2

Fear of the Common Good and the Neglect of Justice

2.1 The Practical and Conceptual Origins of Parochialism

The conceptual foundations of research ethics have been profoundly shaped by a series of problematic commitments (§1.2). These commitments structure its scope and purview, set the terms on which questions in the field can be formulated and addressed, and create a series of fault lines at its conceptual foundations. These fault lines involve important ambiguities and inconsistencies about the relationship between core values—often expressed as the principles of respect for persons, beneficence, and justice—and the requirements they are regarded as justifying. Although these fault lines are latent in domestic research ethics, they are highlighted and stressed when research is sponsored by entities from high-income countries (HICs) and carried out in communities of low- and middle-income countries (LMICs).

This chapter has three goals. The first is to demonstrate how these problematic commitments arise from the cases, policy responses, and intellectual analyses that shaped the birth of research ethics as a distinct field. The second is to illustrate how these views result in a practical and a principled aversion to linking the research enterprise to a larger social purpose that might ground and explain the moral importance of this activity and provide criteria for evaluating its organization and conduct.

The third goal of the chapter is to provide readers who are new to research ethics with some helpful background information about core documents, classic cases, and important regulatory structures. What I offer here is not a proper historical overview, as that is beyond my abilities as a philosopher and unnecessary for our present purposes.[1] Instead, it is intended to reveal

[1] Readers interested in a history of medical research and the development of research ethics in the United States should consult Katz et al. (1972), Rothman (1991), Lederer (1995), Washington (2006), and Reverby (2009).

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where the views that I regard as problematic operate in the field and to show how they are bound up with three important influences on the emergence of research ethics as a distinct field of inquiry in the United States.

The first influence derives from features of the particular scandals that gripped the public's attention and created sufficient perception of an unmet social need to spur lawmakers into action. In particular, early scandals often involved the abuse of marginalized groups at the hands of researchers who relied on and exploited the considerable social power they wielded within traditional, Hippocratic medicine. These common features of early scandals created a public perception that oversight was required in order to protect the rights and interests of individuals from the potential for abuse at the hands of researchers in biomedical and behavioral research.

The second influence derives from the institutional mechanisms that were created in the United States to respond to this social need.[2] In 1973 the US Congress initiated hearings that lead to the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (from now on, the "National Commission"). One of its major achievements was a report entitled "Ethical Principles and Guidelines for the Protection of Human Subjects of Research," which would come to be known as the *Belmont Report*. In this report, the National Commission articulated a set of moral principles for regulating research with humans that formed the template for federal guidelines governing research with humans in the United States.

Prior to the creation of the National Commission, scholars from medicine, law, philosophy, theology, sociology, psychology, psychiatry, and other disciplines would periodically turn their attention to ethical issues raised by research with human participants. There was thus intellectual discourse about the ethics of research with humans, but there was not a distinct field with which scholars from different areas could self-identify. The creation of the National Commission, and the body of work that it produced, can be seen as the catalyst for the birth of research ethics as an explicit field of inquiry in which practitioners, advocates, regulators, and scholars from various disciplines could identify as working on a common subject matter. This is the oft-repeated creation story in which research ethics was conceived in postwar

[2] I don't claim to know or to chart the influence on these developments outside of the United States, and certainly the history and institutional settings in which research is conducted in Europe and elsewhere are likely very different. For example, see Holm (2020).

scandal and born with the formation of a unified social system for regulating research with humans.

The work of the National Commission gave rise to a series of regulations in the United States, intended to provide a unified set of rules to regulate research with humans. These rules would be applied by independent, local bodies of diverse representation, charged with overseeing the ethical conduct of research with humans. In the United States these bodies are known as Institutional Review Boards (IRBs). Although similar boards existed at various institutions in the United States prior to the work of the National Commission, the rule making that followed the publication of the *Belmont Report* consolidated, standardized, and unified both the rules for regulating research with humans and the institutional systems that were required to review those studies and enforce those rules.

The emergence of research ethics out of a practical policy response to particular revelations of abuse provides part of the explanation for why the conceptual foundations of the field are riven with fault lines. The field emerged with a series of regulations and oversight structures that created the scaffolding for subsequent theorizing. In that sense, research ethics is not like a modern city built from a blueprint that might provide a rationale for its layout and reflect a plan for accommodating future expansion. There was no prior intellectual discipline analogous to urban planning or civil engineering that provided a coherent philosophical framework for the practical policy responses that flowed from the work of the National Commission. Instead, research ethics is more like an ancient city that begins with a central square and grows outward over time as the population expands and local stakeholders have to address particular needs on the ground. In this metaphor, the central square of orthodox research ethics is the IRB and the rules and regulations they consult and apply in evaluating research protocols.

Nevertheless, the work of the National Commission did not take place in an intellectual vacuum and there is an important respect in which contemporary research ethics reflects a third, more intellectual influence. This influence is the victory of a particular perspective on the place of research in a decent political community and the normative force of the claims that it can make on individuals. Undoubtedly, one reason for the ascendancy of this perspective is that it dovetails nicely with, and provides a philosophical justification for, the scope and focus of the field that emerged out of these very practical origins. On a deeper level, however, it reflects the philosophical and conceptual perils that were associated with linking the research enterprise to

larger social purposes. For our present purposes it is the structure and relationship of the positions that assert this more intellectual influence that is of particular interest.

In §2.2 I show how efforts to forge a connection between research and larger social purposes have been associated with a social imperative that is seen as licensing the abrogation of the rights and interests of individuals in order to advance the common good. This analysis reveals the pivotal role of one problematic commitment, namely, the idea that research involves an ineliminable moral dilemma, a conflict between the good of the individual and the good of society, and the belief that an imperative to carry out research threatens the rights and welfare of individuals. In §2.3 I show how Hans Jonas (1969) addressed this conflict by denying a link between research and the common good and, in doing so, articulated a philosophical rationale for what I regard as a second problematic commitment, namely, treating research as a largely private activity, severed from the larger social purposes and moral obligations of the state of a just social order.

In §2.4 I show how the structure of early cases of research abuse and the policy responses that followed fostered the third and fourth problematic commitments, namely, the idea that the moral purpose and justification for research ethics is inherently paternalistic and that the moral epicenter of research ethics lies within what I called in the previous chapter the IRB triangle—the discrete interactions of researchers and participants overseen by IRBs. It also reveals how these cases and the regulatory response they generated gave rise to a fifth problematic commitment, namely, the tendency to conceptualize research in functional terms, as a set of goals and purposes that guide individual decision-making and that allow the research activity to be distinguished from treatment and medical practice.

In §2.5 I show how two final problematic commitments follow from those discussed so far. The first is a conception of justice that is severed from social institutions, the division of social labor, and the moral standing of community members. As a result, there is relatively little role for justice, as a distinctly social value, in orthodox research ethics. The second is a related tendency to explicate justice in terms that allow it to effectively be treated as a function of the other pillars of research ethics, namely respect for persons and beneficence.

In §2.6 we see how many of these commitments produced a context in which controversies in international research revealed and exacerbated fault lines running through the foundations of research ethics. In particular,

debates over the requirement that research be responsive to host community health needs, that there be provisions for post-trial access to any interventions vindicated in research, and that study participants be provided an ethically appropriate standard of care proved to be divisive and intractable within the conceptual ecosystem described here.

Ultimately, this chapter illustrates several tensions in the foundations of research ethics. One concerns the way that requirements that are supposedly grounded in considerations of justice either appear arbitrary in light of the parochialism of orthodox research ethics or come to be seen as counterproductive. Another concerns an unresolved tension between the pitfalls associated with embracing the idea that research is supported by a moral imperative to advance a set of larger purposes and the perils of neglect that can result from eschewing such social purposes and focusing instead on paternalistic protections of research participants. Chapter 3 then explores how these common commitments can be marshalled in ways that radically undermine core commitments of orthodox research ethics.

2.2 The Peril of Larger Social Purposes

2.2.1 Research as a Progressive Undertaking

The idea that there might be a moral and political imperative to carry out research casts a long shadow over research ethics. On the one hand, this idea reflects a widespread social conception of science as a progressive undertaking. The clinician might inoculate or heal the individual, but the scientist who discovers the vaccine or the therapeutic produces the means of saving countless lives. Pushing forward the boundaries of knowledge creates the means of advancing humanitarian purposes, but on a greater scale than could be achieved by individual compassion alone. Once discovered, new knowledge can be used repeatedly, at different times and in different places, to prevent avoidable suffering and disease, to heal the sick and injured, and to generally improve the conditions of life.

The progressive aspects of science dovetail with and seem to draw especially powerful support from the moral imperative of beneficence and the just ends of society. In the former case, if science holds out the means of advancing not merely the good of a single individual, but the much greater good of many more individuals, then it must be supported by a correspondingly greater

moral imperative. Likewise, if the purpose of a just social order is to secure the common good of its members, then science seems to dovetail with and draw support from the legitimate ends of political communities.

Ideas of this kind provide the ground for what has subsequently been referred to as the research imperative.[3] As I will use the term, the research imperative refers to a moral obligation to carry out research for the greater good. The general idea is that advancing social progress by producing the knowledge and the means to avoid premature death and alleviate avoidable suffering is not a morally optional goal. In an influential paper on the ethics of research with children, for example, the theologian Paul Ramsey used this term to describe research of such significant social value that "it is immoral not to do the research" (1976, 21).

On the other hand, Ramsey worried about cases where such research could only be carried out on terms that would themselves represent a moral transgression. Such cases would create a moral dilemma in which "moral agents are under the necessity of doing wrong for the sake of the public good" (1976, 21). It is this potential for conflict, and the challenge of how to mitigate it, that has cast a long shadow over research ethics.

Writing in the immediate wake of the *Belmont Report*, the noted researcher and child psychologist Leon Eisenberg asserted that the recognition of science as a progressive undertaking had been lost in revelations of scandal and that research ethics had lost touch with the moral mission of research to advance morally significant social ends. As a result, he says, "peculiar to this time is the need to restate a proposition that, a decade ago, would have been regarded as self-evident, namely, that fostering excellence in medical research is in the public interest" (1977, 1105).

At the close of his paper, Eisenberg quotes from the speech that Louis Pasteur wrote for the occasion of the founding of the Pasteur Institute. Pasteur writes:

[3] Wayne and Glass (2010) claim that Paul Ramsey (1976) was the first to coin this phrase. Ramsey was worried about cases in which it would hinder the public good not to conduct research, yet the requisite studies required the involvement of children who could not consent for themselves. If such research did not hold out the prospect of direct benefit to the children, then he worried that not conducting the research would hinder the public good but conducting it would violate the sanctity of the individual and the prohibition on using individuals in research without their express informed consent. This phrase is also associated with Dan Callahan, who often defined it broadly as the goal of using science to overcome the natural limits imposed on human life including to "overcome death itself" (2000, 654).

> Two opposing laws seem to be now in contest. The one, a law of blood and of death, ever imagining new means of destruction, forces nations always to be ready for battle. The other, a law of peace, work and health, ever evolving means of delivering man from the scourges which beset him. The one seeks violent conquest, the other the relief of humanity. The one places a single life above all victories, the other sacrifices hundreds of thousands of lives to the ambition of a single individual. The law of which we are the instruments strives even in the midst of carnage to cure the wounds due to the law of war. Treatment by our antiseptic methods may save the lives of thousands of soldiers. Which of these two laws will ultimately prevail, God alone knows. But this we may assert: that French science will have tried by obeying the law of Humanity, to extend the frontiers of life. (quoted in Eisenberg 1977, 1110)

Pasteur was keenly aware that the methods of science could be yoked to the purposes of war and destruction as easily as to purposes of "peace, work and health." But his identification with the latter invokes the importance of science as an engine of social progress, working to discover the "means of delivering man from the scourges which beset him," including the scourges wrought from the carnage of war.

Eisenberg thinks that this conception of research has been lost in the reforms carried out by the National Commission because the social discourse around research with human participants shifted so heavily toward the protection of participants from abuse and the hands of researchers. To invoke another frequently used metaphor, Eisenberg thinks that the pendulum of public opinion has swung too far, emphasizing protection for individuals but leaving out the social role of research. As he puts it, "I do not deny the necessity for surveillance of the ethics of the research community; the point I stress is that medical research, applied to medical practice, stands alone in its ability to avert unnecessary human suffering and death" (1977, 1106).

2.2.2 Two Sides to the Ledger of Progress

I am interested in Eisenberg's essay, not because of any historical prominence or social impact it may or may not have had, but because it reads like a chart capturing the shifting trajectories of constellations of ideas that stood out in the intellectual firmament of that time. In the ascendency of protectionist

norms that emphasize the rights and interests of study participants, it is easy to lose sight of the larger purposes that research rightly advances.

Eisenberg's essay is prescient in that it locates a central part of the social value of research in its unique ability to winnow the wheat of beneficial medical practices from the chaff of harmful and unnecessary theory and practice. It envisions a moral imperative to carry out research that is grounded, in part, in the idea that even when our ability to do good in medicine is not hampered by greed, incompetence, or lack of commitment to the common good, we very often lack adequate knowledge about what practices help and heal and which hurt and harm when we set out with the intention to treat and to aid. The public too often conflates the benevolent intent of medical practitioners with their ability to confer actual medical benefit. As he puts it, the public naively assumes that "what is usual and customary in medical practice" aligns with "what is safe and useful." But this assumption is false, and critics who embrace it are "surprisingly naive about the extent to which medical practice rests on custom rather than on evidence, [and] fail to appreciate the necessity for controlled trials to determine whether what is traditional does harm rather than good" (1977, 1105). Medical research produces information that is necessary to ensure that medical practice is capable of actually bringing about outcomes that are consistent with its therapeutic intention.[4]

If the state has a responsibility to safeguard the rights and welfare of its members, then the work of the National Commission reflects the state's interest in managing the way that research with human participants can put these at risk. At the same time, however, Eisenberg argues that unchecked sickness and disease also fall under the purview of the state and that research is needed to improve the capacity of the state to safeguard the lives and the welfare of its members. Because restrictions on the rate of medical progress also cause harm, Eisenberg argued that the sides of the ledger must be compared. As he emphasizes, "The decision not to do something poses as many ethical quandaries as the decision to do it. Not to act is to act" (1977, 1108).

Although he is not explicit about how the state ought to weigh the concerns on the different sides of this metaphorical ledger, Eisenberg says that "the systematic imposition of impediments to significant therapeutic research is itself unethical because an important benefit is being denied to the community"

[4] For an argument to the effect that medical beneficence cannot succeed unless it is accompanied by a duty to learn, see London (2020).

(1977, 1108). Even if he is reluctant to be more explicit, the structure of the reasoning here is clear. First, Eisenberg thinks that research produces an important social good—the knowledge that medicine requires in order to alleviate avoidable suffering and death. Second, he holds that the community has an interest in securing these benefits. Third, because the outcomes of actions that are necessary to secure these benefits must be weighed against the outcomes of actions that protect study participants, the interests of individuals must be weighed against the interests of the community.

Eisenberg may be correct in his assertion that in the decade prior to his writing it would have been regarded as self-evident that "fostering excellence in medical research is in the public interest" (1977, 1105). What he nevertheless fails to grasp, however, is the reason why, by the time of his writing, this idea had come to be seen as dangerous and morally problematic and how his own framing of the research imperative recapitulates some of these problems.

2.2.3 Permission to "Play God"

A decade earlier, others were less guarded in their arguments about what followed from the moral imperative to conduct research. In 1967, at a symposium on the "Changing mores of biomedical research" the influential researcher Walsh McDermott opened the meeting by pronouncing that "When the needs of society come into headlong conflict with the rights of an individual, someone has to play God" (1967, 39). Conveniently, McDermott saw playing God as the prerogative of the expert medical researcher, rightfully entrusted by society to advance its affirmative right to the great benefits of medical progress. Although care should be used to reduce the frequency with which society is presented with such moral dilemmas, McDermott was clear that "there is no escape from the fact that, if the future good of society is to be served, there will be times when the clinical investigator must make an arbitrary judgment with respect to the individual" (41).

McDermott's remarks came only a year after the noted Harvard Medical School professor and physician Henry Beecher published a paper in the *New England Journal of Medicine* detailing twenty-two examples, drawn from a larger sample of research studies published in leading medical journals, in which the rights or welfare of subjects had been violated. In three of

Beecher's examples, established effective therapies were withheld from study participants in the control group of a study. In one case, Beecher notes that, "23 patients died in the course of this study who would not have been expected to succumb if they had received specific therapy" (1966, 1356). In a fourth study, a drug linked to possible liver toxicities was administered to fifty "mental defectives or juvenile delinquents who were inmates of a children's center" (Beecher 1966, 1356). Within four weeks, half of the subjects in the study showed signs of hepatic dysfunction. Yet eight of these patients were selected for further study with half receiving liver biopsies. Once their liver functioning returned to normal, these patients were "challenged" with the drug again until liver dysfunction was observed, with one patient receiving a second challenge with the drug. In the eighteenth study, a melanoma from a terminal patient was transplanted to her mother the day before her death. After 451 days the mother died from metastatic melanoma believed to have derived from the transplant.

Beecher's examples reflect in grim detail the exercise of the authority that McDermott claimed for medical professionals—to make an arbitrary judgment against some unlucky individuals. Individuals were denied established effective treatments for severe medical conditions. They were subjected to invasive, burdensome, painful, and sometimes dangerous medical procedures often to achieve ends that would have been attainable through other means or for durations and to degrees that were unnecessary for strict scientific purposes. Many of the people subjected to these interventions were children, persons with developmental delays or cognitive impairments, as well as demented elderly whose capacity to understand what was being done to them was impacted by dementia or severe chronic illness. Many were also drawn from institutionalized populations, including corrections facilities, children's homes, and long-term care wards. In some cases, it was clear that informed consent for study procedures was not obtained; in many others it was assumed that consent had not been obtained.

Even if some portion of these abuses could have been eliminated with more careful planning or by employing less burdensome study designs or procedures, McDermott argued that in research with humans, the "irreconcilable nature of the conflict" between the individual and society creates a "moral dilemma of clinical investigation" that cannot be fundamentally eliminated. Because the future good of society is so morally weighty, "to ensure the rights of society," clinical researchers must sometimes make an "arbitrary judgment . . . against an individual" (1967, 40–41).

2.2.4 The Arbitrary Judgments of Men

As far back as Aristotle, arbitrary dealings deriving from the rule of individuals rather than the rule of law have been a hallmark of injustice. Yet McDermott insists that "it has been most unwise to try to extend the principle of 'a government of laws and not men' into areas of such great ethical subtlety as clinical investigation" (1967, 41). He is particularly concerned about documents like the *Declaration of Helsinki* (*DoH*), adopted in 1964 after contentious debate by the World Medical Association. This succinct set of ethical statements intended as a guide for physicians who conduct medical research opens with the words, "It is the mission of the doctor to safeguard the health of the people" (World Medical Association 1964). It goes on to say, "The Declaration of Geneva of The World Medical Association binds the doctor with the words: 'The health of my patient will be my first consideration.'" In a later section, dedicated to research in which participants have no reasonable expectation of direct benefit, it states that, "In the purely scientific application of clinical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom clinical research is being carried out."

McDermott argues that it may have been possible to satisfy this "double ethical charge" in the nineteenth century when researchers were expanding knowledge of health and disease but did not yet have the capacity to intervene in order to "control disease" (1967, 40). But he says "starting, I suppose, with the yellow fever studies in Havana, we have seen large social payoffs from certain experiments in humans, and there is no reason to doubt that the process could continue. . . . Once this demonstration was made, we could no longer maintain, in strict honesty, that in the study of disease the interests of the individual are invariably paramount" (40).

The yellow fever studies in Havana to which McDermott refers occurred in 1900 and were run by the now famous US Army physician Walter Reed.[5] At the time, the source of yellow fever was a matter of dispute. To test the hypothesis that it was transmitted by mosquitoes, a group of subjects were "challenged" with bites from mosquitos fed on the blood of patients known to have the disease. Three members of this group contracted yellow fever and died, including a doctor who had twice challenged himself with infected mosquitoes.

[5] For excellent accounts of this case, see Lederer (1995, 2008).

Prior to Reed's studies, more soldiers died from yellow fever in the Spanish-American war than from combat. After the source of the disease was identified and eradication efforts were undertaken, rates of both yellow fever and malaria infection were dramatically reduced. For McDermott, the fact that the information produced from Reed's research could be used to save countless lives was of sufficient moral import that it grounded a right on the part of society to the production of such knowledge. On this view, if that knowledge cannot be procured without the deaths of a few study participants, then it is the moral responsibility of the conscientious researcher to make an arbitrary judgment against a few unlucky souls in order to produce this benefit for society.

Because McDermott thinks that medical research necessarily involves a conflict between the individual and society and because he thinks society has a right to medical progress, he argues that documents that treat the individual as inviolable or sacrosanct, "produce the curious situation in which the only stated public interest is that of the individual. The future interest of society and its sometime conflict with the interest of the individual, in effect, are ignored" (1967, 41). McDermott thus asserts about the *DoH* the claim that Eisenberg would later assert about subsequent reforms more broadly, namely, that the protectionist focus of research ethics leaves out the great social good that research produces, which grounds the moral imperative for its conduct and that McDermott thinks is of sufficient importance to override the rights of the individual.

Because Eisenberg is writing after a long series of scandals and after the work of the National Commission, he is more guarded in his language than his predecessor. For example, where McDermott asserts that individual researchers rightfully bear a mantle of responsibility for advancing the right of the community to social progress, Eisenberg hopes for the creation of a "community of shared responsibility for health research," conceding that in research, like "all professional activity, social controls are necessary" (1977, 1108).

Nevertheless, it is not clear how Eisenberg avoids recapitulating the logic of McDermott's position when asserting that "the systematic imposition of impediments to significant therapeutic research is itself unethical because an important benefit is being denied to the community" (1977, 1108). If the community has a right to the benefits of medical progress, and if regulations that safeguard the rights and welfare of study participants are unethical because they pose an impediment to the provision of this good, then what are

the limits to what the community can demand from its members in the production of this information?

Writing after McDermott but before Eisenberg, the eminent physician Louis Lasagna noted his own inability to resolve this question. On the one hand, he asserts that, "In clinical investigation, as in other societal activities, the good of the individual and the good of society are often not identical and sometimes mutually exclusive" (Lasagna 1971, 108). But where McDermott is willing to say that it is the responsibility of the expert researcher to make arbitrary decisions against certain unfortunate individuals, and where Beecher worries about the abuse of this authority, Lasagna is evasive. Instead of stating a normative claim and offering a justification for it, he shifts to a descriptive standpoint in the passive voice, saying, "I believe it is inevitable that the many will continue to benefit on occasion from the contributions—sometimes involuntary—of the few" (109). Lasagna appears unwilling to follow McDermott in his assertion that when the needs of society and the rights of the individual come into conflict, researchers must sometimes play god. Instead, he simply assumes that it is inevitable that someone will do this and his description of the "involuntary contributions" of the few is a thinly veiled euphemism for unlucky souls who are the subject of arbitrary judgments and unwillingly or unknowingly conscripted into service for the greater good.

Lasagna admits that he is "ambivalent" about how to strike a balance between the sides of what he also regards as a deep moral dilemma. He recognizes the importance of medical progress, and he thinks that in the medical context this will require the abrogation of individual rights and that "society frequently tramples on the rights of individuals in the, 'greater interest.' " But, like Beecher, he also realizes that social trust in biomedical and behavioral scientists is not without limits or conditions and that boundaries must be drawn because "we cannot afford to have the cancer of moral decay that comes from frequent and flagrant disregard of human rights gnawing away at the body of science" (1971, 109).

2.2.5 Fear of Moral Decay

The prospect of moral decay from the frequent and flagrant disregard of human rights in science wedded to state purposes had been graphically and dramatically displayed before the world only three decades earlier.

During the Second World War, German scientists had actively and eagerly conducted research in support of the many goals of the Nazi state (Katz et al. 1972; Annas and Grodin 1992). In concentration camps, eminent German physicians and researchers conscripted individuals who the state regarded as morally inferior into often horrific experiments. At Nuremberg, twenty-three Nazi physicians and researchers who had carried out barbaric scientific experiments in concentration camps were tried for crimes against humanity. Of the sixteen defendants who were found guilty, seven were put to death for their crimes, including Dr. Karl Brandt.

In his testimony, Brandt stated that during the time when the Nazi party controlled the German government it imposed a collective system in which "the demands of society are placed above every individual human being as an entity, and this entity, the human being, is completely used in the interests of that society" (Trials of war criminals before the Nuernberg Military Tribunals [Tribunals] 1949, 29). In that period, he argued, "everything was done in the interests of humanity so that the individual person had no meaning whatsoever, and the farther the war progressed, the stronger did this principal thought appear" (30).

Lawyers for the defense argued that, "It would be unjust, however, to conceal the enormous benefit of the human experiment," noting that past discoveries, once made, are often widely adopted and "become the common property of all peoples for the benefit of suffering mankind" (Tribunals 1949, 75). They argued that medical scientists on both sides of the conflict were called on to assist the war effort and that "in nearly all countries experiments have been performed on human beings under conditions which entirely exclude volunteering in a legal sense" (73).

During the cross examination of a witness from the United States, Dr. Andrew Ivy, the defense asked if it was morally permissible to sacrifice the life of a prisoner in a research study if doing so would save the lives of an entire city. When Ivy refused to agree that this was permissible, Brandt's attorney, Dr. Robert Servatius, argued in his closing statement that this response amounted to a view in which "human rights demand the downfall of human beings" (Tribunals 1949, 128).

If the two sides of the moral ledger are in strict conflict, then we appear to be faced with a dire ethical dilemma. If the interest of the community outweighs the sanctity of the individual, then we risk permitting the callous disregard for individual humans in the larger service to humanity. Alternatively, if we regard the individual as inviolable, then we risk elevating

concern for human rights over the suffering and preventable death of human beings.

2.3 From Social Imperative to Private Undertaking

2.3.1 Severing Research from the Common Good

This potential for the humanity of the individual to be obliterated under the demands of the greater good, the needs of society, and the goals of progress was the subject of the philosopher Hans Jonas's famous 1969 paper "Philosophical Reflections on Experimenting with Human Subjects." For Jonas, just as for McDermott and others, research reflects in microcosm a larger social conflict between the demands of the state and the rights and welfare of the individual. In research, as in war, Jonas argued, the demands of the collective too easily reduce the individual—a person with a moral worth that merits unconditional respect—to a mere statistic, a data-point no different from hundreds or thousands of others. When persons are made fungible, their identity and individuality are blotted out and individual concern is replaced by a cold algebra of harms inflicted on small groups, necessitated and balanced out by gains to a substantially larger collective (Donagan, 1977, Fried 1974).

For Jonas, close connections between scientific research and the ends of the state or the common good threatened to overshadow the humanity of the individual and, with this, the sanctity and value of the person. The remarkable feature of his response to this threat, however, was not that he sought to constrain or curb the demands of progress—to strike a balance between the sides of the moral ledger—or that he sought to demarcate the just demands of a just state from the unjust demands of various stripes of totalitarianism. Instead, Jonas took the more radical step of challenging the existence of a social imperative to engage in research with humans by severing the connection between research and the common good.

Against intuition and the popular rhetoric of science, Jonas attacked the idea that there is a social imperative to carry out research. Unlike large-scale military conflicts, in which the continued existence of a people might be placed in question, Jonas argued that sickness, injury, and disease are not a threat to society. Societies can survive the normal death rate from such maladies; it is only individuals who cannot. Because disease is a threat to the

interests of individual persons and not to society, the quest for progress in medical science is a personal rather than a social goal, an individual rather than a social benefit.

Unlike the proverbial Dutch boy plugging holes in a dyke with tiny and insufficient fingers, Jonas's article is rightly famous and widely influential because it strives to stem the potential for a totalitarian tidal wave at its source. If sickness and disease threaten the individual, there is no social imperative grounded in the rights of society or the common good that can be marshaled to override or justify the abrogation of individual rights or interests.

In slightly different ways, Eisenberg, McDermott, and Servatius had argued that there were two sides to the ledger of social progress—one column for the rights and welfare of study participants and another for society or humanity. As such, they saw the protectionist focus on the human rights of individuals as incomplete, neglecting the rights of society and threatening to undermine the cause of humanity. By arguing that humanity and society are not threatened by suffering and disease, Jonas argued that it is no error to proceed as though "the only stated public interest is that of the individual" (McDermott 1967, 41). On this view, the "future interest of society and its sometime conflict with the interest of the individual" (McDermott 1967, 41) are rightly ignored because the interests of society are not threatened by the maladies that research with humans seeks to ameliorate.

2.3.2 An Optional Goal

If scientific progress is not a right of society, and if there is no moral imperative to carry out research, then it becomes an optional goal. Researchers are at liberty to take up its mantle, but they are not required to do so by any social or moral imperative. As an optional, personal project that particular individuals elect to pursue, the research enterprise is severed from a social context in which the vast needs of the collective can so easily outweigh the interests of a few individuals. The interests that motivate research are not the interests of society, they are merely the morally optional personal interests of individuals.

To draw an analogy, committing one's life to perfecting a musical instrument might be a noble undertaking. But it is not so morally weighty that it can

justify the abrogation of the rights and interests of others. If research is similarly a noble personal undertaking, then there may be reasons to patronize science—just as some choose to patronize the arts—but those reasons are not so weighty that they can legitimate the abrogation of the rights or welfare of others.

When Eisenberg laments that research ethics has lost touch with the moral importance of research, his frustration reflects the success of Jonas's gambit. Eisenberg appeals to the value of research in ameliorating the inadequacies of medicine, and in this way he connects the moral significance of medicine to its impact on the lives of individuals. The large-scale delivery of unsafe, ineffective, or positively harmful treatments takes a toll, not on communities, but on individuals. Eisenberg also cautions against seeing death as a part of the human condition and, with this, taking its inevitability as a reason not to recognize an imperative to fight against it. Such an attitude might make sense if we take white, affluent communities of HICs as our reference class. But when we turn to what he calls the "third world," where death from communicable disease is widespread and life expectancies are far lower, the goal of medical progress can readily be seen, not as a quixotic mission to expand the boundaries of long life into some indefinite horizon, but as enlarging the share of humanity that enjoys the life expectancy that has become common in the most fortunate corners of the globe. In these respects, Eisenberg's arguments are prescient.[6]

At the end of the day, however, Eisenberg has no alternative to McDermott's assertion that at the heart of research there is a dilemma in which the rights of society are pitted against the rights of the individual. Without any such alternative, research ethics has found it easier to follow Jonas and to circumscribe the scope of the discipline in a way that forestalls appeals to the common good and the specter of totalitarian science carried with them. Orthodox research ethics reflects Jonas's philosophical reticence about linking research

[6] In a prolific body of work, Dan Callahan argued eloquently against the "underlying logic of the research imperative, which is to overcome death itself" (2000, 654; see also Callahan 1990, 2003). One can agree with Callahan that death is an inevitable part of life, and that suffering cannot be entirely extirpated from human life, while still holding that there is a valuable role for medicine to play in helping individuals retain the capacities they need to live out a normal lifespan in which they can form, pursue, and revise a life plan of their own. The research imperative is also sometimes associated with a drive to pathologize an ever-wider range of human differences (Wayne and Glass 2010). Although some may have such an ambition for science, I see no reason why an imperative of the sort I defend in chapter 4 must entail such excesses.

to the common good, to any sort of social imperative for progress, or to the goals and mission of the state or political community.

2.3.3 Frustration without a Viable Alternative

Occasionally, Jonas's position is challenged by scholars who effectively echo concerns that are already voiced in these early critiques. For example, Eisenberg argues that there must be proportionality between "social controls" that we impose on researchers to prevent wrongdoing and the great good that comes from medical research. We must reconcile both sides of the ledger because there is no escaping the fact that "the decision not to do something poses as many ethical quandaries as the decision to do it. Not to act is to act" (1977, 1108). Basically the same idea is expressed nearly thirty years later by John Harris when he writes, "Where our actions will, or may probably prevent serious harm then if we can reasonably (given the balance of risk and burden to ourselves and benefit to others) we clearly should act because to fail to do so is to accept responsibility for the harm that then occurs" (2005, 242).

However, contemporary discussions of the research imperative reflect the reticence of the field to link research to larger social purposes. They tend not to address the question of whether there is a social or moral obligation to carry out research and, if so, how that obligation should shape the goals and priorities of the research enterprise. They emphasize that the failure to recruit sufficient numbers of participants into studies is wasteful, and they focus more narrowly on whether there is a duty on the part of individuals to participate in research (Caplan 1984; Herrera 2003; Harris 2005; Brazier 2008; Rhodes 2008; Chan and Harris 2009; Schaefer, Emanuel, and Wertheimer 2009).

Harris, like Eisenberg, expresses frustration at the deontological bulwarks erected around the rights and interests of study participants and the comparative social indifference toward the loss of life or avoidable disability incurred as a result of the slow pace of medical progress. Although his rhetoric is more temperate, he points out, like McDermott, that society conscripts its members to serve a wide range of roles and purposes, from the military, to jury duty, to mandating vaccination as a condition of public-school

attendance.[7] Harris has no sympathy for the idea that researchers should have the unilateral power to conscript participants into research and he sees significant policy reasons to avoid such efforts. Nevertheless, he argues that even if it should not be the first option from the standpoint of policy, the good at stake can be such that it would be "legitimate to make science research compulsory" (2005, 245).

To the extent that thinkers like Harris recapitulate older frustrations with the narrow protectionism of research ethics, the reaction to views of this sort largely reflects a similarly venerable horror at the prospect that the utilitarian calculus on which they are predicated will resurrect the specter of totalitarianism that Jonas sought to exorcise.[8] As a result, whether for philosophical or purely pragmatic purposes, orthodox research ethics tend to avoid discussions of the social mission of research, whether medical research is required as part of a just social order and the extent to which the progress that it offers is genuinely incompatible with respect for individuals as free and equal persons. I suspect that this aversion is less of a reflection of the status of these issues as closed and settled than it is a reflection of wariness about fault lines radiating out from the origins of the field and running through the foundations of the discipline.

In challenging the research imperative, Jonas sought to fortify concern for the rights and interests of individuals against the demands of society for scientific progress. In doing so, however, he provides a philosophical justification for relegating research to the status of a socially optional, private activity, unconnected to larger social purposes. Jonas provides a rationale that transforms the de facto parochialism of nascent research ethics institutions into a de jure conception of the relationship between researchers and the social good. Where the institutional focus on the IRB triangle might be seen as an administrative convenience, Jonas provides the rationale for seeing this focus as the proper lens through which to view the interaction between two parties whose respective interests are on a par.

[7] Jones (1993, 86–89) uses the term "soldiers of science" to describe the attitude of Tuskegee researchers toward study subjects. Schaefer et al. (2009, 70) resist the claim that research is sufficiently important to justify compelling people to participate, but they nevertheless say that the duty to serve as a research participant is "in some ways analogous to a wartime call to arms in which not just money but soldiers to fight are needed."

[8] Among others, see Brassington (2007, 2011) and Wayne and Glass (2010).

2.4 Functional Characterization of Research

2.4.1 Practical Influences on Research Ethics

In the previous section I argued that Jonas's arguments provided an explicit philosophical rationale for developments in research ethics that were spurred by much more practical responses to revelations of scandal and abuse. Although this conceptual background is important for the purposes of the present inquiry, the conceptual ecosystem of research ethics was likely shaped more directly by practical responses to revelations of abuse.

In particular, many early cases of abuse involved health care professionals exploiting the discretion and authority that they wielded in virtue of their social role as caregiver to do things that were inconsistent with the duties and obligations of that role. This made it natural to locate the moral epicenter of research ethics in the discrete interactions of researchers with study participants and to conceptualize research in functional terms that would facilitate the ability of IRBs to regulate these interactions.

2.4.2 The Jewish Chronic Disease Hospital Case

Two important cases are worth mentioning in particular. The first, described briefly by Beecher in his 1966 exposé, would come to be known as the Jewish Chronic Disease Hospital Case (Katz et al. 1972, 9–65; Arras 2008). In 1965, the New York State Board of Regents found that researchers at the Jewish Chronic Disease Hospital (JCDH) had carried out a research project on chronically ill residents without properly informing those individuals—many of whom likely lacked the capacity to make decisions for themselves—that they were subjects in an experiment.

Briefly, researchers had learned that it took longer for individuals with cancer to expel foreign cancers cells from their bodies than individuals without cancer. They therefore wanted to know whether this delay was due to the presence of cancer or to the fact that the immune systems of such patients were already compromised. To answer this question, they designed a study in which they would inject foreign cancer cells into the bodies of individuals who were chronically ill but not suffering from cancer. Their hope was that if the delayed rejection time was caused by the presence of cancer, they could

use this knowledge in the quest to fight this fatal disease or to devise a test for its presence. They claimed that they were justified in not informing subjects of the nature of this procedure because the word "cancer" was loaded with such significance at the time that many might have refused to participate, despite the researchers' belief that it was highly unlikely that anyone could contract cancer from exposure to foreign cancer cells.

For the Board of Regents, the case was notable because clinicians had used the broad discretion that at that time attended their social role as caregivers to perform procedures on patients that were not for their individual benefit but for the advancement of science. Even if no participant was harmed, the Board of Regents held that participants were wronged when they were denied the right to decide what should happen to their person.

In criticizing this case, Beecher appealed to the *DoH*. This document largely recapitulated moral requirements that had been articulated decades earlier in the trial of the Nazi doctors at Nuremberg. At that trial, the prosecution argued that Nazi research violated a series of requirements that captured the accepted practices and beliefs about the ethical conduct of research. This set of principles would come to be known as the *Nuremberg Code*, and it begins with the bold assertion that, "The voluntary consent of the human subject is absolutely essential" (Tribunals 1949, 181). Even at the trial, however, the defense had shown numerous cases of Allied research in which consent was not obtained or in which it was obtained under conditions that might compromise its moral validity. Although the *Nuremburg Code* would come to be recognized as a prescient document, it had little impact on the conduct of research by American researchers (Moreno 1999). As a result, the twenty years that followed the Nuremberg trials have been described as "a time of vigorous research characterized by a fragmented community of medical researchers who applied inconsistent ethical standards and employed highly variable research practices" (Freidenfelds and Brandt 1996, 239).

The *DoH* repackaged most of the provisions of the Nuremburg Code, now framed as guidance specifically for individual clinicians. In particular, as research had grown more widespread, nurtured by private investment and public funding, physicians grappled with the tension between their fiduciary duty to the individual patient and the researcher's social obligation to generate information that might advance the health of countless future generations of patients.

2.4.3 The Tuskegee Syphilis Study

The second and perhaps the single most important case that came to light during this same period also involved medical practitioners exploiting the social trust they enjoyed in their role as healers for purely research-related purposes. In the early 1960s, an African American epidemiologist in the US Public Health Service (PHS) named Dr. Bill Jenkins heard about a study that had been initiated by the PHS in Macon County, Alabama in 1932. Since the discovery of Salvarsan in 1910, syphilis had been a treatable medical condition. But with the discovery and mass production of penicillin at the end of the Second World War, a highly effective treatment with few side effects became widely available. Nevertheless, the purpose of the study in Macon County was to document the effects of untreated syphilis in a cohort of 400 African American men.[9]

After sifting through the substantial record of publications detailing the study and its decades-long history, Jenkins wrote to other African American physicians and contacted the media in an effort to raise concerns about the ethics of the study.[10] In 1966, another PHS worker, Peter Buxtun, also began voicing serious moral concerns about the study, both within the PHS and more broadly. Ultimately, the PHS convened a blue-ribbon panel of experts to review the project. In 1969 the panel voted, with only a single dissenter, to continue what it saw as important research (Jones 2008).

When news of what would come to be called the Tuskegee syphilis study made headlines in 1972, however, the public's reaction diverged significantly from the response of the blue-ribbon expert panel that had voted to continue the study only three years earlier. PHS researchers had lied to the men in the study about their medical condition, telling them they had "bad blood" rather than revealing a diagnosis of syphilis. They lied about the purpose of their yearly medical examinations and spinal taps, leading the men to believe they were receiving treatment, never disclosing that these purely research-related procedures were part of a study designed to document the effects of untreated syphilis. Researchers had actively prevented the men from receiving medical treatment from public health programs, as a result of examinations that would have been conducted as part of the draft, or in

[9] There are numerous excellent historical accounts of this event including Brandt (1978), Jones (1993, 2008), and Reverby (2009). Reverby (2011) discusses parallel studies carried out in Guatemala.
[10] https://www.nytimes.com/2019/02/25/obituaries/bill-jenkins-dead.html

the course of routine medical care. The outrage of a public that was already questioning the traditional distribution of power and social authority in major social institutions was swift and hot.

The Tuskegee syphilis study lasted for forty years. It began before World War II, continued after the trials at Nuremberg, the execution of German physicians for crimes against humanity, the publication of the Nuremberg Code and the *DoH*. Although news of the study shocked the conscience of the lay public, it—like the twenty-two cases of unethical research Beecher had detailed in his 1966 paper—was not a clandestine affair within the PHS. The outrage of the public reflected shock at what could pass for normal behavior in a profession entrusted with significant power and authority. The moral calculus of the researchers who conceived, conducted, and perpetuated these studies was jarringly out of sync with the moral sensibilities of the public in whose name these investigations were ostensibly carried out.

It was public outcry over the Tuskegee study that spurred the US Congress to create the National Commission whose *Belmont Report* would be shaped by these revelations from Alabama. The scandals at Tuskegee and places like the JCDH revealed how easily the deference to clinicians and the discretion to control the agency of patients conferred in the Hippocratic tradition of medicine, still operative at the time, could be coopted for purely research-related purposes.

At Tuskegee, for example, it is unlikely that the study could have been maintained for forty years if members of the PHS had not presented themselves as healers and taken advantage of the social trust that Hippocratic medicine demanded from the recipients of medical care. The men who were unwitting participants in the study believed they were receiving treatment. They believed that medical professionals were acting in their interests. In fact, of course, the activities of those professionals were inconsistent with the best interests of those men. They were directed, not by the goal of curing their disease or preventing its spread, but by the goals of documenting the natural course of untreated disease in African American men.

2.4.4 Research versus Treatment

A natural response to the events at JCDH and Tuskegee was to search for criteria that could be used to determine when the interactions between

individuals should be governed by the norms of the doctor-patient relationship and when they fall, instead, into the sphere of research and should be governed instead by the norms of research ethics. The key moral idea is that even if caregivers enjoy some discretion to withhold information or to encourage patients to undertake some course of care, the moral warrant for this discretion would derive from the duty of the caregiver to always act as the fiduciary of the interests of the individual patient. If that same individual professional instead takes up the goals and ends of medical research, then they lay down their sovereign commitment to the medical best interests of patients and, in doing so, can no longer legitimately exercise the discretion of the caregiver. Instead, they must approach patients as researchers and disclose to them the nature of the purposes they are now seeking to advance and conform to the distinct norms of research ethics.

The *Belmont Report* transformed this moral insight into a functional characterization of research as a set of purposes, distinct from the purposes of medical or behavioral health practice. Being able to distinguish "biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other" allowed these activities to be sorted into their proper sphere of oversight (National Commission 1979).

The *Belmont Report* defines medical practice by the purpose of providing "diagnosis, preventive treatment or therapy to particular individuals" (National Commission 1979). It also is characterized by the use of "interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success." The paradigmatic example of practice is when a clinician draws on existing knowledge to deploy established effective interventions for the benefit of the individual patient. In this case, all of the considerations that are relevant to evaluating the use of an intervention relate to its likely impact on the interests of the patient. Few medical treatments are unalloyed goods. They often carry risks and burdens because they involve the administration of toxic and potentially dangerous substances. In administering treatment, therefore, the clinician is required to make the judgment that any risks to the health of a particular patient are outweighed by the prospect of medical benefit for that same patient.

In contrast, the purpose that defines the research activity is to "test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example,

in theories, principles, and statements of relationships)" (National Commission 1979). To do this, research often involves the delivery of interventions whose likelihood of success is unknown or whose value relative to other options is uncertain. It can also involve practices or procedures that are performed on one person in the hope of generating information or benefits that will only accrue, if they materialize at all, to a different group of persons.

On this approach, research is characterized by a network of justificatory reasons that are fundamentally different from treatment. Treatment is the utilization of current knowledge and established interventions for the singular purpose of advancing the medical best interests of the individual patient. Research is the deployment of interventions whose effects are unknown or uncertain, for the purpose of generating generalizable medical knowledge. This functional account of research serves the practical purposes of IRBs by allowing them to determine when activities fall under the norms of medical practice and when they constitute research and must therefore receive special oversight. It also allows research to be understood in a way that fits entirely within what I called the IRB triangle in the previous chapter—the interactions between researchers and participants that it is the purview of IRBs to oversee.

This way of understanding research, as an activity defined by a distinct set of goals and purposes that can be taken up and pursued by individual researchers, further dissociates research from larger social purposes. Yes, the purpose of research is to generate generalizable knowledge, but the value of generalizable knowledge is left unstated. Conceived of as a set of purposes an individual can adopt, research is severed from any connection to the social institutions that make its conduct possible and that are required to translate generalizable information into practices, procedures, or interventions that actually advance the health interests of patients. Ensconced within the IRB triangle, research is dissociated from any sort of division of social labor and the larger purposes of a just social order that might be relevant to regulating the terms on which that labor is divided and for what purposes it can be justified.

As we will see in more detail in chapter 5, this functional approach to research, with its critical emphasis on the individual decision-maker, reinforces the perception that there is a fundamental moral dilemma at the heart of research with humans. In particular, if research is a set of goals and

purposes that guide individual decision-making, and if these goals are inherently distinct from the goals and purposes of clinical medicine, then individual decision-makers will at least sometimes have to compromise one of these sets of objectives in order to advance the other.

2.4.5 The Ecosystem of Paternalism

As the name of the National Commission and its most famous report indicate, the birth of research ethics in a practical policy response to revelations of abuse fundamentally shaped the protectionist stance of the field. Researchers would have to submit to IRBs protocols detailing the nature of their proposed study, its anticipated risks and benefits, and a plan for securing the free and informed consent of participants. Only if this plan meets the approval of this independent oversight body will it be permissible to offer participation to study participants. IRB review would thus mediate the interaction of researchers and study participants with the mandate to protect study participants from abuse. Both conceptually and historically, the protectionism of research ethics is easily seen as a paternalistic effort to safeguard the rights and welfare of people who cannot do this for themselves (Dworkin, 1972; Miller and Wertheimer 2007; Jansen and Wall 2009; Edwards and Wilson 2012).

The paternalism of orthodox research ethics is thus closely connected to the other problematic aspects of the conceptual ecosystem of orthodox research ethics that I have been detailing here. On a practical level, it reflects a concrete policy response to cases of scandal and abuse. On a conceptual level, it reflects the perception that the professional obligations of caregivers and researchers impose conflicting and incompatible goals on the decision-making of individuals that reinforce the larger tendency of the underlying utilitarianism of research to run roughshod over the rights and interests of individuals. Defining research in functional terms facilitates a vision of research oversight in which the most critical ethical issues arise in the interactions of researchers with study participants. A framework that can sort the actions of caregivers and the actions of researchers into different bins, where they can be subject to different moral requirements, facilitates the protectionist goals of IRB review and advances the pragmatic goal of avoiding the types of abuse that set the reforms of the National Commission into motion.

2.5 Justice: The Last Virtue of Research Ethics

2.5.1 Justice Untethered

Severing the research enterprise from larger social purposes and defining research in functional terms that fit neatly within the IRB triangle effectively removes this activity from the sphere that is primarily regulated by considerations of justice. The philosopher John Rawls famously calls justice "the first virtue of social institutions" (1971, 3) because it regulates the operation of social systems that both require social support and create the social order that determines what rights, duties, and opportunities individuals have and their prospects for being free to pursue a life plan of their own on equal terms with their compatriots.

Although the *Belmont Report* lists respect for persons, beneficence, and justice as the three fundamental moral principles to which research must be responsive, justice is arguably the last virtue of research ethics. At the conceptual level, it is the least well defined and clearly grounded. At the operational level its recommendations are the least well translated into explicit, practical requirements. In terms of the volume of scholarship produced in the field it is the least studied, and in the institutional structures that regulate research it has the least influence.

2.5.2 The Consequences of Neglect

The neglect of justice in research ethics has three distinct consequences. First, the justifications for requirements that are linked to this value are often unclear. Second, early discussions of justice in research ethics explicate this value in terms that allow it, implicitly if not explicitly, to be reduced to a function of the other values that constitute the twin pillars of research ethics. Thirdly, considerations of justice that cannot be reduced to applications of respect for persons and beneficence seem to fall outside the scope of the field, to be unwarranted, or in the worst case to be inconsistent with more clearly understood and firmly grounded commitments of the field.

To make the case for these claims, consider how each of these principles is explicated in the *Belmont Report*. Respect for persons, sometimes referred to as respect for autonomy, reflects the importance of being able to make decisions that impact the shape or the quality of one's own life. It is

operationalized for persons with decisional capacity through the requirement of free and informed consent. Although informed consent had been elevated to the status of a necessary condition for ethical research in the Nuremberg Code, it was not until the work of the National Commission that this value came to play a dominant role in regulating medical research. Its prominence is grounded, in no small measure, in the fact that if this requirement had been widely adopted after Nuremberg it likely would have been sufficient to avoid most of the scandals that spurred the creation of the National Commission. Because informed consent has been the subject of such voluminous scholarship and discussion, it is almost synonymous with research ethics.

The second core value of research ethics is beneficence, which ranges over the domain of individual welfare or well-being. The *Belmont Report* uses "beneficence" to name the principle that ranges over all considerations that affect individual welfare or well-being. Others sometimes divide this concern for individual welfare or well-being among two values. In the influential terminology of Beauchamp and Childress (2001), for example, beneficence is reserved for an affirmative concern for welfare or well-being while nonmaleficence refers to the negative concern to avoid harm or some other way detracting from well-being. Regardless of how one wants to divide the values that range over this domain, the concern for individual welfare or well-being is operationalized by balancing risks and benefits.

To avoid confusion, I follow the more expansive view of beneficence as including the principle of nonmaleficence. In other words, beneficence ranges over both the avoidance of harm and the provision of benefits.

A key point is that beneficence is not limited to the consideration of whether the risks and burdens of research participation for a given individual are reasonable solely in light of the benefits likely to accrue to that same individual—although satisfying this condition is a clear way of satisfying the requirements of beneficence. Rather, the risks and burdens to one person can be offset by the expectation that benefits will accrue to future beneficiaries of research. Considerations of beneficence thus require judgments in which risks and burdens to some individuals are balanced or traded off against the expectations that benefits will accrue to other individuals. In this sense, beneficence is concerned with the distribution of benefits and burdens both to the same individual and across different individuals.

The *Belmont Report* introduces justice by saying that it addresses the question "Who ought to receive the benefits of research and bear its burdens?"

Understood this way, both justice and beneficence range over the same domain, namely, the distribution of benefits and burdens. Similarly, both deal with judgments about how benefits and burdens are distributed across different individuals or groups.

Justice is also defined as the principle that "equals ought to be treated equally" (National Commission 1979). But this formulation is not very useful without specifying the space of equality—the set of concerns or the domain over which individuals have a right to be treated equally (Sen 1982, Daniels 1990, Korsgaard 1993, Anderson 1999). After all, as consequentialists are fond of observing, beneficence is also grounded in the commitment to giving equal treatment to equals; beneficence involves assigning equal value to the welfare of every individual. Beneficence treats the space of equality as the domain of welfare—individuals have an equal claim to have their welfare be given equal weight to the welfare of everyone else. Because more welfare is better, beneficence requires choosing acts or policies that produce the greatest net welfare. In research ethics, part of the justification for allowing risks to one person to be offset by benefits to others is the prospect that the burdens to the one are outweighed by the benefits to the others. For consequentialists, therefore, giving equal treatment to the welfare of all, impartially considered, is a central feature of the moral point of view. So merely saying that justice requires giving equal treatment to equals is not sufficient to distinguish it from beneficence.

The *Belmont Report* does not indicate the respect in which justice in research requires equals to be treated equally. Instead, we are told that social justice requires that vulnerable groups not be chosen for inclusion in research simply because of their "easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied" and that this requirement was widely violated in the nineteenth and early twentieth centuries when "the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients" (National Commission 1979).

On the surface, beneficence and justice might be distinguished by the specific requirements they place on the distribution of benefits and burdens across different groups. For example, beneficence is operationalized in terms of having a favorable balance of risks and expected benefits. In contrast, justice is operationalized in terms of "fair procedures and outcomes in the selection of research subjects" (National Commission 1979). Whether this

surface difference translates into a substantive moral difference depends on the extent to which the considerations that determine the fairness of procedures and outcomes are distinct from considerations that determine the favorability of the balance of risks and expected benefits.

2.5.3 Minimalism about Justice: Reducing It to Beneficence and Autonomy

Part of the problem, however, is that although the *Belmont Report* asserts that fairness requires certain conditions, it does not explain *why* those conditions represent requirements of fairness. For example, we are told that fairness at the procedural level requires not recruiting favored groups for "potentially beneficial research" while selecting "only 'undesirable' persons for risky research" (National Commission 1979). Likewise, "when research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved."

But both of these restrictions can be explained in terms of beneficence. The *Belmont Report* treats marginalized or disadvantaged groups as already burdened. If research relies disproportionally on members of groups that are already burdened, then it will have a higher risk profile than if it were to rely instead on individuals drawn from groups that are comparatively better off. The reason is that involving a population that is already less burdened is likely to result in fewer harms, or to result in harms of a lesser magnitude. This can be for several reasons.

First, groups that are less marginalized may not be willing to participate in research that is unacceptably risky, and their more stable social position may make it more difficult to force them to participate. Second, to the extent that better-off people experience less stress, fewer physical insults, and suffer from fewer medical problems, they may be less likely to experience some adverse events in the course of research. Third, if they do experience those adverse events, their effects may not be as pronounced either because bearing a lower burden of stress and illness makes them more resilient or because having greater access to social resources enables them to more effectively mitigate harms and cope with their aftermath. As a result, the wrongness of a violation of procedural fairness can be explained in terms of the other core

values of research ethics—it is more likely to involve coercion or a form of influence that violates respect for persons or to cause more harm than an approach that relies instead on individuals drawn from better-off groups.

Similar reasoning applies to ensuring that "some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are [not] being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied" (National Commission 1979). Relying on such groups in cases where they do not expect to benefit directly from research participation is more likely to result in a violation of respect for persons or to produce more harm than an approach that relies on less marginalized groups. In contrast, when a study addresses a problem that is experienced by individuals in a group, then their participation is more likely to be voluntary because they are more likely to view the risks as reasonable in light of benefits to themselves or to members of a group with which they identify. And if the research is related to the health needs of the groups included, then it is likely to produce a favorable risk benefit ratio for those groups.

My point is not that the pronouncements in the *Belmont Report* cannot be grounded in justice. It is, rather, that at best the distinct content of justice in the *Belmont Report* is unclear. At worst, the *Belmont Report* is consistent with what I refer to as the minimalist view of justice. On this view, requirements of justice are reduced to a function of beneficence and respect for persons. To ascertain whether a transaction or a social arrangement satisfies the requirements of justice requires a determination of whether it is conducted on terms that satisfy respect for persons and beneficence. Returning to the requirements in the *Belmont Report,* if it is unfair to use deception, force, or fraud to secure the participation of marginalized groups, then it looks like this unfairness can be explained in terms of, and therefore reduced to, respect for persons and informed consent. If it is unfair to conduct research in populations that bear higher risks than less burdened populations, then this seems to reduce fairness to beneficence since fewer harms will result by including less marginalized populations in research. The pressure to frame issues in research ethics in terms that are manageable within the narrow confines of the IRB triangle adds to the tendency to neglect the distinctively social aspects of justice and to explicate it, instead, in terms that derive from the more familiar and central pillars of the field.

2.5.4 Requirements without Grounds

When justice is linked to issues outside of the IRB triangle, stakeholders are left with no justification for the claims that are made. For example, in an important passage the *Belmont Report* says:

> Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research (National Commission 1979).

Although it is clearly stated *that* these requirements are supposed to be grounded in considerations of justice, no clear justification for this claim is offered. However, several features of this claim are puzzling.

First, whether a research discovery provides advantages to people who cannot afford it depends critically on how the larger health system is organized. Even if treatments can be procured at no cost, they often must be administered within health systems that have their own organizational structure and funding model. It may well be the case that a just health system should provide universal access to medical care. But the point for the present purpose is that in the context in which this claim is made, no such position is defended. Since at the time there were no provisions for universal access to health care in the United States (at the time of this writing there still are no such provisions), it is unclear why the use of public funds in one social system (biomedical research) should be sufficient to justify altering entitlements within another social system (the provision of health services).

Second, it is not clear why research that is supported by public funds should be subject to special requirements. If a research group is investigating treatments for a debilitating or fatal disease for which there are currently no effective therapies, would it be ethically permissible for that group to recruit exclusively from populations that are unlikely to benefit from subsequent applications of that research as long as they receive only private funding? On the one hand, even private firms enjoy various forms of social support, from public policies that provide for intellectual property protection to the fact that most research builds on prior findings, a large portion of which are generated from research with federal funding. On the other hand, heaping

burdens on already marginalized people in order to generate benefits for people who are already better off seems wrong no matter how that activity is funded.

A major problem with the *Belmont Report* is that it recognizes that aspects of research with humans that fall outside of the IRB triangle can affect the justice of this undertaking, but it lacks the resources to make these connections clear and to provide substantial normative guidance about them. In particular, its focus on the relationship between research and the delivery of health services—on the importance of ensuring access to the applications of knowledge produced in research—reflects a dim recognition that research is one activity that takes place within a larger division of social labor. It is a recognition that issues of social justice are raised by the relationship between systems of knowledge production and the systems that put this knowledge into practice in the form of treatment and preventative services. But the rationale for this focus is left largely unarticulated. As we see in §2.6 similar problems affect requirements in international guidance documents that are ostensibly grounded in justice.

2.5.5 Protectionism and Neglect

As other commentators have noted, the *Belmont Report* emphasizes relationships that must be avoided. For example, marginalized groups must not be recruited because of their "easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied" (National Commission 1979). But it does not say that researchers, study sponsors, or anyone else has a responsibility to carry out research that advances the unique health needs of groups that are marginalized, oppressed, or that suffer from excess burdens of morbidity and mortality. As a result, one way to satisfy the protectionism of its recommendations is to avoid carrying out research in such populations altogether.

While such a move avoids a certain kind of wrongful treatment, it leaves some of the most disadvantaged populations subject to the ravages of lethal neglect. As others have pointed out, explicating justice in largely protectionist terms fails to recognize the ways in which groups that are perceived as being vulnerable to exploitation or abuse in research can be harmed when their distinctive medical needs are not the subject of extensive scientific investigation (Dresser 1992; Kahn, Mastroianni, and Sugarman 1998).

Already in 1977, Eisenberg criticized the culture of research regulation for losing sight of the social imperative to carry out research and for being too complacent about the human toll that neglect would produce for those who suffer the highest burden of sickness, injury, and disease. He argued that the importance of this imperative and the toll of neglect was most palpable when one considered "the third world, where infant mortality may be as high as 20 percent and life expectancy no more than 30 years" (1977, 1109). For Eisenberg, "there is a clear moral imperative in developed nations for medical research in tropical diseases to seek to permit two-thirds of the world's population to share in the freedom from pain and untimely death we have achieved for ourselves" (1109).

2.6 International Research Stresses Fault Lines

2.6.1 The Zidovudine Short-Course Controversy

The fault lines outlined previously have been stressed, deepened, and brought into sharp relief in subsequent debates over the ethics of international research. Since the volume of such research began to rapidly increase in the 1990s (Rehnquist 2001; Thiers, Sinskey, and Berndt 2007), international research has been the subject of voluminous and at times acrimonious debate (Angell 1997; Lurie and Wolfe 1997; Annas and Grodin 1998; Benatar 1998; Crouch and Arras 1998; Glantz et al. 1998; Attaran 1999; Benatar and Singer 2000; Macklin 2001; Resnik 2001; Benatar et al. 2003; Flory and Kitcher 2004; London 2005). International ethical guidelines, such as the *DoH* or the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* from the Council for International Organizations of Medical Sciences (from now on, "CIOMS *Guidelines*" for short), stipulate a range of ethical requirements that must be met in order for international research to be ethically acceptable, some of which are explicitly grounded in the value of justice. But these requirements suffer from some of the same problems that arise for the requirements of justice in the *Belmont Report*. Their normative justification is unclear, they often make demands on stakeholders who are outside the IRB triangle, and they are criticized for being inconsistent with some of the core principles of research ethics.

Without a unified moral foundation to anchor their interpretation, the requirements of various international guidance documents have spawned

heated and at times divisive debate (Singer and Benatar 2001, Kimmelman, Weijer and Meslin 2009). This was dramatized by early debates about the standard of care in international research.

In 1975 the *DoH* was revised for the first time and two new requirements were added in section II on "Medical Research Combined With Professional Care (Clinical Research)":

> II.2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
> II.3. 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. (World Medical Association 1975)

These requirements remained unchanged in the 1983 revision. In 1996 a sentence was added to the end of the text in II.3 to indicate that "this does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists" (World Medical Association 1996). When the *DoH* was revised in 2000 these distinct statements were combined into a single requirement:

> 29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. (World Medical Association 2000)

This text was retained in the 2004 revision but, at the last minute, a "note of clarification" was added. That note stated that a "a placebo-controlled trial may be ethically acceptable, even if proven therapy is available," under two circumstances:

> —Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
> —Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not

> be subject to any additional risk of serious or irreversible harm. (World Medical Association 2004)

For many, this note of clarification was a bombshell. For nearly thirty years the *DoH* had been consistent in holding that the prophylactic, diagnostic, or therapeutic merits of a new medical intervention should be tested against those of the best current alternative. But what was presented as a note of clarification appeared to contradict the main requirement of the text. All that was required to justify withholding the best current alternative from study participants was a sound methodological reason. Since vocal proponents of placebo-controlled trials often championed such designs on methodological grounds, many worried that the note of clarification was effectively a free pass for researchers to expand the use of placebo controls.

The inconsistency in the 2004 *DoH* was a major blow to its status. It dramatized the limited value of pithy injunctions untethered from clear normative grounding and exemplified the extent to which that document had become a victim of its own success. In particular, since 1997 the *DoH* had been at the epicenter of a major controversy surrounding the ethics of placebo-controlled trials. That was the year that a pair of editorials published in the *New England Journal of Medicine* decried as unethical a proposal to test a short-course of zidovudine (also known as AZT) for the prevention of maternal-infant HIV infection against a placebo control in sixteen countries in sub-Saharan Africa, Southeast Asia, and the Caribbean (Angel 1997; Lurie and Wolfe 1997). These studies did not originate with industry. They were a collaborative effort among the US National Institutes of Health (NIH), the US Centers for Disease Control and Prevention (CDC), foreign governments, and international public health institutions. Their goal was to find a regimen of zidovudine that might represent a feasible intervention to stem the tide of perinatal HIV transmission in some of the world's poorest countries.

The study was controversial, in part, because a few years earlier a large-scale randomized clinical trial—referred to as the AIDS Clinical Trial Group (ACTG) 076 study—had demonstrated that a long course of zidovudine (from now on, the "076 Protocol") was highly effective at preventing HIV transmission from pregnant mothers to their newborn children, reducing transmission rates by two-thirds. Against this background, the then-editor of the *New England Journal of Medicine*, Dr. Marsha Angell, compared the use of a placebo control in the short-course zidovudine studies to the Tuskegee

syphilis study. In her argument in support of this analogy, she quoted the requirements outlined in III.2 from the 1989 *DoH*.

Angell's argument connected the requirements of the *DoH* with the concept of equipoise (this concept is discussed at length in chapters 5 and 6). For now, equipoise can be understood as honest uncertainty among experts about the relative clinical value of a set of interventions for treating a particular medical condition. Angell argued that equipoise between the interventions on offer in the arms of a study is a necessary condition for ethical research and that if there is solid evidence in favor of the superiority of one intervention, then "not only would the trial be scientifically redundant, but the investigators would be guilty of knowingly giving inferior treatment to some participants in the trial" (1997, 847). Extending this logic to placebo-controlled trials, she evoked the language of the *DoH*, holding that "only when there is no known effective treatment is it ethical to compare a potential new treatment with a placebo. When effective treatment exists, a placebo may not be used. Instead, subjects in the control group of the study must receive the best known treatment." The crucial fact for Angell was that "zidovudine has already been clearly shown to cut the rate of vertical transmission greatly and is now recommended in the United States for all HIV-infected pregnant women" (847).

The comparison between the short-course studies and Tuskegee enflamed passions on both sides. For critics, it illustrated the gravity of the transgression involved in denying participants in a clinical trial access to established effective care. Among the initiative's proponents, it sparked outrage since, they argued, the placebo design was necessary to find a method of preventing perinatal HIV transmission that could be implemented in some of the world's poorest countries to stem the tide of a disease that was ravaging their populations.

Ironically, both sides of this debate agreed that finding an alternative to the 076 Protocol that might be feasible for use in LMIC settings was an important and appropriate public health goal. At the time, the zidovudine regimen in the 076 Protocol cost about $800 per mother-child pair. As the heads at the time of the NIH and the CDC, Harold Varmus and David Satcher noted, this was as much as 600 times the per capita health expenditures of some Sub-Saharan countries (Varmus and Satcher 1997).

In addition, the 076 Protocol was resource intensive in other ways. Mothers had to be identified early in pregnancy so that they could begin a lengthy oral regimen of zidovudine. They also had to present at a treatment

center for birth so that they could receive intravenous zidovudine. Newborns were then placed on a six-week regimen of oral zidovudine and mothers were required to formula feed their infants because breast feeding is a known rout of HIV transmission. In many cases, however, women in the communities that faced the highest burden of HIV were also underserved by their health systems. As a result, they frequently did not receive prenatal care early in pregnancy and often did not give birth in a healthcare setting. Similarly, while the 076 Protocol required new mothers to avoid breastfeeding, many LMIC communities also suffered from high rates of waterborne diseases which often posed a grave threat to the health of infants. This meant that, in some cases, avoiding breast feeding was untenable.

The widespread support for research that would find an alternative to the 076 Protocol reflects the implicit assessment that it would be more efficient and effective to find an intervention that could be deployed under conditions that were feasible in LMICs than to bridge the economic and infrastructure gaps that made the 076 Protocol an infeasible alternative for LMICs. As a result, the debate in the literature tended to accept the permissibility of pursuing research of this kind and focused, instead, on the choice of control that should be used in such studies.

Nevertheless, it was clear that specific disputes about trial design were being driven by a larger set of issues, often inchoate and unarticulated, with implications that reached far beyond the choice of study control. There was, therefore, an uncanny sense that the debate over the ethics of the placebo control was a kind of proxy war between larger philosophical positions that often remained unarticulated, but which covertly exerted tremendous influence on the judgments of the warring camps.

2.6.2 Two Distinctions and Four Standards of Care

Early attempts to resolve the dispute over the design of the short-course trials focused on explicating the nature of the requirements in the *DoH* and what was meant by the "best current" or "best proven" alternative. Considerable attention focused on what I have called the relevant reference point from which such judgments should be made: were these terms asking about the best alternative in the local population or in some more global center of excellence, such as in the United States or France (London 2000b)?

Proponents of the placebo control argued it did not deny participants care that they would have otherwise received and that it did not impose new or additional health burdens on participants (Grady 1998, 36; Francis 1998; C. Levine 1998, 46; Salim and Abdool 1998, 565).[11] They thus defended using the local reference point for determining the standard of care. But their arguments also tacitly presupposed that the standard of care was to be determined by the actual medical practice in the reference location. This framed questions about the standard of care as largely descriptive questions about the de facto medical practice in the reference community.

In response, some criticized using the local reference point in determining the standard of care. Local practices might reflect what happens as a result of poverty and deprivation rather than the application of sound scientific knowledge. The relevant moral baseline, they countered, referred to a more global reference point where medical practice reflects the current state of medical knowledge. As Angell put it, the recommendation in the United States that all pregnant women with HIV receive zidovudine set the relevant baseline to which the short-course studies should be compared.

But arguments framed as supporting the global reference point were often tacitly rejecting the appeal to de facto practice. In particular, those who appealed to the concept of equipoise often interpreted the standard of care as a normative principle, taking references to "proven" or "established" treatment as indicating practices that are normative. Because they are supported by evidence and reflect the sound clinical judgment of informed experts they are required as the means of discharging a clinician's duty of care. On this de jure interpretation, the standard of care is not set by what actually happens, but by what ought to be provided to study participants given what is known about the safety and effectiveness of the alternative diagnostic, prophylactic, or therapeutic options (London 2000b).

Implicit in this acrimonious debate, therefore, were two distinct sets of issues: Is the relevant reference point local or global? And is the standard of care determined by the de facto practices of some reference community or by a de jure determination based on what is known about the likely safety and effectiveness of alternative practices, policies or interventions? These two

[11] During the debate over the *DoH*'s requirement that subjects in clinical trials receive the "best proven diagnostic and therapeutic method," one proposed revision would have required 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" (Brennan 1999, 529). See also Levine (1998, 1999).

axes created the possibility for four distinct interpretations of the standard of care.

For our present purposes one key point is that appeals to the *DoH* were insufficient to surface these alternative interpretations, let alone to adjudicate between then. Without a coherent rationale grounded in a compelling normative foundation, the pronouncements of the *DoH* could be interpreted in different ways. Within the parochialism of orthodox research ethics, two of these interpretations exerted outsized influence.

The first was the *local* de facto interpretation, which holds that the standard of care in a clinical trial is determined by what patients in the host community would actually receive if no trial or research initiative were to take place. In the case of maternal-fetal HIV transmission, this amounted to nothing. The local de facto standard of care was attractive because it takes what happens in the absence of outside intervention as the normatively relevant baseline for assessing alternative actions. If no studies were carried out, women and children in LMIC populations would not receive effective prophylaxis for perinatal HIV transmission.

The second interpretation that received outside attention was the *global* de jure interpretation. This interpretation was embraced by those who rejected the idea that descriptive accounts of the status quo in host communities are normative for determining the care to which participants in clinical trials are entitled. This interpretation holds that the standard of care must be determined by what experts regard as the best means of addressing the problem in question. It combines this de jure interpretation with a global reference point in which the relevant experts are located in global centers of excellence.

Two other interpretations of the standard of care are possible, but these were largely overlooked. One combines the global reference point with the de facto interpretation of the standard of care. This interpretation holds that the standard of care in a clinical trial is determined by the descriptive account of the care that patients receive outside the context of research in global centers of excellence. One reason why the local/global axis was so salient stems from the fact that, in this case at least, both the global de facto interpretation and the global de jure interpretation identify the 076 Protocol as the standard of care. The only difference lies in the rationale for each standard. When Angell appeals to the fact that the 076 Protocol is the standard of care in HIC health systems, it can sound like she is arguing that researchers in LMIC contexts are obligated to provide the 076 Protocol to study participants because this is what would happen (as a descriptive claim) in HICs. But if the standard

of care is to be set by the de facto medical practice, then it would be unclear why the actual practice of one community (HIC centers of excellence) should constrain how research is carried out in different communities where patients routinely receive an entirely different level of care. The only morally relevant rationale for appealing to the practices of clinicians in HIC health systems is that those practices reflect the judgments of informed and conscientious experts that the 076 Protocol represents the best way to discharge their duty of care.

A fourth possibility that was also overlooked combines the de jure appeal to the judgments of conscientious and informed experts with the local reference point. The *local de jure* interpretation holds that the standard of care is determined by what conscientious and informed experts judge to be the most effective means of addressing a problem under conditions that are attainable and sustainable in the health systems in which the intervention in question will be deployed (London 2000b). The consensus on all sides of the debate appeared to be that it was morally permissible to search for an alternative to the 076 Protocol that would provide LMIC communities with a meaningful public health tool for reducing perinatal HIV transmission because the 076 Protocol was too resource intensive and logistically demanding to be effectively or equitably deployed on a large-scale basis in those communities. Given this, the local de jure standard of care holds that the short course should be compared against the best proven alternative for preventing maternal-fetal HIV transmission that can be effectively and equitably deployed under conditions that are attainable and sustainable in those communities.

The position that I develop in this book adopts and defends the local de jure standard of care. For our present purposes, however, I want to consider why this position was overlooked in these early debates and why proponents of a de jure standard of care tended to support the global reference point.

2.6.3 The Role-Related Obligations of Clinicians

Angell and others were attracted to what I am calling the *global de jure standard of care* by the basic idea that the existence of equipoise—uncertainty about the relative therapeutic merits of the available medical options—is a necessary condition for ethical research. When this uncertainty exists, it is supposed to create a bridge between the social value of research and the

clinician's duty to do her best for each individual before her. The guiding idea is that, in the face of such uncertainty, it does not violate the clinician's fiduciary duty to her individual patient to allow the interventions that they receive to be determined by randomization.

However, if there is no uncertainty about the relative merits of the interventions in a trial, "not only would the trial be scientifically redundant, but the investigators would be guilty of knowingly giving inferior treatment to some participants in the trial" (Angell 1997, 847). Moreover, Angell argued that in order for equipoise to exist between the interventions in a trial that uses a placebo control, it must be the case that there is not already an established effective treatment for the condition in question. "When effective treatment exists, a placebo may not be used. Instead, subjects in the control group of the study must receive the best known treatment" (1997, 847). So Angell rightly recognized that in order for equipoise to exist, it must not only be the case that there is uncertainty about the relative merits of the interventions to which they might be randomized in a trial, but there also must not be an alternative intervention that is known to be superior to one or more of those options (see chapter 5).[12]

Angell argued that a placebo control was unethical in the short-course studies because the safety and efficacy of the 076 Protocol was established on the basis of substantial evidence. Its adoption in the United States and other HICs reflected consensus in the expert medical community about its status

[12] Here it seems like Angell is replicating a common mistake about equipoise because she initially frames the question as uncertainty regarding only the interventions that are compared within a trial. This would be a problem because a researcher could design a study to test the relative merits of interventions A and B when in fact there is an option C that is known to be superior to both A and B. If equipoise only referred to the arms of a trial, then a comparison of A and B would be ethically permissible, but it would violate both of Angell's desiderata. That is, the scientific value of such a study would be questionable—given that C is known to be superior to both—and an investigator randomizing participants to A or B would be guilty of knowingly giving inferior treatment since C is known to be the superior option. But this is not the case, as demonstrated by her assertion that if an effective intervention exists a placebo is not morally permissible. Kukla (2007) asserts that debates over the standard of care reveal fundamental problems with the concept of equipoise since that concept deals only with interventions being tested in a clinical trial. Kukla formulated the principle of equipoise (PE) as follows: "In order to begin or to continue an experiment on human subjects, one must be in a state of equipoise with respect to the relative expected health outcomes for participants in different trial arms" (179). However, prior discussions of equipoise in precisely this context were explicit that such a formulation would be unacceptable. London explicitly formulated the principle of equipoise to require a comparison between interventions on offer in the trial and those outside the study:

> Equipoise exists between interventions I1 and I2 relative to problem P in a treatment setting S, just in case credible doubts exist about the relative net therapeutic advantage of I1 and I2 for treating P in S and there is no intervention I3 that is preferable to either or both I1 and I2 for treating P in S. (2001, 324)

as the best method for preventing maternal-fetal HIV transmission. In light of this knowledge, she contended, testing the short-course zidovudine regimen against a placebo would violate equipoise and, with this, the clinician's duty not to deny study participants access to interventions that are known to be safe and effective.

The traditional conception of equipoise thus seemed to entail what I referred to as the global de jure interpretation of the standard of care. When considering whether a study begins in equipoise, it must not be the case (in this view) that there is an intervention that is regarded as preferable to one or more of the study arms anywhere in the world. Because the 076 Protocol was recognized as superior to placebo in centers of excellence in HICs, a study that would randomize participants to the short course of zidovudine or a placebo would violate this standard.

2.6.4 Problems for the Global De Jure Standard of Care

What I have called the global de jure standard of care appears to gain considerable support from an idea that is so widespread and intuitive that it functions as what I describe in §5.1.1 as the first dogma of research ethics. This is the idea that the fundamental moral norms governing the interactions between the parties within the IRB triangle derive from the role-related obligations of medical professionals. The global de jure standard of care is required in order to ensure that there is sufficient uncertainty at the beginning of a study to reconcile the researcher's duty of personal care with the requirements of sound science.

One important problem with the global de jure standard of care, however, is that it undermines the position it is supposed to support. It not only rules out comparing the short-course of zidovudine to a placebo, it rules out comparing it to the 076 Protocol as well (London 2001, 318–319). Those who opposed the placebo-controlled trial design as unethical did not oppose the larger project of finding an alternative to the 076 Protocol that might represent a feasible public health intervention for LMICs. Rather, they argued that the short course regimen should be tested against the 076 Protocol, since it was clearly the best proven alternative. However, although proponents of this design pointed to evidence suggesting that a short-course would likely be preferable to a placebo (Lurie and Wolfe 1997), it was unlikely that the short-course would be as effective as the full 076 Protocol. If it was unethical

to compare the short course to a placebo because the latter was known to be inferior to the 076 Protocol, then it would be similarly unethical to compare the short-course to the 076 Protocol since there was widespread agreement that the short-course was likely to be inferior to this alternative.

Stated in more general terms, the global de jure standard of care rules out as morally impermissible efforts to find interventions that might have a meaningful impact on public health in the context of LMIC health systems if those interventions are not expected to be at least as effective as available alternatives—even if those alternatives require a background infrastructure and social and economic conditions that are unobtainable or unsustainable in LMIC settings. Setting out to look for interventions that would produce widespread health benefits in LMIC settings but that are unlikely to be as effective as the strategies that can be implemented in the most advanced infrastructure of the most resource-rich countries simply cannot be reconciled with the goal of ensuring that no study participant is denied a level of care that falls below the global de jure standard.

Another implication of the global de jure view is that open questions of science only arise in global centers of excellence. The reason is that global centers of excellence possess sufficient resources to turn existing knowledge into the most effective clinical practices. This is why their practices are treated as the standard of care, on this view. In such contexts, if a medical goal cannot be achieved, then this inability reflects a lack of knowledge, rather than a lack of personnel, proficiency, infrastructure, technology, or some other social or material resource. As a result, on this view, knowledge gaps that are the appropriate targets for clinical research only arise in such high-resource contexts because it is only in such contexts that we clearly see the limits of existing knowledge.

From this standpoint, the 076 Protocol represents a prime example of such a best practice. In global centers of excellence in the United States and France, the 076 Protocol could be effectively implemented, cutting maternal-fetal transmission rates by two-thirds. Health systems in LMICs fell short of the financial, human or institutional resources that typify these global centers of excellence. As a result, they experienced a gap between the health needs of the populations they serve and their ability to meet those needs as effectively and efficiently as they can be met in global centers of excellence.

Embracing the global de jure standard of care entails that health systems that fall short of the financial, human, or institutional resources that typify

global centers of excellence have two options for closing this gap: *trickle down* or *develop up*. The first option is to wait for the benefits of new knowledge to trickle down to them. In other words, wait until the various costs of implementing gold-standard practices fall to the point where they are within the reach of less well-off health systems. The second option is to increase the resources devoted to their health systems to develop up to the point where gold-standard interventions are no longer out of reach.

What health systems that fall short of the abilities of global centers of excellence cannot do, on this view, is undertake research initiatives that seek to identify alternatives to the global de jure standard of care that might enable less robust health systems to more effectively, efficiently, or equitably address the health needs of the people they serve. If we accept the global de jure standard of care, then anyone looking for a less efficacious but more affordable and easier to deliver alternative to the 076 Protocol would be acting unethically.

The argument against the use of placebo controls in the short-course zidovudine trials that Angell presents deploys a package of values that are the bread and butter of orthodox research ethics and that were, therefore, widely shared in the research ethics community. But it has the embarrassing implication that it rules out as unethical the alternative approach to international research that Angell and others endorse. This inconsistency reflects deeper problems in orthodox research ethics that arise when the research activity is evaluated in isolation from its relationship to background social institutions and larger considerations of justice.

2.6.5 Not Just a Problem for International Research

Arguments about international research challenged orthodox research ethics because its narrow focus on interactions within the IRB triangle rested on unstated presumptions about the relationship between research and a wide range of background conditions. Disconnected from the larger purposes of a just society, research is evaluated relative to role-related obligations of professionals without a clear sense of how those obligations relate to background considerations of justice within health systems, let alone justice across national boundaries. But the positions that were defended in the international context would also have unexpected consequences on domestic research initiated and conducted in LMIC settings.

If research must be consistent with the global de jure standard of care, that would rule out a wide range of domestic research that might be conducted in LMICs by LMIC health authorities. Although the controversy over internationally sponsored research was the *occasion* on which these arguments were formulated, the arguments themselves are perfectly general. If there is uncertainty about the merits of interventions A and B for a particular medical condition but it is known that in a global center of excellence C is superior to both, then it follows that participants cannot be randomized to A or B, no matter who is doing the randomization.

The awareness that parochial debates about trial design had such far-reaching implications was illustrated powerfully by a memorable exchange from the short-course debates. In their defense of the short-course trials, Varmus and Satcher (1997) concluded by quoting from a letter to the NIH written by Edward K. Mbidde, chairman of the AIDS Research Committee of the Uganda Cancer Institute. The quote read:

> These are Ugandan studies conducted by Ugandan investigators on Ugandans. Due to lack of resources we have been sponsored by organizations like yours. We are grateful that you have been able to do so. . . . There is a mix up of issues here which needs to be clarified. It is not NIH conducting the studies in Uganda but Ugandans conducting their study on their people for the good of their people.

In a letter to the editor of the NEJM, Carel IJsselmuiden argued, "Since the Tuskegee study was conducted by Americans on Americans, this argument obviously does not stand" (IJsselmuiden 1998, 838).

For Angell, IJsselmuiden, and others in their camp, withholding treatment that is known to be effective (in global centers of excellence) that results in serious harm to study participants is wrong, no matter whether the study is conducted across national borders by international sponsors or within national borders by domestic health authorities—whether American (Tuskegee) or Ugandan (as in the short-course zidovudine studies).

Despite the logic of the argument just outlined, IJsselmuiden's letter goes on to focus again on the use of placebo controls. It says that "it violates the principle of justice that a continent impoverished through colonialism, and forced to continue to be unable to provide gold-standard treatment because of debt traps, will continue to provide the human laboratory where placebo-controlled trials can be conducted because locally affordable care is often

no more than placebo treatment" (IJsselmuiden 1998, 838). Gold-standard treatment is identified with the practices of HICs and so reflects what I'm calling the global de jure standard of care. It is contrasted with the de facto state of affairs in LMICs where actual medical practice often reflects deprivation. Given the history of extractive relationships between northern sponsors and host countries of the global south, IJsselmuiden sees the short-course studies as unjustly taking advantage of deprivation to run placebo-controlled trials.

In a subsequent letter to the editor in the NEJM, Mbidde rejects the charge that the short-course studies are designed to take advantage of circumstances of deprivation. In doing so he argues that the design of the studies reflects the health needs and priorities of Uganda and the importance of conducting research that addresses the health needs of Ugandans:

> Ugandan studies are responsive to the health needs and the priorities of the nation. Research subjects have been selected in such a way that the burdens and benefits of the research will be equitably distributed, and the appropriate authorities, including the national ethics review committee, have satisfied themselves that the research meets their own ethical requirements. With these requirements met, if Ugandans cannot carry out research on their people for the good of their nation, applying ethical standards in their local circumstances, then who will?

Mbidde's reply is emblematic of the frustrations experienced by both sides of this debate. The global de jure standard of care seems to follow from core commitments of research ethics. If it is correct, then it would not be permissible for Ugandans to conduct research on their own people, in response to their own health needs and priorities, if that research entails a deviation from the best practices for treating or preventing a disease that have been established to be effective in the most resource rich centers of excellence. However, everyone involved in this debate wants to endorse the moral permissibility of conducting research that is aimed at enhancing the ability of LMIC health systems to meet their own health needs and priorities. But if it is morally permissible for nations to conduct research of this kind in order to address the health needs and priorities of their people, then the global de jure standard of care must be rejected.

This exchange illustrates how the debate about placebo controls had the feel of a kind of proxy war in which narrow issues of clinical trial design were

being asked to do the bidding of larger positions that remained covert and hidden. The arguments being offered in support of particular trial designs had implications that reached far beyond the choice of control, but orthodox research ethics lacked the resources to foreground those larger issues and to engage them in a way that might resolve the resulting dilemma.

This exchange also illustrates frustrations generated from a failure to clarify all of the possible formulations for the standard of care and the justifications that might support them. Proponents of the local de facto standard of care argued that this baseline does not deny study participants access to care they would otherwise receive and, in turn, allows research to generate evidence about whether new interventions are superior to the status quo. But when the status quo reflects poverty, deprivation, indifference, or exclusion, the level of care that individuals from marginalized groups actually receive can fall below the level of care to which they are entitled. In those cases, gaps in care may not represent knowledge gaps at all. In other words, there can be cases where individuals are routinely denied a level of care that is attainable and sustainable in their own community. When that occurs, the local de facto standard of care doesn't track circumstances where new knowledge is needed. Angell, IJsselmuiden, and others were correct that this standard of care licenses powerful parties, whether local or domestic, to exploit the most disadvantaged members of the most disadvantaged communities without thoughtful concern for whether such research represents the most effective or efficient way of responding to their needs.

In contrast, the global de jure standard of care prohibits any use of research to generate the knowledge that less-advantaged communities might need in order to address important health needs under the unique social, political, and economic constraints that could realistically be achieved in their community. In order to avoid extractive relationships, it closes off research as an avenue for social progress and requires LMIC populations to wait for innovations to trickle down or until they can develop up to the capacity needed to support the global best practices.

The language in Mbidde's reply can be seen as an attempt to escape a dilemma created from envisioning only these two possibilities. Invoking a nation's "own ethical requirements" raises the possibility that different moral standards might govern research in different communities. But the prospect that ethical standards for research might be lower in LMIC communities raises the specter of an ethical relativism that devalues the lives of people in LMICs. The desire to avoid double standards in international research

(Macklin 2004) reflects the idea that there should not be one set of norms to evaluate research in HICs and a different set of norms to evaluate research in LMICs.

It was in this context that the World Medical Association became the epicenter for political lobbying that ultimately resulted in the note of clarification in the 2004 revision of the *DoH*. Its inclusion was a serious blow to the document's credibility not just because of the contradiction it introduced into the text, but because its inclusion seemed to confirm that its pronouncements rested on a foundation of arbitrary institutional authority. If lobbying the organization could change the rules, then those rules must reflect institutional power rather than sound moral reasoning.

2.6.6 Research Unmoored from a Just Social Order

In the conceptual ecosystem of orthodox research ethics, the local de jure standard of care was not a salient option. That standard of care requires that study participants be provided with what experts judge to be the most effective strategy for preventing or addressing the problem in question under conditions that are attainable and sustainable in the local health systems where the intervention in question will be deployed (London 2000b). But a defense of this standard depends on there being a morally significant relationship between research and health systems such that falling below this standard is unjust while providing more than this standard might be permissible, but not a strict moral duty. Moreover, any such defense would have to explain how to apply this same standard coherently and consistently to domestic research in HICs and LMICs as well as to international or cross-national research (see chapter 9).

Orthodox research ethics had no account of the relationship between research and the social structures or institutions of a community that might motivate or make the local de jure standard salient. Kukla (2007) argues that this problem reflects the fact that some concepts in orthodox research ethics presuppose highly idealized background conditions. In particular, Kukla says that the concept of equipoise presupposes an "an idealized research context of unlimited resources and access to care that rarely is incarnated" (173). However, if the concept of equipoise assumed a background of unlimited resources then it would be surprising that it has been regarded for so long as a valuable guide to reconciling social value with the rights and welfare of study

participants in the context of domestic research in HICs. After all, as Kukla is well aware, there is no community in which medical resources are unlimited.

The problem, rather, is that concepts like equipoise, fiduciary duty, and optimal care have been deployed in orthodox research ethics unmoored from explicit connections to more general requirements of a just social order that shape and limit the obligations and entitlements of community members. There was no explicit guidance about how to link questions about the standard of care and equipoise to the background social and economic conditions of the communities in which research takes place. Because such background questions fall outside the narrow boundaries of orthodox research ethics, stakeholders were left to fill in these details for themselves.

Orthodox research ethics relied on the tacit presumption that researchers and research ethics committees would share the same set of implicit background assumptions about the significance of various health needs and the economic, social, and material conditions under which those needs are to be met. When researchers in New York consider whether equipoise obtains between a set of interventions, for example, they may tacitly frame this question against the background of infrastructure and resources that are typical of the health contexts in the United States. When they submit research protocols to a research ethics committee, the latter would be more likely to evaluate them under a similar set of expectations. Likewise, researchers in Uganda, conducting domestic research in Uganda, might implicitly frame the question of equipoise against the background of the infrastructure and resources that are typical of health contexts in Uganda. When they submit their protocols to a Ugandan research ethics committee, the latter would likely evaluate it under a similar set of background presumptions.

Research ethics was unprepared for cases in which disagreements turned on these larger questions. In that sense, international research was the occasion to consider these issues, but the issues that were raised were more general and would have implications for research ethics, regardless of where research would be conducted or who would conduct it.

2.6.7 Responsiveness and Reasonable Availability

Despite the controversy that they generated, the short-course zidovudine trials were aimed at developing interventions that might make a meaningful public health impact on perinatal HIV transmission in LMICs.

Proponents of these studies argued that they were broadly in line with additional requirements found in international guidelines that are grounded in considerations of justice. Subsequent controversies challenged these additional requirements, in part because they clashed with more straightforward applications of beneficence and respect for autonomy.

The claim that collaborative international research should be responsive to the health needs of the host community was first enunciated in the CIOMS *Guidelines*.[5] In the discussion of justice in the opening section on "general ethical principles," we are told that "in general, the research project should leave low-resource countries or communities better off than previously or, at least, no worse off." Here again we see justice equated with the distribution of benefits and burdens. This line is followed with the claim that such research "should be responsive to their health needs and priorities in that any product developed is made reasonably available to them, and as far as possible leave the population in a better position to obtain effective health care and protect its own health" (2002, 18).

The statement that research should be responsive "in that any product developed is made reasonably available" blurs the distinction between the requirement of responsiveness and the requirement of post-trial access. This may reflect a more general lack of clarity at that time about the relationship between these requirements. For example, as late as 2004, the *DoH* did not explicitly state that medical research must be responsive to the health needs of the host population although it contained a statement about post-trial benefit. Paragraph 10 of the 2004 version said that "Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research." This statement, however, was often cited by commentators as an instance of the requirement that research be responsive to the health needs of the host community (Annas and Grodin 1998; Macklin 2001).

The relationship between these two requirements has been clarified in subsequent versions of these guidelines. Guideline 10 of the 2002 text on "research in populations and communities with limited resources" states that:

> Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:
>
> - the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and

- any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.

I will refer to the first condition as the "responsiveness requirement" and the second condition as the requirement of "reasonable availability."[13]

For someone like Eisenberg, these requirements might be seen as reasonable consequences of a moral imperative to carry out research that staves off preventable suffering and premature death. In order to carry this imperative to fruition, research must focus on unmet health needs that produce the largest burden of avoidable morbidity and mortality, and its fruits must then be made available to the populations suffering under these burdens of sickness, injury, and disease. In chapter 4 I will defend the existence of such an imperative and then in chapter 9 I will provide a defense of these requirements on roughly these terms.

However, in a conceptual ecosystem in which research is effectively treated as an optional undertaking, severed from the larger social purposes of a just social order, the focus on ensuring that research leaves host communities better off, and no worse off, grounds these requirements on a foundation that provides compelling reasons for rejecting these very requirements. Arguments to this effect are the subject of chapters 3 and 8. For our present purposes it is sufficient to note that if the underlying moral value that motivates these requirements is that host populations not be made worse off and be made better off by research participation, then these requirements appear arbitrary at best and affirmatively harmful at worst (e.g., see Wolitz et al. 2009). We can illustrate these concerns with the Surfaxin case.

2.6.8 The Surfaxin Case

Surfactants are naturally produced substances that are essential to the lungs' ability to maintain proper airflow and oxygen absorption. Extremely premature infants often do not produce enough surfactant to maintain adequate airflow and gas exchange in their lungs, a potentially life-threatening

[13] A similar clarification was made in the 2008 *DoH* in paragraph 17 which states, "Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research." A survey of other documents that articulate similar requirements can be found in London and Kimmelman 2008. On requirements of post-trial access see Sofaer and Strech (2011).

condition known as respiratory distress syndrome. Respiratory distress syndrome can be successfully treated with the use of surfactant replacement therapy, in which artificial or naturally derived surfactants are used to increase the surface area of the lungs that can absorb oxygen and facilitate gas exchange. By 2001 roughly half a dozen surfactant agents were commonly used to save the lives of desperately ill newborns in HIC health systems.

In 2001, the pharmaceutical firm Discovery Laboratories proposed a double-blind, randomized, placebo-controlled clinical trial of their new surfactant agent, Surfaxin, in impoverished Latin American communities where neonatal intensive care units are often poorly equipped and where children did not have access to surfactant replacement therapy. Discovery Laboratories proposed to upgrade and modernize the intensive care units in the host countries so that all of the children in the clinical trial would receive improved medical care. Children in the trial would then be randomized so that half would receive Surfaxin and the other half would receive a placebo.

Critics argued that the study was in conflict with established guidelines for international research ethics. Whereas the zidovudine short-course studies were motivated by the health needs of host communities, this study seemed to be motivated by the pecuniary interests of a firm from a HIC. Surfactant replacement therapy was not widely available in the settings where the study was planned but there was nothing about Surfaxin that made it particularly attractive for LMIC settings. If this was not a violation of the requirement that research in LMICs should be responsive to host community health needs, it was at least a deep tension.

Second, Discovery Laboratories was looking to LMIC health systems as a way to quickly generate the evidence needed to secure regulatory approval from the FDA so that it could tap the lucrative drug markets of HICs. As such, there was no pre-trial agreement that Surfaxin would be made reasonably available in the LMIC settings where it was being tested if its efficacy was established in the proposed studies. This bolstered concerns about the responsiveness of the trial to host community health needs and represented a transgression of the requirement that study sponsors, researchers, and host communities establish before the initiation of a trial a plan to make any product vindicated in the research reasonably available in the host community.[14] Without such an agreement, numerous commentators argued that

[14] CIOMS Guideline 15 from 1993 reads "As a general rule, the sponsoring agency should agree in advance of the research that any product developed through such research will be made reasonably available to the inhabitants of the host community or country at the completion of successful testing.

researchers and their sponsors exploit participants and host communities (Annas and Grodin 1998). As such, critics charged that the study represented the unfair use of LMIC populations for the profit of a private firm whose product would primarily benefit patients in HICs.

Finally, critics of this study argued that a placebo control would not have been permissible in the United States and that its use in an LMIC constituted an unfair double standard (Lurie and Wolf 2007). Randomizing roughly 325 dangerously ill newborns to placebo violated the requirement to ensure that every participant in the trial would receive an adequate standard of care. Given the availability of established effective surfactant agents, critics argued, the study should have tested Surfaxin against a known effective alternative. Although the use of a placebo control might generate information about the efficacy of Surfaxin relative to a baseline of not administering surfactant replacement therapy, that baseline was only relevant to health systems in which such treatment was not a feasible option. Because Discovery Laboratories was looking to market their product primarily in HICs, where surfactant replacement therapy was the standard of care, the placebo design seemed to address the wrong scientific question.

In response to these objections, proponents of the trial argued that conducting the trial in LMIC settings represented a win-win solution to a bad problem. As Robert Temple of the US Food and Drug Administration put it, "If they did the trial, half of the people would get surfactant and better perinatal care, and the other half would get better perinatal care. It seems to me that all the people in the trial would have been better off" (Shah 2002, 28). If the trial had to be redesigned and Discovery Laboratories decided to locate the more expensive active-controlled trial to a HIC, then nobody in the host community would receive any of the benefits the study promised. As a result, everyone would be made worse off. Discovery would have to spend more money and take a longer time to generate the information needed to gain access to the market. This in turn would delay the availability of a new therapeutic agent for patients who might need it and it would not improve the welfare of anyone in the LMIC host communities who might otherwise have had access to the benefits of this study.

Exceptions to this general requirement should be justified and agreed to by all concerned parties before the research begins" (CIOMS 1993).

2.6.9 Minimalism about Justice

Temple's position is a straightforward application of the traditional values of established frameworks for research ethics and represents the core of what I am calling the minimalist approach to questions of justice (§2.5.3). The minimalist approach seeks to avoid becoming bogged down in long-standing and protracted debates about thick or substantive conceptions of justice. Instead, it adopts a thin or minimal view that focuses narrowly on whether discrete interactions are mutually beneficial and freely undertaken. In this respect, issues of justice are effectively reduced to a function of principles that play a more familiar and well worked-out role in research ethics, namely, beneficence and respect for persons.

Temple's position was that randomizing roughly 325 dangerously ill newborns to placebo does not violate the nonmaleficence requirement because newborns in these communities did not otherwise have access to surfactants. The roughly 325 participants who received Surfaxin would likely be made better off since the expectation was that Surfaxin was likely to confer a net therapeutic advantage over the baseline of not receiving surfactant replacement therapy. If the trial were not conducted, newborns in the host community would not receive surfactant replacement therapy. So, participating in the trial would not make them worse off than they otherwise would have been and would likely make at least some of the participants better off.[15]

Nothing in these requirements specifies how significant the improvement over the status quo must be for a research initiative to be permissible, or how the host community must benefit from the research initiative. There are principled reasons, however, that make the minimalist reluctant to specify further substantive constraints on research. According to the minimalist, these details about the level and type of benefit require value judgments that are best left to the discretion of those in the host community. From this point of view, in fact, imposing stronger restrictions on international medical research appears misguided at best, and positively malevolent at worst, because they might prevent host communities from participating in research that could provide them with *some* net benefit. Stronger restrictions on

[15] The minimalist takes the placebo to be consistent with the relevant "standard of care," because that is defined as the treatment that participants would have received had there been no clinical trial. The study participants randomized to placebo are therefore not made worse off. For a similar statement in the context of perinatal HIV intervention trials, see Grady (1998, 36). For critical assessment of such views, see London (2000b). This issue is discussed in chapter 9.

international medical research are therefore viewed as working against the autonomy of LMIC populations and, with this, their ability to look after their own interests as they see fit. Stronger restrictions are unjustifiably paternalistic, on this view, because they limit the autonomy of LMIC populations to decide for themselves which benefits make research activities worth participating in.

In effect, the minimalist position derives the content of justice from the accepted pillars of contemporary bioethics, and of research ethics in particular. A just research initiative is one that faithfully adheres to the standard principles of nonmaleficence, beneficence, and respect for autonomy. Put in slightly different terms, the minimalist holds that any research initiative that satisfies the conditions of nonmaleficence, beneficence, and respect for autonomy is morally permissible because it offers *fair terms of cooperation* to the host community.

The minimalist's requirements are intended to ensure that the benefits of research do not accrue solely to the sponsoring party while the host community bears all of the burdens. They leave room for host communities to bargain for the best terms of cooperation that they can get, and they prohibit agreements that do not in some way serve the interests of the disadvantaged party. Initiatives that meet these conditions are viewed as fair because they provide mutually beneficial terms of cooperation that each party can freely accept. From the perspective of the minimalist, there may be many reasons that researchers and their sponsors should be as generous as possible when carrying out international research initiatives, but *requiring* more than the minimalist's conditions risks creating scenarios in which *everyone is worse off*.[16]

Without a justification for giving special weight to the knowledge and information that research produces, two considerations weigh in favor of rejecting responsiveness and reasonable availability and broadening the

[16] There may be cases, however, where the minimalist will require that researchers or their funding agencies make the fruits of a research initiative available in a stronger sense. If, for instance, the host population itself must allocate significant resources to carry out a clinical trial—whether in terms of money, personnel, or something else—then a stronger guarantee might be needed in order to ensure that the research initiative as a whole does not violate the beneficence requirement. That is, guarantees of free access, or price reductions, may be required in order to ensure that the host community receives a net benefit from the research initiative. Such guarantees, therefore, compensate for the burdens assumed by the community in facilitating the particular research initiative. Here again, though, the reasons for requiring such an agreement derive from the more fundamental need to ensure that the nonmaleficence and the beneficence conditions are met, and respect for the autonomy of the host community requires that it be the judge of whether the compensations repay the costs.

range of goods that should be relevant to evaluating the fairness of research transactions.

One consideration is that different stakeholders can reasonably support research for different reasons. Some support it in pursuit of profits from intellectual property and the sale of medical interventions. Others might seek smaller benefits in the form of compensation or incentives offered for study participation. Some support it as a means to publication, promotion, tenure and perhaps also reputation and fame. Others might seek the medical benefits that come from access to care, or from access to investigational interventions that might offer a chance of relief or cure where existing methods have failed. Still others may want to contribute to the fight against a disease that they have experienced, that someone in their family has experienced, or that takes a significant toll in their community. Respect for autonomy seems to press in favor of respecting the judgments of individuals about the reasons that they might be willing to participate in research.

A second consideration is that research itself can be an avenue for the provision of a wide range of benefits. Researchers or study sponsors can provide medical services, food, access to transportation, or provide money directly to study participants. Research can provide employment to people in host communities, increase economic activity, and be a conduit for improving laboratories, hospital facilities, or other aspects of the infrastructure in a community.

If the goal is to ensure that research does not make LMIC communities and participants worse off, and to ensure that it leaves them better off, then it has been argued that this can be more reliably and effectively achieved by embracing the plurality of motives that may lead stakeholders to want to support research and the plurality of ways in which research can produce benefits for those stakeholders. On this view, what matters when assessing the fairness of research transactions is not the distribution of specific kinds of goods, but whether the various parties to the transaction receive a sufficient amount of benefit to render the transaction non-exploitative (Participants 2002, 2004; Wertheimer 2010, chapter 8).

The responsiveness and reasonable availability requirements presuppose something special about the relationship between the social systems that produce new knowledge and the social systems that apply that knowledge for the benefit of individuals and communities. But orthodox research ethics has been profoundly shaped by a conceptual ecosystem that either resists

connecting research with the larger social purposes of a just social order or, at best, treats such connections as falling outside the purview of the field. Against the background assumption that research is a morally optional private undertaking, the requirements of responsiveness and reasonable availability appear arbitrary to the extent that they prohibit research in which host communities do not receive access to the fruits of that research (if there are any) but in which they would receive an assortment of other benefits that they regard as meaningful and sufficient to make research participation reasonable. If these requirements prevent research from taking place, then burdened communities are harmed to the extent that they are prevented from accessing benefits that they regard as sufficient to offset the burdens of research participation.

In the face of these criticisms, the requirements of responsiveness and reasonable availability seem not just paternalistic, but unjustifiably paternalistic. They appear to limit the autonomy of burdened populations by reducing the range of research in which they can participate even when that research can be presented as satisfying the underlying moral requirements that supposedly justify and motivate those very moral restrictions.

2.7 Conclusion

Recent debates about the ethics of international research expose some of the fault lines running through the foundations of orthodox research ethics. Unmoored from a clear account of justice that links the research enterprise to the larger purposes of a just social order, requirements that are ostensibly grounded in justice appear arbitrary at best and self-defeating at worst. Given the tendency to explicate justice in terms of access to benefits and ensuring that host communities are not made worse off, orthodox research ethics appears to assert requirements that frustrate this goal and can be challenged in terms of both beneficence and respect for autonomy.

As we see in the next chapter, the consequences of reducing justice and fairness in research ethics to the maintenance of mutually beneficial agreements between free and informed persons has the potential to undermine a broad set of commitments in orthodox research ethics. It undermines not only the field's paternalistic focus, but also widespread commitments to protecting participants from unfairness, injustice,

exploitation, commodification, and even threatens the status of informed consent. The goal of the next chapter, therefore, is to illustrate these far-reaching consequences and to motivate the search for an alternative that recovers the connection between research and the larger purposes of a just social order without licensing the denigration of persons or the abrogation of their rights and interests in the process.