The Real Problem With Equipoise

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ABSTRACT: The equipoise requirement in clinical research demands that, if patients are to be randomly assigned to one of two interventions in a clinical trial, there must be genuine doubt about which is better. This reflects the traditional view that physicians must never knowingly compromise the care of their patients, even for the sake of future patients. Equipoise has proven to be deeply problematic, especially in the Third World. Some recent critics have argued against equipoise on the grounds that clinical research is fundamentally distinct from clinical care, and thus should be governed by different norms. I argue against this "difference position," and instead take issue with the traditional, exclusively patient-centered account of physicians' obligations that equipoise presupposes. In place of this traditional view, I propose a Kantian test for the reasonable partiality that physicians should show their patients, focusing on its application in clinical research and medical education.

KEYWORDS: equipoise, clinical trials, therapeutic obligation, medical education, doctor-patient relationship, Immanuel Kant

Clinical research often raises the possibility of conflict between a research subject's best interests and the welfare of third parties. For instance, if one of two interventions studied in a randomized controlled trial is inferior to the other, then the patients randomized to this arm will receive a treatment that is not in their best interests; and yet, the information provided by this study may help to save the lives of others in the future. Such research, though of tremendous potential value to society at large, appears to threaten the traditional view that physicians ought not to compromise their patients' welfare for the sake of others.

Historically, clinical investigators have sought to reconcile clinical research with the therapeutic obligation of fidelity to the individual patient by applying the *equipoise requirement*. Equipoise requires genuine uncertainty about the relative therapeutic merits of the interventions studied. If two treatments are in equipoise, then there is no good reason for believing one to be superior to the other. Therefore, a doctor would not be guilty of *knowingly* compromising her patients' interests by offering either treatment; nor, for that matter, in randomizing her patients to one or the other treatment. In this way, clinical research has been thought to be compatible with the traditional patient-centered ethic of medical care.

In recent years, however, this consensus view has proven to be deeply problematic. First of all, the equipoise requirement is poorly suited to research on sustainable and desperately needed

therapies for use in poor countries. In many cases, we might have good reason for believing that an affordable treatment is somewhat less effective than a very expensive treatment used in wealthy countries; yet, knowing that the first rather than the second is the only thing we may realistically have to offer, we may still need information about its relative effectiveness before persuading a state or donor agency to implement it. Supporters of equipoise have claimed that the equipoise requirement, properly understood, is compatible with well-designed research in search of sustainable remedies for use in the Third World. I will argue on the contrary that equipoise raises insuperable difficulties for such research, such that even the studies that these authors support would be ruled out by such a standard.

Furthermore, some recent critics of equipoise have noted other ways in which the conduct of clinical trials departs from the exclusive focus on the individual patient characteristic of typical clinical practice. Believing these departures to be ethically defensible, they have attacked one of the central presumptions behind the equipoise requirement, which they call the *similarity position*: the claim that clinical research ought to be governed by the ethical standards appropriate to clinical care. In its place they offer a *difference position*, claiming that clinical research and clinical medicine are fundamentally distinct enterprises with different aims and different ethical requirements. On this position it is misconceived to suppose that clinical investigators have *any* therapeutic obligations (at least, *qua* investigators) to research subjects.

While I also believe that the equipoise requirement is unworkable, this appeal to a difference position strikes me as unnecessarily radical. Splitting off clinical research from clinical medicine in this way is more likely to frustrate rather than serve the interests of patients. Furthermore, I argue, these critics' grounds for adopting such a difference position for clinical research would apply just as well in many other contexts, with undesirable consequences. Therefore, I here argue against the equipoise requirement by rejecting a second presumption. While I maintain the similarity position that clinical research should be governed by the same principles that guide clinical practice, I reject the uncompromising account of these principles that underlies the equipoise requirement. In some circumstances, I will argue, clinicians ought to be willing to compromise their patients' interests for the sake of third parties. Although physicians should not give *absolute* priority to their own patients, I here propose a Kantian standard for the *reasonable* priority that physicians—including physicians in ordinary practice settings as well as clinical investigators—should show towards their patients.

The Roots of the Equipoise Requirement

Recall that the equipoise requirement was introduced to reconcile clinical research with clinical investigators' therapeutic obligations to their patients. To fully understand the rationale for equipoise, therefore, we must examine the general account of physicians' therapeutic obligations that it presupposes. This is the traditional view that physicians should offer treatments that are in the best interests of the individual patient, without regard for the welfare of third parties. This underlying rationale for the equipoise requirement has seemingly gone unnoticed by many, who might wish to reject this uncompromising, traditional account of the therapeutic obligation while accepting the equipoise requirement as a constraint on clinical research. In fact, the two are inextricably linked.

The equipoise requirement had been articulated by early authors such as Bradford Hill (Hill 1963), and Lawrence Shaw and Thomas Chalmers (Shaw and Chalmers 1970), but was more fully developed in the pioneering work of Charles Fried (1974). Fried grounded the equipoise requirement in a physician's "duty of personal care," which he understood in terms of a "demand

for undivided loyalty to the interests of the patient" (Fried 1974, 148). Such a duty, which Fried analogized to fiduciary duties in law and business, would not allow clinicians to compromise their patients' interests even for the sake of great potential benefits to others. For this reason Fried insisted on equipoise—genuine uncertainty about the relative merits of different arms in a trial—as an ethical precondition of clinical research, regardless of the potential benefits to third parties.

Later refinements of Fried's equipoise requirement maintained this commitment to the traditional account of physicians' therapeutic obligations. For instance, Fried's writing was ambiguous between two readings of equipoise: one on which the requisite uncertainty is in the mind of the individual clinician and another on which the uncertainty is a lack of consensus within the professional community. Benjamin Freedman, in his famous article in support of the second reading, followed Fried in identifying "the requirement that the patient be offered the best treatment known" as the principle underlying the demand for equipoise (Freedman 1987, 142).

While this uncompromisingly patient-centered ethic was largely taken for granted at the time of Fried's writing and still was widely accepted when Freedman published his article, most of us would now admit that there are circumstances in which physicians ought to compromise their patients' interests for the sake of others. For instance, psychiatrists consider it a professional duty to break confidentiality when they believe a patient poses an immediate threat to an identifiable person. (It is interesting to note that the first *Tarasoff* ruling was handed down in the same year that Fried's book was published and was still a matter of ongoing controversy when Freedman went to press.)

If we no longer accept the uncompromising principle on which the equipoise requirement is premised, then the strict equipoise requirement seems to lack an ethical foundation. Suppose that we have reasons for believing one treatment to be somewhat inferior to another, but also that research into the relative merits of the two treatments would likely help us prevent the deaths of many future patients. On the absolute patient-centered ethic presupposed by Fried (1974) and Freedman (1987), such research is unacceptable because the two treatments are not in equipoise, and therefore in giving the first treatment we would knowingly compromise the interests of some patients for the sake of benefits to third parties. However, for those of us who reject this absolute principle, the pertinent question is not whether the two treatments are in equipoise, but instead whether the potential benefits to third parties are sufficient in this case to justify the less-than-optimal care given to some of the patients in the study. Let us revisit one such case that has been discussed at great length, though its implications for the equipoise requirement have not, I think, been fully recognized.

The Perinatal Zidovudine Trials, Reconsidered

The problems with equipoise are most evident when this requirement is applied to research in developing countries. In wealthy countries, new treatments can often be tested against established therapies (or, if there is no established therapy, against placebo) when there is genuine doubt about which is better. Serious problems arise, however, when there is an established therapy in wealthy countries that would be too expensive or otherwise impractical to implement in poor countries, leading investigators to search for more cost-effective or otherwise more sustainable approaches. (Similar dilemmas may soon arise in developed countries, given the continuing expansion of expensive treatments for chronic conditions and the growing financial pressures on health systems [see Lie 2004]).

A recent case that has aroused much controversy concerns the use of zidovudine (AZT) to prevent maternal-to-fetal transmission of HIV. In the mid-1990s, the standard method of

prophylaxis in wealthy countries was the 076 protocol, which involves roughly 12 weeks of antepartum AZT treatment, intrapartum AZT administration, and 6 weeks of postpartum AZT treatment for the infant. This regimen had been shown to reduce the risk of maternal-to-fetal transmission from 23% to 8%; however, it cost approximately $800 per mother, well above the $8 per capita health expenditures of many developing countries. In 1994 the World Health Organization called for research on alternative, more affordable treatments that could be sustainably implemented in poor countries. In particular, several groups undertook clinical trials on the effectiveness of a shorter course of AZT treatment, such as one involving 5 weeks of antepartum treatment and 3 days of treatment postpartum.

In 1997 the *New England Journal of Medicine* published an editorial condemning the design of many of these studies, which compared a shorter-course intervention group with a placebo control group. In this editorial, Marcia Angell explicitly appealed to the equipoise requirement, opening with the claim that, "an essential ethical condition for a randomized clinical trial comparing two treatments for a disease is that there be no good reason for thinking one is better than the other" (Angell 1997, 847). According to Angell, the placebo-controlled studies violated the equipoise requirement and, by extension, the professional obligation to give the best available treatment: the trial investigators knowingly gave an inferior (indeed, biologically inert) treatment to the women in the placebo group. The informed consent of the research subjects to randomization was not, in her view, sufficient to justify this abrogation of professional obligation. On these grounds, Angell argued for studies comparing the short-course AZT treatment to a long-course 076 control group, rather than to a placebo control.

Yet this position is vulnerable to an embarrassing objection. As Alex John London (2001) has pointed out, on Angell's understanding of equipoise her own proposed study would violate the equipoise requirement. Given what we knew about AZT and about viral replication and transmission, there was good reason to believe that the placebo would be less effective than the short-course protocol. But given all of these considerations, there was just as much reason to believe that the short-course protocol would be less effective than the long-course protocol; therefore, this study too would not be in equipoise.[1] Indeed, as London remarks in response to Angell,

> if we are to take the requirements of equipoise seriously, and if we embrace her interpretation of them, then it becomes unclear how we could ever justify searching for less expensive, less cumbersome, more portable interventions that might provide some significant but less than optimal degree of relief to populations of the developing world. (London 2001, 319).[2]

This consequence of the equipoise requirement, at least on Angell's interpretation of it, is on my view clearly intolerable. Even if we are inclined to agree with her that these particular placebo-controlled trials were unethical, the principle to which she appealed would seem to rule out all manner of desperately-needed research—including the alternative studies that Angell herself proposed. Such a restrictive standard would have disastrous implications for the populations most in need of medical aid.

London argued that the problem lay not with the equipoise requirement itself, if properly

[1] As London notes, this suspicion has since been confirmed by a subsequent trial comparing long- and shortcourse regimens, in which the shortest-course arm had to be discontinued early (Lallemant et al. 2000).

[2] Similar concerns are expressed by Ugandan activists and researchers in Specter 2003.

understood, but only with Angell's unduly narrow interpretation of it. London proposed a broader interpretation of equipoise on which judgments about the therapeutic merits of two interventions would involve not only sheer considerations of biological effectiveness, but also practical considerations such as their ease of administration, side effects, and the sustainability of their implementation in the relevant population.[3] On this broader conception, investigators in the proposed study would not knowingly be offering an *inferior* treatment to the subjects in the short-course arm—although the long course is more biologically effective, the short course has other practical advantages when considered from a population perspective.

However, I believe that London's attempt to resolve the conflict between equipoise and the serious demand for international research also fails. Recall that the equipoise requirement was introduced as a reflection of the traditional, patient-centered "duty of personal care," on which physicians must offer treatments that are in the best interests of their individual patients. From the perspective of a patient in a clinical trial, considerations of cost or sustainable implementation in her population are irrelevant to the determination of her best interests—study participants are treated free of charge, and a participant in a study would not have self-interested grounds for preferring a less effective treatment because it is easier to implement in her population. If a patient were enrolled in a trial comparing a short-course regimen with the long-course 076 protocol, *her interests* (and her child's interests) would be best served by being in the 076 arm, and an unrestrictedly partial physician would not allow her to be randomized to the short-course arm. Thus, London's proposal, with its appeal to the relative merits of treatments among populations, cannot preserve the traditional, fully patient-centered conception of physicians' obligations that equipoise was intended to accommodate.[4]

It thus seems that the equipoise requirement, presupposing a very strict "duty of personal care," has more restrictive implications for international research than either Angell or London fully appreciated. Indeed, I suspect that they as well as other supporters of equipoise would find these implications intolerable. If we are to respond to the urgent moral demand for research into less expensive, sustainable treatments for implementation in poor countries, the equipoise requirement must be given up.

Against the "Difference Position"

So far I have criticized one of the central claims underlying the equipoise requirement: that doctors should never compromise the interests of an individual patient for the sake of benefits to third parties. This criticism of equipoise should be distinguished from a quite different criticism that has recently been advanced by Franklin Miller, Howard Brody, Donald Rubenstein and others. These authors accept the traditional claim that doctors must always promote the best interests of

[3] Note that there are "broad" practical, extra-biological considerations here of two types, which London does not distinguish in his paper: considerations that affect the desirability of some treatment from the perspective of an individual patient (e.g., side effects), and considerations that affect the desirability of some treatment from a populations perspective (e.g., the sustainability of its implementation).

[4] Perhaps the broadened demand proposed by London could be given a quite different theoretical justification, one that does not appeal to considerations from clinical ethics (such as the traditional conception of physicians' therapeutic obligations) but that instead articulates demands of justice and development with specific application in international research. Such a proposal might have important merits; however, it would depart significantly from the equipoise requirement defended by Fried and his successors, not only in its application but also in its underlying rationale. I think it better to consider such a proposal on its own terms, and not under the heading of "equipoise." (I would like to thank Sharon Street for raising this point in conversation with me.)

their patients. However, they reject a second claim underlying the equipoise requirement, a claim that I wish to preserve—this is the claim that clinical investigators are subject to the same professional obligations as doctors. According to the "difference position" advanced by these critics, clinical research and clinical care are fundamentally distinct activities, which should be governed by different ethical standards.

In other words, while these authors agree with me that the equipoise requirement should be given up, we disagree about where the equipoise requirement goes wrong. Let us examine their grounds for so sharply distinguishing between clinical research and clinical practice.

These authors have noted other respects in which clinical trials involve compromises in patient care for the sake of gathering information that may be useful to others in the future. For instance, clinical trials typically require that not only patients, but also their treating physicians be "blinded"—that is, kept ignorant of which intervention a given patient is receiving—even though access to this information may be helpful to the patient's physician in formulating an overall plan of care suited to the patient's circumstances. To ensure that the data collected in clinical trials can be universally applied, the protocols governing such trials typically restrict flexibility in the dosing of study drugs and the use of other treatments. In many cases, trials require an initial "washout" period, in which patients stop taking other treatments that may be beneficial to them, so that the efficacy of the treatments investigated can be measured from a drug-free baseline. Also, data-gathering in clinical research often involves extra interventions that carry independent risks of injury or discomfort, such as blood draws, biopsies, lumbar punctures, and imaging procedures, and which are not undertaken for the sake of therapeutic benefits to the individual patient but instead for the sake of evaluating efficacy (Miller and Brody 2002, 2003; Miller and Rosenstein 2003; Brody and Miller 2003).

Of course, this would only be inconsistent with the ethics of clinical practice if we presume that physicians' therapeutic obligations strictly prohibit them from compromising patients' interests for the sake of third parties. For instance, Miller writes:

> Clinical trials routinely administer interventions whose risks to patients are not compensated by medical benefits but are justified by the anticipated value of the scientific knowledge that might be gained…. Clinical research, including treatment trials, would be impossible if it were held to the ethical standard of promoting the medical best interests of patients that governs therapeutic medicine. (Miller 2003, 42)

Note, however, that if we reject the claim that therapeutic medicine should always be governed by the ethical standard of promoting the medical best interests of patients, then these practices need not be inconsistent with the similarity position.

A positive argument presented by these authors for the difference position is the claim that clinical research and clinical practice involve two fundamentally different aims, and as such represent two entirely distinct activities to be governed by different ethical standards:

> Clinical medicine aims at providing optimal medical care for individual patients…. Clinical research is dedicated primarily to promoting the medical good of future patients by means of scientific knowledge derived from experimentation with current research participants—a frankly utilitarian purpose. (Miller and Brody 2003, 21)

Thus, on this view, clinical investigators in fact have *no* therapeutic obligations to study

subjects. In place of therapeutic obligations, these authors propose a different set of ethical requirements to govern clinical trials, focused on ensuring the scientific value of the study and protecting research participants from exploitation rather than on curing illness or benefiting study participants as patients.

Here again these authors seem to presume that, if clinical research is not organized so as to provide optimal medical care to individual patients, then the therapeutic obligation does not properly apply. Yet this argument would seem to prove too much. Similar reasoning could be applied just as well in other contexts where some activity is not organized to provide optimal care, but where we should be unwilling to deny that the therapeutic obligation applies.

Consider a topic with important similarities to clinical research: the use of patients in medical education, for instance in teaching medical procedures.[5] Medical interns and residents (as well as older physicians mastering new techniques) attain proficiency in these procedures in the course of performing them on patients, usually in teaching hospitals. While they are encouraged to learn about these procedures in other ways—from books, from observing more experienced hands, and from practicing on rubber models, computer simulations, and sometimes on animals and cadavers—there is ultimately no substitute for working with a living patient (Gawande 2002).

When a physician is still relatively inexpert at performing some procedure, her patient's interests will be better served if she finds some more senior or otherwise more experienced physician to perform the procedure: the risks from the procedure and the likelihood of discomfort will then be lower. But, of course, if all physicians were to refuse to perform procedures when a more experienced physician is available, then most physicians would never master such procedures (at least, not during their formal training), and would all be much less able to benefit their patients. Such an unyielding commitment to the interests of the individual patient would ultimately be self-defeating, which is presumably why medical education allows for certain compromises in the care of present patients for the sake of future patients.

Allow me to consider one complication. Robert Adams has introduced a distinction between "action-aims" and "outcome-aims" as follows:

> We can say that I have doing the best for my patients as an *action-aim* insofar as I am disposed to do (now) what I think is best for my (present) patients. I have it as an *outcome-aim* insofar as I am disposed to try (now) to bring it about that I do (in the rest of my career) the best for my (present and future) patients (Adams 1989, 449-50)

In the previous paragraph I supposed, as Adams does, that the therapeutic obligation should be understood in terms of action-aims rather than outcome-aims. However, if we interpret the therapeutic obligation in terms of outcome-aims, then the resident may still be acting partially when she inexpertly performs some procedure on a patient now (serving that individual patient's interests less well) for the sake of better serving her patients in the future. Yet we can still generate the problem if we recognize that, in teaching hospitals, responsibility for patients is shared between the interns or residents and the supervising physicians. From the supervising physician's point of view, even given the outcome-aim of doing what is best for his present and future patients, he would do better by performing all the procedures himself rather than allowing interns and residents to

[5] Francis Moore, one of the earliest writers on the ethics of clinical research, also drew this parallel between ethical problems in medical education and in clinical research, but to my knowledge this parallel has not been pursued. (Moore 1969, 503)

perform them. But if this disposition were adopted by all medical educators, patients as a whole would ultimately suffer.

So it seems that medical education, like clinical research, would be impossible if it were governed by the ethical standard of promoting the medical best interests of patients. In some circumstances, medical education requires compromises for the sake of perpetuating the medical profession by teaching new physicians. But this doesn't yet give us grounds for dividing these aims between two different activities, with different normative standards, as follows:

> Clinical medicine aims at providing optimal medical care for individual patients…. Medical education is dedicated primarily to promoting the medical good of future patients by means of expertise and skill derived from practice on current medical-training participants—a frankly utilitarian purpose.

We should be loath to make the analogous proposal that interns and residents in teaching hospitals don't have an obligation to treat or otherwise benefit the sick people they encounter, but only to refrain from exploiting them in the course of their education. After all, perhaps the most important thing that medical trainees must learn to do is to take responsibility for the care of their patients. But a difference position applied to medical education would deny this as a real possibility.

In medical education we see the aim of treating patients balanced against the aim of training new physicians—but this does not, I think, give us grounds to claim that this represents some activity wholly distinct from medical care, or to deny that the "interventions" administered in university hospitals are indeed treatments intended to cure. But so far, the cases for a difference position in medical education and in clinical research strike me as symmetrical. In either case, the presence of two different aims need not reflect two entirely separate activities governed by different norms, but may instead reflect a single activity in which two aims constrain one another.

Would the "Difference Position" Serve the Interests of Patients?

A third argument offered by advocates of the difference position is that the similarity position undermines informed consent by fostering a therapeutic misconception among study subjects. But in formulating this argument, we must be careful in specifying the content of the misconceived belief.

If, for instance, by the *therapeutic misconception* we mean a belief that clinical trials are continuous with, rather than distinct from, medical practice, then to call this belief a misconception is already to *presuppose* the difference position, and so cannot be the basis of an argument for the difference position itself. If, on the other hand, we use this term to mean a belief that all facets of a clinical trial will be directed towards the subject's medical best interests, then we can agree that this is a misconception. However, I believe that this sort of misconception would be best avoided by taking greater care to educate study subjects about the limitations on personal care imposed by study designs, rather than by adopting an ethic (wholly unfamiliar to patients) absolving clinical investigators of any professional obligation to advance patients' medical interests (Appelbaum et al. 1987).

I believe that there is cause to question whether adopting a difference position would in fact serve the interests of patients. We should recall that an important feature of clinical research, as opposed to other scientific studies that take healthy volunteers as subjects, is that they begin in a context of illness and vulnerability. A clinical trial designed to measure the effectiveness of a medical

intervention must begin with subjects who suffer (or are likely to suffer) from some disease and whose medical needs may be quite urgent. Typically, such subjects enroll in studies because the prevailing treatments for their conditions are in some ways unsatisfactory, so that the chance of being randomized to a novel therapy represents their best hope for a good outcome. In other words, study subjects often have a therapeutic aim in enrolling in clinical trials, and for many of them this aim should be regarded as fully reasonable, rather than as misconceived.

For many patients, then, participation in a clinical trial is an integral part of their treatment plan. For instance, as Brody and Miller (2003, 331) note, fully 70% of pediatric cancer patients are now enrolled in clinical trials. I suspect that most of these patients, even after being properly educated about the compromises inherent in the design of clinical trials, would not wish to be forced to choose between being treated by scientists who regard them primarily as research subjects, or by pure clinicians without access to the most promising new interventions (Grunberg and Cefalu 2003).

Furthermore, it is not altogether clear what protections would be afforded to study subjects if they are no longer regarded as having a therapeutic relationship with clinical investigators. Would these be the very limited protections against fraud and misrepresentation inherent in contract, or even the more limited protections suggested by the "frankly utilitarian" rationale that these authors ascribe to clinical research?

It should be said that advocates for the difference position have proposed detailed guidelines for clinical research, governed by what they call an ethic of non-exploitation. However, as others have noted (Kim 2003; London and Kadane 2003), it is not clear what principle underlies these specific guidelines rather than some weaker set of guidelines, other than the simple fact that they strike the authors as intuitively reasonable. Consider, for instance, how little consensus there is in our political culture about what counts or does not count as "exploitation" in ongoing controversies over pornography, the outsourcing of labor, advertising in public schools, open markets for human organs, collegiate athletics, and union-only work environments.

It is difficult then to see how a notion as open to interpretation as non-exploitation could ever be the ground for stable public deliberation over the appropriate weighting of subjects' interests and public interests in the conduct of clinical research. This is especially problematic given that, on the difference position, clinical research would no longer be constrained by the expectations built into the roles of physician and patient. These are roles, after all, with which study subjects and clinical investigators already have lifetimes' worth of experience and that can therefore serve as a context for shared intuitions regarding what is or is not appropriate within them. But the difference position would replace this familiar physician–patient relationship with one that most subjects would find entirely unfamiliar, without the benefit of past experience or a determinate principle to draw upon in judging what they are owed by investigators.

A Kantian Universalizability Test

By contrast, there is already some measure of consensus about how to weigh patients' interests against the interests of third parties. In psychiatric practice, patients have proven willing to accept certain limitations on confidentiality as reasonable. In medical education, most patients are willing to participate when assured of appropriate supervision. Although patients might wish, in their own cases, that their physicians could be single-mindedly devoted to their welfare, most also recognize the social importance of these compromises as a matter of general policy—all patients are better off if they all accept these compromises than they would be were everyone to insist on their private welfare.

In the remainder of this article I hope to sketch a principle that can accommodate these intuitive judgments about how physicians should weigh their patients' interests against the interests of third parties. I also hope to suggest how this principle can be extended to matters of current controversy. Consider first two familiar but extreme views about how to weigh the claims of patients against the claims of third parties. On an *absolute-priority* position, patients' medical interests must always take precedence over the interests of others. One example of this position is understanding of the "duty of personal care," which generates the equipoise requirement and which has here been shown to be deeply problematic. At the other end of the spectrum is a *no-priority* position, on which physicians should give equal weight to the interests of patients and third parties. An example of this position is classical utilitarianism, which would license forms of medical research that most people would find intuitively objectionable.

Historically, Kant's ethical system has often been depicted as the natural opposite to utilitarianism, so it is unsurprising that advocates of absolute-priority views such as Fried (1974) have appealed to Kantian claims in defending their position. However, I think there is a natural reading of familiar Kantian principles that suggests a *limited-priority* position, on which physicians should give somewhat greater weight to the interests of their patients.

Consider a Kantian universalizability test, applied to the priority that physicians give to their patients' interests. Such a test would ask us: Could we reasonably want all physicians to give preference to their patients in a given way?[6] Applying this test, many considerations tell in favor of physicians being *very strongly* partial towards their own patients and hence extremely reluctant to compromise the interests of their own patients for the sake of third parties. For instance, if physicians gave no priority to their patients' interests, then patients could have no confidence that their physicians' recommendations were ever offered for their own sake, rather than for the sake of others. Patients also could not trust physicians to keep their medical information confidential, seeing that access to such information could be very useful to others for public health, consumer research, or even law enforcement purposes. Overall, patients would be much less inclined to follow medical advice, even when adherence would actually benefit them. Such collective impartiality would ultimately be self-defeating, in that it would make us all much worse off, even when considered from an impartial perspective. We could not reasonably want to live in such a world, or even a world in which physicians gave only very weak priority to their own patients.

However, the examples given in preceding sections also suggest that we could not reasonably want all physicians to give absolute priority to their individual patients. In medical education, if all training physicians were unwilling to ever compromise the care of their present patients for the sake of future patients, then most would never master medical procedures. Similarly, if physicians conducting clinical trials refused to allow any compromises in patient care in the conduct of these trials, then it would be impossible to properly test interventions against one another. Such an absolutist ethic, if ever fully adopted, would render competent medical practice unsustainable.

So here I think that a Kantian universalizability test supports a reasonable middle position, in between absolute priority and no priority to the interests of the individual patient. On this view, the therapeutic obligation is not always an obligation to provide the *best available* treatment or the treatment that is in the patient's strict best interests. In some cases, we should say, the therapeutic obligation can be discharged by providing *good enough* treatment—as when an intern or resident

[6] This I take as a rough gloss on the Kantian test—see important discussions in Kant 1964, Nagel 1991, Scanlon 1998, and Parfit 2004. A more specific interpretation of the test applied here is developed in Chiong 2005.

performs a procedure that he is still learning even though more experienced physicians are available—when doing so is necessary for discharging obligations to future patients. Of course, the application of this principle (e.g., what is to count as "good enough" and in what contexts) is clearly more complicated than the application of either extreme position, and requires the exercise of judgment.

In medical education, the question of whether an intern or resident should perform some procedure or call for help can be especially difficult. After all, every physician who routinely performs some procedure must, at some point, have performed it on a patient for the first time. Although few of us would wish to be that patient, we can all recognize the necessity that *someone* be the first patient. Furthermore, the acquisition of these skills is often a graduated process, in which mastery of a simple procedure may be a necessary step towards proficiency in more complicated techniques—so even procedures that a physician will never use in ordinary practice may have educational value.

Despite these complexities, we can still demand of medical educators and trainees that they have some available answer to the question, "What would it be like if everyone did that?" A rough-and-ready test for the universalizability of some practice, which we all learned as schoolchildren, is whether we would be willing to imagine ourselves, our loved ones, or our peers on the receiving end of some treatment. Along those lines, something that should arouse our suspicion about the current state of medical education in the United States is the fact that the risks of medical education are disproportionately borne by poorer patients in public hospitals, whose social circumstances do not resemble those of most medical students and physicians. A more equitable distribution of these burdens would not only serve the requirements of justice, but would also help to ensure that trainees are not taking unjustifiable risks with their patients' health.

Implications for Clinical Research

I believe that this Kantian principle also offers a foundation for some important intuitions about the ethical acceptability of certain kinds of clinical research, a foundation that is more secure than either the equipoise requirement or the difference position. Although here again, we can be no more precise than the subject allows, I do believe that the universalizability test provides a framework in which the important moral considerations at play can be made salient.

For instance, in the case of international research we may observe that defenders of equipoise, such as Angell (1997) and London (2001), were unable to acknowledge ways in which the study design that they themselves preferred involved compromises in the care of research subjects for the sake of third parties. I submit that the framework provided by the equipoise requirement itself discourages such reflection, as it leaves no space to consider how competing interests might be weighed against one another. On the other hand, advocates of the difference position are led to deny that participation in a clinical trial entitles research subjects to the privileges and protections inherent in a therapeutic relationship—and this, in my view, is simply to ignore another crucial ethical consideration. Furthermore, whereas these authors would ground alternative protections in an ethic of nonexploitation, one of the major controversies at play in the debate over the AZT trials was whether research subjects were in fact *being exploited*, with each side prepared to offer an interpretation of nonexploitation that supported its own view. Thus, appealing to a principle of nonexploitation seems a highly unpromising way to resolve such disputes.

Applying the Kantian principle I have proposed allows us to squarely face the question: What compromises in the care offered to patients in a clinical trial can be justified by the potential

benefits to third parties? Equipoise rejects this question outright, whereas the difference position refuses to acknowledge study participants consideration as patients. However, I believe that this question is crucial. Let us consider, then, how the Kantian principle can be applied to some important features of many clinical trials.

First, there are methodologic features common to almost all well-conducted clinical trials that may involve risks to the individual patient—for instance, blinding and diagnostic interventions when required to assess efficacy. It seems to me that reasonably partial physicians should only balk at these compromises in patient care if they doubt that the study itself is worth conducting or when diagnostic interventions involve risks much greater than those commonly encountered in regular practice. After all, if all physicians were so partial to their patients as to refuse to submit them to the risks of blinding or of reasonably tolerable diagnostic interventions, then clinical research would be impossible. This we could not reasonably will.

Meanwhile, many study designs require washout periods or restricted flexibility in dosing. Here again, we could not reasonably want all physicians to be so partial to their own patients as to refuse to consider such study designs: such partiality here again, if universalized, would make it nearly impossible to study many crucial clinical questions. However, it is reasonable to insist that physicians consider alternative study designs that minimize these features and the attendant risks to patients, even when these risks are minor. In some cases, it may be possible to gather comparably good data without excessive restrictions on patient care, though this may prove more costly or time consuming.

Most controversial is the use of placebo controls when some therapy is known (or at least reasonably believed) to be effective. We should consider two sorts of cases separately. The first concerns international research under local conditions of scarcity, as with the perinatal AZT trials. In many such cases, the known effective treatment is one that is available in wealthy countries, but too expensive to implement in the host country. The purpose of the study is to test a less expensive treatment (such as the short-course AZT protocol) that stands a more reasonable chance of being implemented.

Here, I believe, there is a strong but defeasible presumption against the use of a placebo control, and thus in favor of an active control. After all, we are envisioning a physician faced with the choice between two study designs: one in which half of the patients get the experimental treatment and the other half get a known treatment, and another in which half get the experimental treatment and the other half get nothing. It seems that a reasonably partial physician should choose the first study design unless there are strong considerations against it.

In such cases the burden should therefore fall to advocates of a placebo control to show that an active-controlled study could not be relied upon to produce generalizable data, or would otherwise seriously interfere with the broader societal benefits expected from the trial. For instance, in the case of the perinatal AZT trials, some advocates of placebo-controlled trials argued that active-controlled studies would require a larger pool of subjects to attain statistical significance and would therefore take longer to complete. Such delays, they claimed, could lead to countless unnecessary deaths. However, this argument failed to account for the fact that few provisions had been made to ensure that people in the countries at risk would actually have access to even the short-course AZT protocol following a positive study result. It seems, then, that the compromises in the care offered to subjects in the placebo arm of these trials were not offset by the sweeping global benefits that were predicted. In all, I am inclined to agree with Angell (1997) that in this case the placebo-controlled studies were not justified, though I disagree with her reasoning for this claim.

In wealthy countries, there are times when methodologic considerations favor placebo-controlled trials even though known therapies are available. For instance, the disease of interest may be one in which markers for disease severity are subjective, or otherwise strongly influenced by the placebo effect. Alternatively, a treatment known to be generally effective may show marked variations in response between different groups, such that it could not be counted on to provide a useful baseline against which to measure the efficacy of some investigational treatment.

When these scientific considerations are at stake, placebo-controlled studies may be appropriate if certain conditions are met: the relative harms likely to be suffered by subjects who receive placebo in place of an active control are not permanent or disabling; patients in regular practice settings routinely forego the established treatment because of side effects or disinterest (as in treatments for allergic rhinitis and alopecia); the time period of placebo administration is strictly limited and disease progression is closely monitored; and, placebo administration itself involves insignificant risks (e.g., sugar pills versus sham surgery). When these conditions do not obtain, however, special justification may be required. In the case of sham surgery, we might require positive evidence that an alternative study with a nonintervention or nonsurgical control group could not answer the research question. (For instance, we might insist that a study first be conducted with a nonintervention control group, resorting to a sham surgery control group only if the first study is inconclusive.)

So far I have insisted on the continuity of medical care, clinical research, and medical education, especially with regard to the reasonable partiality to individual patients that a Kantian test recommends for physicians, including clinical investigators, medical educators, and trainees. Let me consider here two further Kantian requirements for medical practice that have special application in clinical research and medical education. The first requirement is the familiar requirement of informed consent. We could not reasonably want all physicians to impose interventions against the wishes of competent patients. Informed consent is especially crucial when risks are imposed on an individual patient, not for the sake of benefits to that patient, but instead for the sake of benefits to others. For instance, patients admitted to teaching hospitals must be aware that much of their care will be provided by trainees, though overseen by attending physicians, and patients in clinical trials must be aware that some features of a study's design will not be directed to their own benefit.

A second requirement is that, when risks are imposed on individual patients for the sake of benefits to others, these burdens and benefits must be distributed fairly. This requirement is, at present, often flouted in medical education and in international clinical research—I have already mentioned inequities in the distribution of the burdens of medical education. In the case of international clinical research, interventions intended for use in wealthy countries are sometimes tested in poor countries to contain costs and evade regulatory scrutiny. (In some cases, the disease that the intervention aims to prevent or treat is also more prevalent in the host country, which eases patient recruitment and may help to ensure a study with adequate power.) Subjecting a patient to the risks of clinical research, without making good faith efforts to ensure that the benefits provided by this research will be available in the patient's own community, suggests a lack of respect and concern for a patient's broad social circumstances that we could not reasonably want physicians to bear towards any of their patients.[7]

[7] For discussion of this issue in a broader political context see London 2005.

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