would not receive medical care outside of a clinical trial are not denied care when they are given a placebo. Rather than providing independent support for the *de facto* standard of care, this is simply an alterna-



tive formulation of the very standard in question. As a result, the truth of this claim itself presupposes the truth of the argument from the local *de facto* standard of care. Those who reject the latter argument would rightly reject this claim on the grounds that it simply assumes the conclusion that is in dispute. This means that proponents of a different standard of care could make an equally valid claim that subjects of medical research *are* being denied medical care to which they are entitled if, for example, they do not receive the same level of care that the researchers or their sponsoring agencies normally provide to people with their condition. I will return to this point in a moment.

For now, consider some of problems that argument (A) faces in its own right. For example, the scope of this argument is more comprehensive than its proponents may be willing to accept. In particular, we want to know whether there are non-arbitrary reasons for keeping this argument, and its supporting rationale, from applying to sub-groups within established political borders (see Kim, 1998, p. 838 and Angell, 1998, p. 843). After all, if the standard of care is set by a community's *de facto* medical practices, and if the actual practices of doctors differ within ethnic, cultural, or economic subgroups, shouldn't those subgroups be governed by different standards of care in research? This is a powerful and potentially damning objection, because most proponents of the placebo design appear to believe that it would be genuinely unethical to conduct short-course AZT trials with a placebo control in the U.S. If this objection cannot be met, it would mean that the members of marginalized or oppressed subgroups, even within a developed nation like the U.S., would be governed by a lower standard of care in medical research than their wealthier counterparts precisely because they have been socially and economically marginalized or oppressed. This, however, is antithetical to the very idea of ethically sound human subjects research. As a result, anyone who is inclined to accept this argument takes on the increased burden of providing non-arbitrary reasons for limiting its scope of applicability.

This is also a powerful objection because it highlights the degree to which the narrow *de facto* standard of care appears to be out of step with the rationale for protecting human subjects in research within the U.S. This way of formulating the standard of care trades on the assumption that the level of care research subjects receive should be determined by factors that are extrinsic to the researcher/subject relationship. Another way of putting this is to say that, on this view, the terms of the researcher/subject relationship are to be determined by circumstances that are largely independent of the existence of that relationship. In order to know what standard of care subjects are entitled to, researchers, on this view, have to look

at the circumstances in which those subjects live. In order to know whether subjects in Tanzania should be subject to the same standards of care as subjects in Tucson, we have to look at the socio-economic circumstances in which they live. Traditionally, however, the debate about the protections that human research subjects should receive has been formulated largely in terms of problems that are inherent to the nature of medical research and the researcher/subject relationship. Socio-economic factors were important but largely because they marked out vulnerable populations where an increased sensitivity to issues of exploitation and competence was warranted. As such, Lurie and Wolfe (1997) were right to argue that this interpretation of the standard of care marks a change in the way research protections are conceived – a double standard for medical research.

Not only is this a different standard, it is a dangerous standard because it fails to take account of the context in which a community's *de facto* medical practices originate. By simply elevating the status quo to the level of a normative standard it does not distinguish between situations of scarcity that are the result of exploitation, force or fraud and those that are not. This leaves it open to exploitation and the danger of being manipulated in unscrupulous ways, on the international level by the economic or military interference of an outside group on the availability of medicines, medical personnel, or medical training within a particular nation, and on an *intra-national* level by these same activities on the part of dominant power groups.<sup>7</sup>

The fact that argument (A) unreflectively embraces the status quo may sometimes be overlooked because of an ambiguity in the notion of a 'practice'. As it has come to be used by some (communitarians, for example), a practice is a norm-governed activity in which people engage, in part at least, for the sake of goods that are internal to the practice. On this view, a practice is an activity through which people pursue certain goods and understand themselves, their community, and perhaps their larger world. Because practices of this kind can play an integral part in the identity of individuals or communities, they may deserve special protections or carry special normative weight. However, the *de facto* 'practice' of physicians in Thailand, for example, is not such a practice.<sup>8</sup> Thai physicians understand that they are unable to effectively prevent maternal-infant transmission of HIV and are themselves calling for the international help required to change this. As Lurie and Wolfe rightly point out, "In developing countries, the standard of care ... is not based on a consideration of alternative treatments or previous clinical data, but is instead an economically determined policy of governments that cannot afford the prices set by drug

companies” (1997, p. 855). So we must be careful not to confuse this kind of *de facto* practice with the more normatively weighty sense of “practice” favored by communitarians.

#### IV. THE LOCAL *DE JURE* STANDARD OF CARE

When the crux of the debate over the standard of care is framed, not as a question of the relevant reference point, but as hinging on the choice between the local *de facto* and local *de jure* interpretations, many of these problems with argument (A) become salient. For the proponents of a *de jure* standard, the local *de facto* standard is formulated in response to the wrong question. The latter standard answers the question of what research subjects may be entitled to outside of the research context, what they would be entitled to if research were not taking place (with the dubious assumption that their current situation is unfortunate and not unjust). But this is not what is at issue. What is at issue is what subjects are entitled to within the context of research itself, given the nature of scientific research and the fact that the researchers studying them have the knowledge and training – and often work for governments or institutions with the resources – to prevent some of the harms they encounter as a result of their vast, unmet healthcare needs. It may be true that the use of analogies with past research scandals has not generally helped to advance the present debate, but critics of this position are right to point out that this idea – that research subjects are only entitled to what they would otherwise receive outside of the research context and that researchers are under no independent obligation to prevent outcomes that would occur outside of the research context anyway – was also used to support the studies at Tuskegee and Willowbrook.<sup>9</sup> It may also be true that the proposed short-course trials were crucially different from these scandalous studies. But this point only highlights the need for those who defend the former studies to reject a moral justification that would also license the latter. After all, the claim that roughly the same states of affairs would likely have obtained even if no research had been conducted does not obviate the fact that, in the actual case, the state of affairs that actually obtains is at least partially a product of the explicit choices and activities of specific individuals and agencies.

For this reason, the *de jure* standard is founded upon the researchers’ obligation to ensure that subjects of clinical trials are not knowingly exposed to foreseeable and preventable harms. Clinical trials are not the products of natural events or inevitable processes; they are the result of deliberation and choice on the part of actual individuals and agencies. The

*de jure* requirement that researchers provide the treatment that has been shown to be most effective against the relevant illness is itself a corollary of the requirement that equipoise exist in order for a clinical trial to be morally permissible.

Clinical equipoise exists when there is genuine uncertainty among experts as to whether a proposed intervention is as good as or better than the current, known beneficial treatment for the illness at issue (Freedman, 1987 and 1990). A trial of a short course of AZT that used a placebo control group within the United States would be unethical because the 076 protocol has been shown to cut maternal-infant HIV transmission rates by more than half. In order for clinical equipoise to exist, the short course would have to be tried against the 076 regimen *and* there would have to be reason to believe that the short-course of AZT might be equally or more effective than its established counterpart.

By linking the standard of care to the knowledge and abilities of researchers, argument (C) highlights the fact that medical research is a human activity, the terms of which are fundamentally shaped by human agency and choice. The fundamental goal of medical research is not to provide health care but to gather medical knowledge which, it is hoped, will result in the development or perfection of interventions that will benefit future patients. Because the design of a trial is the result of the exercise of such agency and choice, the researchers and agencies that sponsor clinical trials are responsible for the ramifications that trial designs have on the welfare of the people who submit themselves to scientific study. The requirement that clinical equipoise obtain is essential to the conduct of acceptable medical research because it ensures that researchers do not undertake trials in which the welfare of some individuals is knowingly sacrificed in exchange for knowledge, and ultimately, the welfare of future patients. By providing the *de jure* standard of care, researchers and their sponsoring agencies ensure that the subjects of clinical research are not exploited, even for what we can all agree is a noble end.

Now that the rationale for the *de jure* standard is clear, it remains to elucidate the implications of this standard for international medical research. I suggested above that, to some degree, support for the local *de facto* interpretation may be rooted in the perception that a higher standard of care would place unduly stringent restrictions on the use of placebos in international research. Although this may be true for the global *de facto* standard, is it true for the local *de jure* standard as well?

V. THE COMPLEXITY OF THE *DE JURE* FRAMEWORK

I want to suggest that the local *de jure* standard of care does not yield as unequivocal a restriction on the use of placebo controls as one might think and that answering this question will be more complicated than it may first appear. In particular, because this standard is built around the concept of clinical equipoise, the severity of the restriction that it does yield will depend in large part on the nature of the conception of clinical equipoise that we embrace. This is an important claim, because it points to a way in which we might formulate the debate over the moral legitimacy of the use of placebo controls in international research from within the framework of the local *de jure* standard of care itself. In order to see how this is so, and why it might be desirable, let me explain how some placebo controls might be justified according to the local *de jure* standard of care.

In her original article in the *New England Journal of Medicine*, Marcia Angell argued for what I am calling a *de jure* standard of care. However, it is not clear how sweeping a restriction she takes this standard to yield. At one point, for instance, she says that “only when there is no known effective treatment is it ethical to compare a potential new treatment with a placebo” (1997, p. 847). This has encouraged some to frame the debate as a question of what I call the local *de facto* standard versus the best therapy available anywhere in the world (e.g., Levine, R.J., 1998, p. 6). But Angell’s claim can be interpreted in two different ways:

- I1. Only when there is no known effective treatment for illness *x* anywhere in the world is it ethical to compare a potential new treatment with a placebo.
- I2. Only when there is no known effective treatment anywhere in the world for illness *x* within a population *p* is it ethical to compare a potential new treatment with a placebo in population *p*.

Although the local *de facto* standard is often contrasted with interpretation I1 – the more restrictive standard – this interpretation is itself out of step with the rationale of the *de jure* conception of the standard of care. The reason is simply that such substantial differences between treatment populations can exist as to warrant genuine and credible doubts in the medical community about whether a treatment that is effective in one population will be effective in another. As a result, interpretation I2 most accurately reflects the *de jure* standard of care. It yields a more reasonable and defensible standard because it recognizes that the same standard can yield different conclusions if it is applied the same way in sufficiently different

contexts. It is also less restrictive than its critics, and perhaps its proponents, may recognize.

Exactly how restrictive I2 is, however, will depend on our conception of clinical equipoise. If we embrace a narrow conception of clinical equipoise according to which effectiveness is measured solely by the brute biological impact of an intervention on the illness in question relative to some end point, then the resulting standard of care will likely permit the use of a placebo only in cases where the biological differences between populations are substantial enough to cast credible doubt on the intervention's ability to function effectively in the trial population.

If we subscribe to a more robust concept of clinical equipoise, however, the ability to effect beneficial healthcare outcomes within a population will be measured as a product of a wider range of factors. For instance, Freedman (1990) has argued that the attractiveness of a drug in comparison to its alternatives should always be determined by a "compendious measure of a drug's net therapeutic advantage" (p. 2). Here, however, the concept of "net therapeutic advantage" is conceived of as a "*portmanteau* measure including all the elements that contribute to the acceptance of a drug within clinical practice" (p. 5). In addition to concerns about relative toxicity, this sort of robust conception of clinical equipoise will include factors such as ease of administration and availability. Some recent commentators have argued for the importance of relying on this conception of clinical equipoise when evaluating the short-course AZT trials (Crouch and Arras, 1998, p. 27). But their arguments have mainly emphasized the fact that doing so enables researchers to design trials that will change clinical practice. This is an important point, but one which also supports the local *de facto* standard of care and whose implications I criticized above. What needs to be stressed, instead, is that the rationale for including such broader factors in our concept of clinical equipoise can be supported by the epistemological concerns central to the *de jure* standard of care itself. The reason is that in order to know whether a treatment will be effective within a specific population we need to know whether it can be successfully administered in that context. This, however, will likely depend on a variety of social, cultural, and economic factors.

Consider, for instance, a treatment protocol that required frequent and prolonged hospital stays. Such a protocol might fail to have a significant health impact in a nomadic population if compliance required what members of that population viewed as unacceptable changes to their way of life. The same might be true for a highly diffuse and largely immobile population with few hospitals if the travel that would be required for compliance required unacceptable social or economic sacrifices. Like-

wise, consider the case of an illness that can only be treated by a surgical procedure that requires sophisticated equipment, an extended intensive care stay, and frequent, sophisticated follow up treatments. This procedure is the *de jure* standard of care in wealthy nations with well-established, high-tech healthcare infrastructures, because it can be safely and effectively administered in such a setting. In a country that lacks this kind of setting it may be practically impossible to establish the conditions under which it could be effectively implemented even for a small group of people.

These examples are put forth as suggestive instances of cases in which equipoise could exist in one population even though it is disturbed in more developed nations, for other than purely biological reasons. The point of sketching them is to suggest that, in instances such as these, a *prima facie* case can be made – on the very grounds that support the *de jure* standard of care – for the legitimacy of a placebo control when testing a more portable intervention (assuming that one does not already exist). This kind of argument does not rest solely on the need to design a clinical trial that will provide a clear answer to a clinical question, although it ensures that all morally acceptable trials will have this feature. Nor does it rest on the claim that the subjects of such trials are not denied care that they would not otherwise receive. Instead, it rests on the claim that it may be ethically permissible to answer this particular question with a placebo-controlled trial because, in doing so, researchers would not knowingly be denying subjects *care that has proven effective for their illness in their population*.

As I said earlier, the implications of this position are far from clear and it may in fact raise more questions than it answers. For my present purposes, it is sufficient simply to note (a) that there are compelling reasons to treat equipoise as a broad measure of a treatment's effectiveness, and (b) that as we broaden our measure of an intervention's effectiveness the use of a placebo control may become acceptable in a wider variety of situations. Unlike the global *de facto* argument, this standard pays greater attention to substantive differences in social, cultural, and economic contexts and their impact on the permissibility of international research. Unlike the local *de facto* argument, however, it would prohibit the use of a placebo control in cases of international research where an intervention is known to be effective (where effectiveness is broadly construed) for illness *x* in population *p*, even if it is not currently available in population *p*.

Nevertheless, difficult questions would need to be resolved in order to make this a workable standard. We still need to know, for example, which social, cultural, and economic factors should bear on the question of equi-

poise and how much weight different factors should be afforded. For instance, what if we had a safe, effective, easily administered treatment that was simply so expensive that it could not be reasonably supplied to significant numbers of a developing population? Should this fact alone be sufficient to establish equipoise in the relevant population? What should we do in situations where the *de jure* standard in one population can be administered to members of the control group in another population, even though it could not be made available to members of the larger population?

Those who are familiar with the debate over the short course AZT trials will recognize many of these questions. The fact that they can be raised from within the framework of the local *de jure* argument testifies to its complexity. I believe that it also testifies to the fact that we can retain some of the most substantive areas of genuine dispute over the standards that should govern international research even if we agree that the local *de facto* standard of care is a bad, if not a perfidious, standard. In itself this is an important point because it may help us to reorient the current debate in a way that makes the actual lines of dispute salient. Not only might this allow both sides to agree on the values that structure the problem and then to recognize the operative areas of genuine dispute, it might make it possible to find a way towards building a more stable and sustainable consensus on these issues.

One thing that we can say, even from this admittedly terse sketch, is that relocating the debate within the context of the local *de jure* standard of care will provide a more coherent framework for relating technical questions that concern the conduct of specific clinical trials to ethical issues that arise at a broader social and political level. At the trial level, for instance, this standard requires researchers to ensure that their choice of trial design does not allow some participants to suffer harms that could be foreseen and prevented with reasonable care. At the policy level, however, this standard requires researchers, their sponsoring agencies, and relevant political bodies to ensure that conducting a clinical trial represents a responsible means of addressing the healthcare priorities of the population in question. In cases where equipoise exists in one country but not in another we will have to consider whether equally or more profound healthcare outcomes could be achieved, perhaps with the imposition of fewer burdens, by altering some of the conditions that cause equipoise to exist in the one case when it does not exist in the other. In other words, not only is it necessary that morally acceptable clinical trials be effective and efficient, it must also be the case that conducting a clinical trial represents the most effective and efficient means of addressing the healthcare needs of a particular population.



The short course AZT trials have generated a lengthy and trenchant debate because they are open to reasonable challenges on a variety of fronts at both of these levels. As a result, I agree with those who remind us that tough cases generally make bad policy. The local *de facto* standard of care may be attractive for the way it promises a simple solution to this complex debate, but this simplicity is purchased at the price of important ethical principles. I have tried to argue that the local *de jure* standard of care may not yield as simple a solution as either its proponents or its critics may think, but that this is itself an exciting discovery. The possibility that both sides of this debate may be able to articulate their concerns within a shared framework holds out the possibility of moving beyond the present state of affairs in which the proponents of different standards of care appear only to be entrenching and fortifying their positions. I hope that the present study is sufficient to show that the work it will take to explore the complexities of the *de jure* standard, and its implications for the short-course AZT studies and future international research, is important, and remains to be done.<sup>10</sup>

## NOTES

1. The most prominent versions of the following argument can be found in Levine, R. J., 1998 and Grady, 1998.
2. Lurie and Wolfe's claim (1997, p. 855) that researchers have a responsibility to ensure that the treatment of research subjects conforms to the appropriate standard of care in the sponsoring country lends itself to this sort of interpretation. This is how their position is sometimes understood by those who respond to it. However, their emphasis on researcher's duties to prevent foreseeable harms indicates that they actually hold some sort of *de jure* view.
3. Bloom (1998) in effect raises the possibility that local and global *de jure* standards might diverge if different communities believe that different treatments constitute the *de jure* standard of care. Although such disagreements are possible, they are also resolvable in principle by comparison trials.
4. This dichotomy is given its clearest expression in Levine, R. J., 1999, p. 532.
5. Crouch and Arras (1998, p. 29) argue that subjects of a clinical trial might be entitled to receive this kind of supplemental medical care, but not the best standard of care available anywhere in the world.
6. For an argument that exploits the distinction I draw here, see Brennan (1999).
7. This gives rise to the possibility of some very counterintuitive situations. For example, if in response to human rights violations a country was subjected to economic sanctions so severe that they made medical resources scarce, research subjects enrolled in clinical trials in that country would find themselves justly subjected to a lower standard of protection than they were prior to the sanctions.
8. This objection is behind the charge that this kind of "standard" of care is no standard at all, as in C. Levine (1998, p. 47).

9. First raised by Angell in 1997 and defended again in 1998, this particular point has been reluctantly granted even by some defenders of the short-course trials. See, for instance, Lie (1998, p. 310). For the use of this justification at Tuskegee and Willowbrook, see Rothman (1982).
10. This paper was written with the support of a post-doctoral fellowship at the University of Minnesota's Center for Bioethics. I would like to thank Jeff Kahn and Dianne Bartels for their enthusiastic support and Jeff for his comments on a draft of this paper.

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