7

A Non-Paternalistic Model of Research Ethics and Oversight

7.1 Introduction

The last three chapters introduced the egalitarian research imperative and provided a substantive defense of the claim that its core requirements can be reconciled in both theory and practice. One of the implications of the present work is that IRB review alone is not an adequate mechanism for ensuring that the diverse stakeholders in research act in ways that promote the egalitarian research imperative. In this chapter, however, I examine the role that prospective review of research before bodies of diverse representation can play in creating conditions necessary to advance the egalitarian research imperative.

In particular, I argue that research oversight should not be framed in paternalistic terms. Rather, the justification for research oversight, on the view I propose here, is to provide concrete and credible social assurance that the research enterprise constitutes a voluntary scheme of cooperation; that this scheme of social cooperation offers an avenue through which diverse stakeholders, often pursuing their personal ends and interests, can contribute to the common good; that this cooperative enterprise includes checks and balances designed to prevent it from being co-opted to unfairly advance the parochial ends of particular parties at the expense of the common good; and that in contributing to or participating in this scheme of social cooperation, stakeholders will not be subject to the arbitrary exercise of social authority including antipathy, abuse, coercion, domination, exploitation, or other forms of harmful, unfair, or disrespectful treatment.

Because these conditions are necessary to ensure the justice of this undertaking, providing credible social assurance that they are met establishes the warrant for public trust in, and support for, this enterprise. Since the egalitarian research imperative requires that the research enterprise be organized as a voluntary scheme of social cooperation, this credible social assurance

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also provides the warrant for the personal support of diverse stakeholders including the participants who make their bodies available to science in the process.

It is my contention that both critics and proponents of orthodox research ethics mislocate the source of the need for research oversight by focusing on deficiencies in individual agents rather than potential conflicts or shortcomings in the structure of the *social system* in which they participate. The paternalism of orthodox research ethics locates the need for research oversight in defects of individuals—the inability of some community members to adequately protect their own interests in the research context is regarded as justifying a system of oversight whose moral mission is to limit the risks of research for all participants (Miller and Wertheimer 2007; Jansen and Wall 2009; see also Edwards and Wilson 2012). The purpose of research oversight, on the view I propose in this chapter, is not to remedy deficiencies in *agents*, but to address structural features of the *strategic environment* in which diverse agents, often pursuing a diverse set of personal or parochial interests, engage in a long series of interactions over an extended period of time.[1] This chapter thus builds on a theme that runs throughout this book, namely, the importance of adopting a fundamentally social understanding of the research enterprise.

An effective system of research ethics should foster the sustainability of this scheme of social cooperation by helping stakeholders resolve coordination problems that threaten its ability to advance the common good on terms that respect all participants as free and equal. We saw one such coordination problem in §5.8.5 with the claim that research represents a prisoner's dilemma. In §5.9.3 I demonstrated that this claim is false and that research participation has the structure of a stag hunt. In this strategic interaction, research participation is an option that is rational for an agent to choose so long as two critical conditions are met. First, participants must regard the information a study is likely to produce as sufficiently valuable that they are willing to take on and adopt participation, with its various risks and burdens, as a personal project. Second, participants must believe that it is sufficiently likely that enough people will participate that

[1] In particular, the position I defend does not presume that any community member lacks autonomy or the cognitive and affective capacity to advance his or her own interests. Nor does it presuppose that any researcher has nefarious intent. My argument does not make these presumptions because it does not require these claims to justify its core conclusions. Nor does the argument I make here preclude the participation in research of individuals who lack decision-making capacity.

the study or studies in question will produce the valuable information they are designed to generate. The more risks and burdens to participants decrease and the value of the information likely to be produced increases, the more attractive research participation will be for a greater number of people.

In §7.2 I argue that prior to the work of the National Commission, this coordination problem was resolved by the use of social authority to conscript captive or easily manipulated populations into research. The result was a system that was poorly aligned with each of the requirements of the egalitarian research imperative—not only was the moral equality of study participants denied, but peer review was insufficient to ensure that this professional discretion advanced the greater good rather than the more parochial interests of researchers.

I then argue that prospective review helps to solve two additional coordination problems that would otherwise plague unregulated research and frustrate the willingness of various parties to contribute to it. The first, discussed in §7.3, is a social dilemma known as the tragedy of the commons. In this situation, reasonable choices by diverse actors pursuing their individual interests wind up exhausting the store of public trust on which the research enterprise depends.

The second coordination problem, known as the lemons problem, is discussed in §7.5. In this situation, low-quality studies that are easier to field crowd out higher-quality studies that are more costly and time intensive to design and carry out. Oversight practices that help communities avoid this dilemma provide assurance that research participation is likely to contribute to an important public good.

Conceptualizing research oversight explicitly as helping to resolve these coordination problems corrects another significant deficit in orthodox research ethics. In §7.6 I argue that some of the backlash to research oversight stems from the perception that prospective review represents a paternalistic intrusion into an otherwise private transaction that primarily implicates the interests of researchers and prospective participants. This narrow framing obscures the larger social purposes that research serves, including its relationship to the ability of basic social institutions to advance the basic interests of community members. Rejecting paternalism and adopting a view of research oversight as fostering the twin branches of the egalitarian research imperative better aligns the rationale for research oversight with the important benefits that it produces.

The system of research regulation in the United States is far from perfect and the purpose of this chapter is not to defend red tape and bureaucracy. Rather, the point is that any effort to reform and improve this system must have a clear conception of the goals to be achieved and promoted and the problems to be minimized or avoided. I argue that prospective review advances important goals that are currently overlooked but that should be emphasized and strengthened. Understanding how prospective review before bodies of diverse representation helps to create a system in which free and equal persons can see research as a viable avenue through which they might advance the common good is essential to ensuring that reforms do not cast out the ethical baby with the administrative bathwater.

7.2 Democratizing and Legitimating Research as a Social Practice

7.2.1 Social Authority and Abuse

Although the reforms brought about in the 1970s by the National Commission were motivated and understood on protectionist grounds, some of the policies and institutions they engendered have effects that can be understood in quite different terms. In particular, they laid the foundations for a system of research that more closely approximates the ideal of a voluntary scheme of social cooperation.

The post-war period from the passage of the Public Health Service Act in 1944, authorizing the NIH to conduct clinical research, up to the founding of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1974, was a period of tremendous growth in research (Rowberg 1998). During that period, members of the various professions that drove the research enterprise could see themselves as committed to social advancement through freedom of inquiry and enterprise and view their choice of profession as an expression of democratic freedom (Katz, Capron and Glass 1972, 1–2). Scientific and medical research were noble undertakings directed at advancing an important social good, and pursuing a career as a researcher offered individuals an outlet to develop their talents and abilities while contributing to that end.

In contrast, research participation and research participants were not thought of in comparable terms. To meet the demand for research with

human participants, the system of research in the United States relied heavily on captive populations and relationships of inequality. Although respect for study participants was desirable, it was regarded as unavoidable that some "already unlucky individuals" would have to be subject to "an arbitrary judgment" in order to secure to society its right to medical progress (McDermott 1967, 40). Given the perceived conflict between the rights of the individual and of society, many in the research community shared Walsh McDermott's frank assessment that it would be "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).

That research prior to the reforms of the National Commission was predicated on exploiting highly unequal social relationships is exemplified by the extent to which it was concentrated in institutionalized populations. Already at the trial of Nazi doctors at Nuremberg, for example, the defense had argued that, not only was there no explicit legal prohibition against conducting research on prisoners, but from the frequency of reports of such research in professional and popular media one must conclude that it "does not violate the basic principles of criminal law of civilized nations to carry out experiments on convicts" (Tribunals NM, 51).

Almost half a century later, the Advisory Committee on Human Radiation Experiments would put the matter this way:

> It is difficult to overemphasize just how common the practice [of using prisoners in research] became in the United States during the postwar years. Researchers employed prisoners as subjects in a multitude of experiments that ranged in purpose from a desire to understand the cause of cancer to a need to test the effects of a new cosmetic. After the Food and Drug Administration's restructuring of drug testing regulations in 1962, prisoners became almost the exclusive subjects in nonfederally funded Phase I pharmaceutical trials designed to test the toxicity of new drugs. By 1972, FDA officials estimated that more than 90 percent of all investigational drugs were first tested on prisoners. (1996, 273)

Many of the perceived advantages of these populations stemmed from their being subject to institutional control. Their behavior, including intake of food, fluids, medicine, and their schedule, could be closely monitored and controlled. They could be sorted into uniform groups on the basis of

characteristics such as weight, height, ethnic background, and so on, with little worry that they would be lost to follow-up.

Research on these populations was also largely hidden from public view. As a result, researchers had only to justify their conduct to their peers and to the authorities that operated host institutions. To the extent that researchers were viewed as responsible for advancing the greater good, or as being members of professions that had a special prerogative to advance the greater good, they could count on a certain amount of discretion from their peers, and perhaps even from the public, over the rights and welfare of research participants. To the extent that research brought economic benefits to host institutions, or a sense of prestige that often attaches to the scientific enterprise, researchers could count on a fair degree of accommodation and deference from facility administrators.

Finally, researchers could also count on a certain social leniency about subjecting institutionalized or otherwise marginalized populations to practices or procedures that would be questioned or repudiated if used on more fully enfranchised citizens from more "sympathetic" social groups. In other words, it was easier to deny the moral and political equality of populations that were already regarded as "lesser," in some morally important respect. Convicts, the disabled, the poor, and racial minorities were subject to severe social prejudice that downplayed or denied their humanity and often conceptualized them as consuming social resources without providing an offsetting social contribution. Against such background presumptions, harmful, demeaning, degrading, or otherwise disrespectful treatment could be "redeemed" in the eyes of the public by the idea that research offered an avenue through which otherwise "burdensome" populations could make a social contribution.

In his exposé of widespread ethical problems in research, Henry Beecher worried that the increased resources and institutional pressures to carry out research "may be greater than the supply of responsible investigators" (1966, 1354). For Beecher and others (Lasagna 1971), the surest path to ensuring ethically responsible research was a more concerted investment in the character and virtue of the individual researcher. But, as we will see in more detail momentarily, this perspective ignores the extent to which these individuals interact in a strategic environment—a environment in which they face a range of incentives—that encouraged conduct that was inconsistent with respect for the basic interests of research subjects. It also ignores the extent to which the institutions of scientific research placed relatively few

constraints on the extent to which researchers could advance a wide range of interests at the expense of the rights and welfare of study participants.[2] In some cases, these were interests, such as publication, promotion, notoriety, and other forms of individual success, that a more virtuous researcher might refrain from advancing in ways that would exact such harsh sacrifices from participants. But Beecher's position ignores the extent to which this environment permitted, if not encouraged, researchers to make arbitrary judgments against individuals, not from selfish motives, but from the otherwise virtuous motive of advancing scientific and social progress.

Revelations of abuse at places like Tuskegee and in the exposé of Henry Beecher drove home the extent to which the *institutions* of scientific research constituted a social arena in which researchers were vested with considerable discretion and study participants could be subject to the arbitrary, and sometimes debilitating and lethal, exercise of social authority. Deception, coercion, avoidable suffering, injury, and death were concrete and visceral horrors. But they reflected the potential for excess inherent in the largely unregulated exercise of social authority.

7.2.2 Unnecessary Risks and Inadequate Social Value

The system of research in the United States prior to the work of the National Commission was objectionable, not only because it failed to reflect basic concern for the rights and welfare of study participants, but because it lacked adequate assurance that the social authority of key stakeholders was exercised in ways that were necessary for social progress. For example, Tuskegee lasted forty years; it left behind a legacy of deception, manipulation, and harm. If the researchers involved in this study were to argue that these wrongs and harms were justified by society's right to social progress, they would have to demonstrate that this study actually contributed to that goal. But this research produced no great bounty of scientific progress. In its final report, the Ad Hoc Advisory Panel charged with evaluating this research noted numerous scientific and ethical shortcomings of the study, including the absence of an explicit study protocol. As a result, they concluded:

[2] Calabresi (1969) is one of the few early commentators to note that research with humans was subject to few systems of social control and oversight, and that the absence of these systems of control threatened trust in that activity. He also recognized that informed consent was likely to play only a limited role in rectifying those shortcomings.

> However, the conduct of the longitudinal study as initially reported in 1936 and through the years is judged to be scientifically unsound and its results are disproportionately meager compared with known risks to human subjects involved. Outstanding weaknesses of this study, supported by the lack of written protocol, include lack of validity and reliability assurances; lack of calibration of investigator responses; uncertain quality of clinical judgments between various investigators; questionable data base validity and questionable value of the experimental design for a long term study of this nature. (US Public Health Service 1973, 7–8)[3]

Overshadowed by larger debates about whether the perceived utilitarian goals of science could ever justify the sacrifice of individual autonomy and welfare was the hard fact that what actually occurred at Tuskegee could not be justified in these terms. In other words, even if we were to grant, for the sake the argument, that egregious harms to participants can be justified if they are necessary to generate sufficient social value, the Tuskegee syphilis study could not be justified on such terms because it failed to yield any meaningful scientific advances.

Similar concerns could be raised about other cases of research abuse. In his exposé, for example, Beecher questions the value of some of the studies he identifies or whether such knowledge could have been procured through less harmful, less demanding, or less disrespectful methods.[4] But if the discretion invested in researchers is intended for the public purpose of advancing medical progress, these defects cast grave doubt on the ability of stakeholders in this endeavor to hold one another to account, both for respecting the interests of study participants and for using their discretion and authority to advance meritorious social purposes that could not be advanced through other means.

Peer review and the open publication of research were insufficient safeguards because they would only expose behavior that was regarded as deviant or objectionable against the background social norms that were shared

[3] For more general concerns about the way this report frames the ethical issues raised by the Tuskegee study, see Brandt (1978).

[4] In their long study of the research conducted on institutionalized children at the Willowbrook State School, Rothman and Rothman note that at the same time that Saul Krugman was infecting children with hepatitis to differentiate its different types, another scientist, Baruch Blumberg, was unlocking similar results in laboratory research. As they conclude, "those with a utilitarian bent, who might be prepared to give Krugman leeway with his means because his ends were important, will have to consider that, however accidentally, we would have learned almost everything we needed to know about hepatitis B in the laboratory" (Rothman and Rothman 1984, 267).

within the expert medical and scientific community. They were insufficient checks against conduct that was widespread and driven by norms and social dynamics that applied across the profession.

7.2.3 Curbing the Arbitrary Exercise of Social Authority

The reforms of the National Commission are easily seen as grounded in and guided by the goal of protecting the welfare and autonomy of study participants. But these protectionist reforms changed the strategic environment in which research was conducted. Prospective review before bodies of diverse representation effectively repudiated the broad discretion vested in researchers. Gone was the idea that research subjects could be treated as "soldiers for science," whose autonomy and welfare could be unilaterally abrogated by researchers in order to advance the frontiers of scientific progress.[5]

Without the socially sanctioned authority to conscript or to dominate large populations of institutionalized people, the increasing demand for scientific evidence as a foundation for responsible medical practice and as an engine for innovation would have to be met by engaging a larger proportion of participants from more enfranchised groups. However, these reforms also repudiated the unilateral discretion of researchers to determine the acceptable level of risk in research and to withhold information, to actively deceive participants, or to otherwise manipulate people into research participation.

Instead, researchers would have to submit to bodies of diverse representation protocols that explain how risks to participants have been minimized, how remaining risks are reasonable, and then detail a plan for communicating this and additional information to prospective study participants or their surrogates in order to secure their free and informed consent. The adequacy of risk assessment and information disclosure would now be assessed relative to norms that would reach beyond common or accepted practices among a narrow class of professionals.

Although these reforms may have been understood in protectionist terms, my contention is that they had the effect of moving the social institutions of

[5] The term "soldiers of science" is used by James H. Jones (2008) to describe the reasoning of the US Public Health Service when it prevented the men who were the unknowing participants in a scientific study from attempting to join the US military to fight during World War II. Rather than being soldiers in the military, if these men were to be put in harm's way, it would be as soldiers of science.

medical and scientific research into better conformity with civic republican ideals that have deep roots in American political life.[6] In particular, these ideals include the importance of freedom from arbitrary interference and the important role of law and social policy in reducing the prospect that citizens will face socially sanctioned domination at the hands of more powerful parties.[7]

Prospective review provides public assurance that antipathy or disregard of the welfare and the rights of research participants is not an acceptable element of the practice or institutional structure of research with humans. Repudiating the permissibility of exposing participants to unnecessary or unreasonable risk is a means of curbing the arbitrary exercise of social authority within important social institutions.

In §5.11, I distinguished two models of research participation embodied by Pat and Sam. The reforms of the National Commission moved away from a model in which researchers had the socially sanctioned authority to treat participants on the model of Pat, as conscripts whose autonomy and welfare interests could be set aside and subordinated to purposes that they need not share. Instead, substantive constraints on research risks and an informed consent process that requires an accurate depiction of the goals of a study, the risks and burdens associated with participation, and a clear statement that participants can withdraw at any time helps to better approximate a context in which study participants are treated like Sam. This is a context in which more enfranchised populations, with a wider range of social resources and opportunities, can see research as an avenue through which they can contribute to a social good. Just as a researcher would have to persuade colleagues of the merits of a study in order to secure their collaboration and participation as investigators, they would have to approach their compatriots as autonomous persons like Sam in §5.11.2 and explain the nature, purpose, and merits of a study in order to secure their free and informed consent to participate.

[6] On the link between regulation relating to the FDA and civic republican values, see Carpenter (2009).

[7] Compare to Philip Pettit's articulation of the civic republican conception of freedom and equal standing: "Being unfree consists in being subject to arbitrary sway: being subject to the potentially capricious will or the potentially idiosyncratic judgment of another. Freedom involves emancipation from any such subordination, liberation from any such dependency. It requires the capacity to stand eye to eye with your fellow citizens, in a shared awareness that none of you has the power of arbitrary interference over another" (1997, 5).

I have been careful to say that the reforms of the National Commission helped to better approximate an institutional setting governed by respect for participants as free and equal persons. Foreclosing the reliance on captive populations in research did not foreclose shifting to other populations, including poor or disenfranchised populations, whose autonomy could be influenced through offers of various types of benefit. Nor did it correct for the harm to groups whose medical needs have not been subject to careful investigation as a result of protectionist norms (Dresser 1992; Kahn et al. 1998).

Rather, the point of these remarks is to highlight aspects of the current system of research oversight that are responsive to important parts of the egalitarian research imperative so that these aspects can be preserved and strengthened. This is also helpful to the extent that it demonstrates that the egalitarian research imperative is not completely incompatible with core structures and practices in research ethics, even as we identify aspects of those structures and practices that are in need of reform.

7.3 Preventing a Social Dilemma: The Tragedy of the Commons

7.3.1 The Standard Formulation

In the previous section I argued that reforms instituted in the 1970s, including prospective review before committees of diverse representation, helped to alter the strategic environment in which research takes place. Better approximating a voluntary scheme of social cooperation among free and equal participants likely facilitated the ability of the research system to absorb a dramatic increase in the supply of resources and to better satisfy the demand for research participants. To illustrate how this could happen, it is important to understand some of the forces that conspire to make the unregulated practice of human research prone to coordination problems that threaten the interests of all stakeholders to the research enterprise.

The "tragedy of the commons" refers to a dilemma that arises from a lack of coordination among individuals who rely on a shared resource (Hardin 1968). In particular, multiple agents recognize that they all depend on a shared resource for survival and therefore that it is in their individual and collective long-term interest to maintain the viability of this

resource. Nevertheless, when each acts on his or her own initiative, rationally pursuing his or her own goals or objectives, all wind up depleting that resource.

Here is a simplified version of the problem. A community of herders shares a large pasture where they graze their animals. Each recognizes that their livelihood and continued survival depends on maintaining sufficient grasslands to support their herd. Periodically the herders have the option to grow their herd by keeping and raising the offspring of their livestock. Larger herds bring several rewards to their owners including greater economic wealth and elevated social status. Herders who opt to raise larger herds capture more social goods for themselves. They may benefit in nonrelational ways, to the extent that they are better able to meet their needs, and in relational respects, to the extent that they garner greater social status and competitive advantage. Each therefore has a strong individual incentive to increase the size of their herd.

The problem is that larger herds also consume more of the grasslands. Each herdsperson reasoning in the same way increasing the size of their individual herds eventually leads to overgrazing. In part, this is because the immediate benefits of adding new animals to the herd accrue directly to the individual whereas the stress on the pasture is spread out among all community members. Eventually the carrying capacity of the pasture is exceeded, the grass cannot recover quickly enough to support demand, and the pasture is ruined.

7.3.2 The Tragedy of the Commons in Research

How is this relevant to research with humans? I will state the analogy briefly and then provide a more detailed discussion. To make the analogy clear, researchers are the herders and their "flock" is the number of morally questionable studies that they decide to carry out, or put into the "field." The common resource that such studies consume is the social support, cooperation, and trust of stakeholders that make the research enterprise possible. In an unregulated market, researchers can garner competitive advantage by putting more questionable studies into the field, and the risk of exhausting the reservoir of public support is spread across the group. Unconstrained in the pursuit of their individual goals, researchers in this environment ultimately reach a tipping point where the density, or the perceived density, of

questionable studies in the field exhausts the fund of social support for their activities.

If this analogy sounds strained, consider how it maps onto some of the prescient concerns that Henry Beecher enunciated in 1966. Beecher argued, in effect, that American medicine was close to such a tipping point:

> I should like to affirm that American medicine is sound, and most progress is soundly attained. There is, however, a reason for concern in certain areas, and I believe the type of activities to be mentioned will do great harm to medicine unless soon corrected. It will certainly be charged that any mention of these matters does a disservice to medicine, but not one so great, I believe, as a continuation of the practices to be cited. (1966, 1354)

Beecher's article was driven by a concern that unethical studies were becoming increasingly common. He claims that he was able to identify 50 cases of unethical research and that merely following the references of these studies led to 186 additional likely examples with "an average of 3.7 leads per study." A sample of 100 studies from a major medical journal in a single year produced 12 that appeared to be unethical.

As a cause of the rise in the unethical behavior he carefully documented, Beecher pointed to several factors. First was the "sound and increasing emphasis of recent years that experimentation in man must precede general applications of new procedures in therapy, plus the great sums of money available" for research. These factors created both pressures and opportunities for ambitious investigators. Second, Beecher worried about the way these pressures and opportunities shaped the incentives facing young investigators. As he noted, "medical schools and university hospitals are increasingly dominated by investigators. Every young man knows that he will never be promoted to a tenure post, to a professorship in a major medical school, unless he has proved himself as an investigator" (1966, 1354–1355).

The pathway to personal and career advancement in medicine wound its way through the corridors of medical research. In the face of demand for results and the requirements of prolific productivity for promotion and tenure, Beecher lamented that "there is reason to fear that these requirements and these resources may be greater than the supply of responsible investigators" (1966, 1354).

Finally, Beecher like others in the research community was aware that social mores around research with humans were changing. The twenty-two

examples outlined in Beecher's article included studies in which known effective treatment was withheld from participants, cases in which participants who experienced life-threatening or debilitating side effects from medication were challenged with the medication again to confirm the source of the adverse effects, and numerous cases in which subjects were unaware that they were involved in a research study. In some cases, death rates from the withholding of known effective therapy were announced in the study results themselves, and in other cases Beecher was left to estimate these himself. Beecher worried that if the values of society relative to research were changing, then what researchers might regard as the costs of doing business would be met with horror and revulsion in the eyes of the public.

In addition to the human toll of these studies, it was unclear that the harms, deception, and disrespect associated with this research was somehow necessary to procure leaps in understanding that would be unattainable without such sacrifice. Rather than a necessary and unavoidable tithe to scientific progress, the human hardship and suffering appeared to be simply a convenience for researchers pressed for time and eager to publish.

As we noted in §2.4.3, it is stunning that Beecher did not have to cull through some secret and arcane tome of clandestine activities to find studies with questionable ethical aspects; he merely had to attend with a sensitive eye to the published medical literature. Beecher feared that the volume and frequency of such studies was increasing and, with this, so was the prospect that the public would rouse from its normal routines and turn a spotlight onto the otherwise private and hidden world of research with human participants. Beecher feared that the revelations that the public would find in doing so would undermine public trust in, and public support for, the institutions of scientific advancement in the United States.

Ultimately, Beecher's fears were well founded. The National Commission and the rule-making and institution building that it engendered effectively imposed outside oversight on the research enterprise. Although it may have been conceived of in protectionist terms, my claim is that the unregulated practice of research in the United States created a strategic environment in which there were strong pressures and individual incentives to push ethical boundaries, that these pressures could affect the conduct of even the most well-meaning and publicly oriented researchers, and that one of the most important benefits of prospective review before bodies of diverse representation is the way that it effectively curtails these pressures. To make this case,

we need to be more precise about some of the dynamics that give rise to these strategic problems and how prospective review resolves them.

7.3.3 Trade-Offs and Incentives

Part of the dynamic that can lead to the exhaustion of the reservoir of public support and social trust stems from the fact that it can be costly for researchers or sponsors to properly manage tensions between generating socially valuable information, respecting the welfare interests of participants, and ensuring respectful treatment. At almost every level, basic aspects of clinical trial design are suffused with ethical decisions between the burdens and risks to the rights and welfare of participants and the size, speed, and inferential power of a trial (Goodman 2007). Efforts to reduce the burdens and risks of research on study participants can increase the time it takes to run and complete a study, the number of personnel required to implement a trial, and, ultimately, the cost associated with answering the research question. This means that efforts to conduct more respectful, less burdensome, and less risky research can frustrate researcher or sponsor interests by inflating costs and delaying timelines. Even when taking more time or using more careful methods can produce socially valuable information without imposing unreasonable risks or burdens on study participants, the costs in time and resources of implementing such methods may conflict with the parochial interests of researchers who face promotion deadlines, grant deadlines, or anxious investors.

Similarly, choice of control represents a case where the narrow health interests of trial participants may be in direct tension with the inferential power of a trial (Temple and Ellenberg 2000). If we assume that all else is equal, testing a new drug against a placebo alone might produce clear data about whether the drug is superior to the comparator of merely interacting with a clinician without receiving effective medical care. In cases where effective treatment or prevention measures exist, however, there are strong ethical grounds for providing all participants in the trial with existing measures to protect their health. This does not preclude the use of a placebo-controlled trial design, since that design can be implemented on top of a baseline of care that includes effective prevention measures for all trial participants (Senn 2001). It does, however, raise the cost of the trial significantly by increasing the number of people who have to participate in order for the trial to generate

statistically significant results (Potts 2000; Leon 2001; Freedman, Weijer, and Glass 1996).

A similar tension arises from other design features. Consider the difference between two approaches to measuring the efficacy of a prevention intervention, such as a vaccine. In one case, researchers randomize participants to receive a vaccine candidate or a placebo and then wait for participants to be exposed to the relevant pathogen. They then have to estimate the efficacy of the investigational intervention by comparing infection rates among the two groups. But they could also take the more direct approach of administering the prophylactic measure to a small number of people and then directly exposing them to or "challenging" them with the relevant pathogen (Miller and Grady 2001). Challenge studies of this kind could enroll far fewer people, practically eliminate ambiguity about who was exposed to the pathogen, and more effectively control for other features of recipients or their environment that might confound trial results.

When the infection in question is relatively benign, like the common cold, the consequences of these trial design features for the rights and welfare of participants will be less momentous than in cases of more severe conditions such as Ebola or HIV.[8] Similarly, how demanding such studies are on participants will depend on whether there are effective rescue interventions available to treat those who become infected and whether participants can be exposed to an attenuated form of the pathogen that is more likely to result in only mild sickness. Such preparatory work itself takes time, since isolating and replicating an attenuated version of a pathogen can be difficult. As a result, decisions about how to investigate the safety and efficacy of prevention measures initiate a cascade of decisions that have profound implications for both the burdens and risks to participants as well as the costs and duration of the study and the way those factors implicate researcher interests.

The process of searching for and implementing a study design that minimizes risks to participants while optimizing the scientific and social value of the information collected can be costly for researchers. In particular, it can be costly in terms of the time that it takes to search through feasible alternative designs and to evaluate their relative merits. It can also be costly in the sense that added safeguards may require additional expense, whether in terms of personnel hours, providing closer monitoring, additional testing, or

[8] For revelations of the lengths that researchers from the US Public Health Services were willing to go to in order to infect research subjects with syphilis in the 1940s, see Reverby (2011).

additional interventions that reduce risks to individual participants. Designs that require a larger sample size or more time to reach statistical significance can also be costly to researchers in terms of the expense of recruiting more participants and the delay in finding study results.

Informing participants about, and making a credible effort to ensure that they comprehend, both the importance of what is being studied and the full range of ways it may affect their health and welfare will always be an expensive proposition. It consumes time and resources and it may slow the pace of recruitment. In contrast, strategies that involve omission, euphemism, or outright deception may appear to be convenient, cost-cutting measures.[9]

7.3.4 Two Asymmetries

Another part of the dynamic that creates the potential for a tragedy of the commons in research with human participants stems from two important asymmetries related to risks and benefits in this context. First, there is an asymmetry in the *ex ante* and *ex post* assessment of a research study. Researchers can evaluate a study from the ex ante perspective—they understand the protocol that is to be initiated before it is carried out. They make and assess probabilistic judgments about the likelihood that relevant benefits or adverse events will materialize in practice or that problems will be uncovered and brought to the attention of the public. Without prospective review, the public is constrained to evaluate research ex post—they only see what was done in practice and thus only detect problematic conduct if it materializes in the form of adverse events.

The problem is that there might be many studies that involve unreasonable or objectionable practices when assessed from the ex ante perspective but the public will only be aware of the few that actually result in serious adverse events ex post. Additionally, there will be studies that are carefully designed with thoughtful precautions that result in serious adverse events just as a matter of bad luck. For this reason, evaluating studies solely from the ex post standpoint makes it difficult for the public to know whether the occurrence of an adverse event represents an unavoidable incident in an otherwise

[9] The prospect that informed consent would delay research, inconvenience researchers, and cause avoidable anxiety in research subjects is a recurring theme in research scandals of the post-World-War II era. For an excellent case study see Arras (2008, 73–79).

sound system or the overt manifestation of a system in which many unwarranted risks are being taken on a routine basis.

Second, there is an asymmetry in the costs and benefits to researchers of making such gambles. In a system without prospective review, researchers who scrupulously inform subjects of risks and benefits or who use trial designs that reduce burdens on participants voluntarily and unilaterally increase their own costs. Moreover, without prospective review, investing time and resources in this aspect of research is unlikely to be salient or visible to stakeholders such as participants or the public. Scrupulous researchers thus bear the costs of implementing these safeguards, but without prospective review there is no direct mechanism for rewarding them for doing so. At the same time, using resources in this way may put such scrupulous researchers at a competitive disadvantage relative to their peers. Researchers who do not incur these costs may be able to stretch scarce resources further and use their cost savings to bolster the depth or breadth of their research portfolio.

Two additional factors may reinforce these asymmetries. First, researchers work in a competitive environment. They compete for grants, personnel support (such as collaborators, post-docs, and lab assistants), institutional advancement, and professional honors. Second, even without such competition, researchers are likely to be biased in favor of their own projects. They would not pursue a research agenda if they did not regard it as important or worthwhile. As a result of their personal investment in and commitment to their particular research program they may overestimate the degree to which its advancement warrants or justifies subjecting others to particular risks or burdens.[10]

Different researchers may be motivated by a mixture of these factors, and these social and competitive forces may affect some researchers more than others. Nevertheless, these dynamics create the context in which rational researchers will be led to increase the representation in their research portfolio of studies that push the envelope in one or more of several directions. They might push the envelope in terms of the burdens placed on participants in the hope of generating benefits for society. They might push the envelope

[10] Indeed, one of the factors that enabled the Tuskegee syphilis study to persist over a forty-year period was the commitment of public health researchers to the idea that understanding the natural history of the disease was of fundamental importance. This professional curiosity persisted even after this information lost any clinical value it may once have had. Moreover, those involved in the study maintained its importance even after it was clear that the study itself had little or no social value. See Jones (1993, 2008).

by reducing costs that would be associated with implementing feasible protections for the rights and welfare of study participants. Or they may push the envelope by using speedy recruiting practices that leave participants uninformed, foster misconceptions about therapeutic potential, or amount to outright deception.

Each researcher knows that when one of these gambles goes wrong, the public is confronted with a case of serious harm or wrongdoing that consumes some of the warrant for the reservoir of social cooperation and trust on which all researchers rely. It is unlikely, however, that any single revelation will exhaust this reservoir of trust and any strategic advantage enjoyed by taking such gambles accrues directly to the individual researcher.

7.3.5 Public Support: A Tipping Point

As I indicated earlier, Beecher worried that the incentives in American medicine were prompting young researchers to increasingly engage in practices that would jeopardize the social standing of research and the public cooperation needed to meet increasing demand. We are now in a better position to understand the variety of ways in which such a tipping point might be reached. This includes increases in the volume of questionable research but it also includes changes in the values that the public uses to evaluate that research and whether they continue to evaluate it from an ex post perspective, or they shift their scrutiny to the ex ante standpoint.

First, the number of ex post scandals could increase because the number of gambles taken by each researcher increases. This would be a situation in which a majority of researchers are led to push certain boundaries. This might happen because failure to do so puts researchers at a competitive disadvantage, thereby increasing the social pressure on all researchers to cut corners.

Second, even if some researchers refuse to compromise their high standards, a tipping point might be reached if a smaller proportion of researchers increases the rate at which they field studies that push the envelope. If a smaller number of researchers are able to increase their rate of productivity by cutting corners and taking gambles, then the total number of objectionable studies would increase.

Both of these dynamics can be influenced by factors mentioned by Beecher. Faculty with more secure institutional positions may have the

time and resources to field studies that better approximate an optimal balance of scientific rigor, social value, and respect for study participants. If the requirements for promotion and tenure place greater emphasis on research productivity, then competition among many investigators for coveted professorships can lead ambitious scientists to press the envelope in the hope of increasing their productivity and producing the results necessary to advance through the ranks.

Alternatively, as funding for research grows, this increase in the supply of opportunity can create a greater demand for professionals to move onto the investigator track. Increasing the number of investigators can increase the overall number of studies and the dynamics outlined earlier can shape the trajectory of the research they produce.

Third, the probability that a tipping point will be reached is not solely a function of the number of questionable studies put into the field. Whether a tipping point is reached can be influenced by changes in the degree of public scrutiny given to the research enterprise. This means that at one point in time, a society might be willing to tolerate a fairly high rate of morally objectionable research so long as that research is hidden from view. Even if the rate of problematic research remains constant, increasing the frequency or the intensity of public scrutiny might produce a public perception that research involves sufficiently questionable practices that it is no longer worthy of social support or public trust.

Alternatively, even if the rate of questionable studies and the rate of public scrutiny remain constant, changes in the norms that are used to evaluate research can result in a public backlash. If, at one point in time, broad segments of the public regard certain classes of people as inferior or socially expendable, then the public might tolerate a fairly high rate of morally questionable research as long as it is sequestered in such marginalized groups. But if public sentiment changes in ways that result in greater recognition of the shared humanity, moral worth, and moral equality of once marginalized groups, then even a fairly low rate of questionable research in such populations might be sufficient to trigger public outrage.

Finally, a sudden shift in focus of the public from ex post problems to ex ante decisions would have a cascading effect since the number of ex post problems likely obscures a much larger number of studies that employed similarly questionable practices but were fortunate enough not to produce high-profile adverse events. If revelations of abuse garner greater

scrutiny from reporters and public officials who then inquire more aggressively into the ex ante decisions of researchers, an otherwise "sustainable" rate of ex post revelations of abuse could be revealed as masking a much higher rate of studies that rest on objectionable ex ante decision-making, creating the perception of a deep and pervasive rot at the core of a vaunted profession.

It is likely that a mixture of all of these factors was responsible for the public outrage that precipitated the formation of the National Commission. The social demand for medical progress and the availability of funding and opportunity it produced increased the status of research and drew more professionals onto the investigator track, and competition and changing metrics for advancement and career evaluation created incentives to avoid costly delays in productivity. Research practices that were once widely accepted were increasingly out of step with changing social values that reflected and facilitated greater capacity to resonate with the humanity of marginalized groups. In a context in which the distribution of power and social authority were increasingly subject to public scrutiny, greater attention was given to a social activity that previously received public attention primarily to trumpet some important medical or scientific achievement.

As in the case of grazing animals, once the tipping point has been reached everyone suffers, not just those who gambled and lost. This is because, when the public is constrained to evaluate research from the ex post perspective, they cannot distinguish scrupulous researchers who bear the costs and burdens of designing studies that respect participant welfare to generate scientifically sound and socially valuable information from those who do not. As a result, it is in the long-term best interests of all parties to find a way to coordinate their individual decisions so that such a tipping point is never reached.

7.4 Benefits of Prospective Review

7.4.1 Eliminating Asymmetries between Ex Ante and Ex Post Perspectives

One of the benefits of the current system of prospective review before committees of diverse representation is that it helps to resolve some of

the dynamics that give rise to the tragedy of the commons. By requiring researchers to submit protocols for review before they are initiated, prospective review evaluates all studies from the ex ante standpoint, eliminating the asymmetry between ex ante and ex post standpoints. This means that researchers are no longer the only parties privy to the way their research manages tensions or conflicts between the health interests of study participants and the scientific and social value of studies. Now those decisions can be scrutinized before they are put into practice. Review boards can flag the imposition of gratuitous risk, unreasonable risk-benefit ratios, studies that use sloppy research methods or that are not sufficiently relevant to an important health or social problem.

This in turn creates a more resilient system in that when bad outcomes occur, or when there are breaches of the public's trust, it is unlikely that public investigation will reveal widespread and systematic disregard for the rights and welfare of community members (Moss 2007). This was illustrated by the TGN 1412 study in which six participants in a phase I trial experienced life-threatening adverse effects after receiving what was expected to be a sub-clinical dose of a novel immunomodulatory drug (Suntharalingam et al. 2006). The disclosure of these severe adverse reactions fueled speculation about unethical research practices. But as one critic of the expanding scope of IRB review concedes:

> However, the impact of these events on confidence in clinical and experimental research has clearly been contained by the evidence of good faith regulatory review: in a situation where research participants were not well able to make judgments for themselves, the regulatory systems had provided a check. The adverse outcome could be explained as entirely untoward and not reasonably foreseeable, precisely because the investigators had not been judge and jury in their own cause. The known risks had been described to the participants and they had voluntarily accepted these. The regulatory institutions have functioned to supply legitimacy to the institutions of biomedical science. (Dingwall 2008)

In other words, prospective review creates a public assurance that the studies put into the field reflect responsible balancing of these core values and allows the public to better distinguish studies that cut corners and which may or may not produce adverse effects in practice from studies that result in serious

adverse events even though from the ex ante standpoint they did not cut corners or evidence antipathy, disrespect, or disregard for the rights or welfare of participants.

7.4.2 A Check on Self-Serving Assessments

Prospective review before committees of diverse representation also reduces the likelihood that judgments about how to balance risks and burdens to participants against social benefits will be based on biased judgments of a narrow class of professionals. Recall that as concerns about the ethics of the Tuskegee syphilis study were building within the US Public Health Service, a scientific review committee was convened in 1969 to review the study (Jones 2008). The vote of this body to allow the study to continue was in sharp contrast to the public reaction to its eventual revelation in the popular media. The presence of non-researchers and lay members of the public on boards that conduct prospective review is intended to provide a check on the potential for professional prejudice and to give voice to community values.

In practice, there is significant evidence that community members often do not constitute a strong, independent check on proposed research. As such, there is significant room to strengthen and improve the role of community members on such committees. But it will be difficult to improve the IRB review process if it continues to labor under a faulty and overly parochial conception of its ultimate rationale and social purpose.

7.4.3 Risk of Delay Changes Incentives

It is important to emphasize that many of the aspects of IRB oversight outlined previously do not need to be perfect in order to improve the conduct of researchers. This is because the knowledge that protocols must be submitted for review itself changes the incentives that researchers face. For instance, researchers do not know whether the lay person on the IRB will assert a strong voice and play a leading role in public oversight or largely go along with the consensus of the rest of the board. They do not know whether the board will pay careful attention to the social value of a study or restrict

their assessments more narrowly to the verbiage on the informed consent form. But researchers do know that if their protocol is returned because it is morally objectionable, they will suffer a costly delay. As a result, even if IRBs vary in these practices and even if researchers know this, the incentive to avoid delays associated with lengthy revisions to rejected protocols provides strong incentive for researchers to write protocols that reduce the probability of being returned for significant revision.

As a result, the public criteria that IRBs use to evaluate research and features such as the presence of a public voice on the IRB likely exert their most powerful influence by changing the incentives that researchers face when they are *designing* their studies and writing their protocols. Knowing that their research will be reviewed by committees of diverse representation and assessed on specific criteria—including whether unnecessary risks have been eliminated, remaining risks are reasonable, and the adequacy of the proposed procedures for informing prospective participants of the nature of the study and its incumbent risks—creates an incentive for researchers to search for study designs that more closely approximate the optimal balance of those criteria.

The knowledge that protocols will be assessed relative to their risk-benefit ratio and the quality of their procedures for informed consent creates an incentive for researchers to spend the time and resources necessary to more closely approximate an optimal ratio of risks and benefit. The reason is that, in a system with prospective review, the efforts of scrupulous researchers who dedicate time and resources to promoting social value, scientific rigor, and respectful treatment are no longer invisible. Reviewers can see the lengths to which investigators go to achieve these goals and they can reward the scrupulous by approving their protocols expeditiously and penalize the careless or the unscrupulous by requiring revisions in order to demonstrate a more careful concern.

The fundamental point is that the public knowledge that protocols will be reviewed on these terms creates an upstream incentive for researchers to conform to the norms they expect the IRB to enforce. This public expectation reduces, and possibly eliminates, the competitive advantage that would otherwise be gained from pressing the envelope either in terms of trying to reduce costs by lowering protections for participants or trying to increase the social value of a study by demanding larger sacrifices from them.

One of the upshots of the argument in this section is that despite its protectionist and often paternalistic justification, prospective review before committees of diverse representation helps to facilitate aspects of the egalitarian research imperative. In particular, it helps to approximate a context in which free and equal people can voluntarily participate in research as an avenue for advancing the common good. It does this imperfectly, and indirectly, by incentivizing researchers to ensure that risks in research are not gratuitous, that they are required for meritorious research, and that study involvement will be carried out under conditions of respect.

IRBs are limited in their ability to influence the full range of stakeholders who make decisions that shape the way research is conducted. Nevertheless, my contention is that we should jettison the paternalistic justification for prospective review and, with this, its protectionist stance and instead more explicitly align IRB review with the requirements of the egalitarian research imperative. The goal of these reforms is to more explicitly and directly shape the incentives for researchers to ensure that proposed studies contribute to the production of a public good while respecting the status of participants as free and equal.

7.5 Quality Assurance and the Lemons Problem

7.5.1 The Standard Formulation

If research participation has the strategic structure of a stag hunt, as I argued in §5.9.3, then the willingness of individuals to participate in studies hinges on reducing the risks and burdens associated with participation to the point where participants can see them as a reasonable and unavoidable cost required to advance a valuable personal or social goal. Resolving the tragedy of the commons that plagues an unregulated system of research advances this goal by reducing the risk and burden side of this equation.

When IRBs view their purpose and justification as paternalistic in nature, they frequently view questions regarding the social value of research as beyond their purview. Nevertheless, I now want to demonstrate how prospective review before committees of diverse representation has the effect of helping to solve a problem that reduces the quality of research and that can, as a result, erode support for the research enterprise. This is the so-called lemons problem (Akerlof 1970).

The dynamic of the problem is easily understood with an example from commerce. Some used cars are "cherries" and some are "lemons." The cherries don't have major defects, they run well, and with routine upkeep they will be reliable transport. In contrast, the lemons are plagued with problems. They require extensive maintenance and are ultimately expensive and unreliable transport.

The "problem" results from three factors: asymmetric expertise and information, asymmetric cost, and uncertainty about outcomes. The asymmetric expertise and information stems from the fact that the dealer has the knowledge and the means of ascertaining the true state of the car whereas the buyer often lacks the relevant expertise and has limited opportunity to evaluate the car. Moreover, the buyer is almost entirely dependent on the dealer for information about the car.

The asymmetry in cost refers to the fact that it costs a dealer more to procure a cherry than a lemon. Uncertainty about outcomes refers to the difficulty that consumers face in ascertaining whether a used car is actually a lemon, even after purchase. The car may work fine for a while before problems emerge, and it may take an extended period before it is clear that it suffers from extensive problems.

The result of these factors is that consumers have a difficult time ascertaining ex ante who is selling cherries and who is selling lemons. This is because all dealers extoll the virtues of their products and talk up their value and reliability. They also charge roughly the same price for the same make and model car. Because consumers cannot tell ex ante who is selling cherries and who lemons, they cannot direct their consumption behavior so as to reward only reliable dealers. As a result, vendors who purchase lemons and sell them at cherry prices realize a larger profit margin than vendors who procure the more expensive cherries and sell them at the same price. Those who sell lemons thus achieve a competitive advantage that allows them to crowd out those who sell only cherries, and this puts pressure on the latter to introduce some lemons into their inventory.

The result of this dynamic is that markets with these features are prone to poor-quality products. Because consumers cannot reliably detect cherries or lemons in any particular case, they shun such markets and, if left unchecked, the fear of being taken advantage of chills participation and the market withers. Those who inhabit such markets, used-car dealers in this case, are also stigmatized and lose some of their social status.

7.5.2 The Lemons Problem in Research

Each of these factors is present in an unregulated research "market." Asymmetric knowledge and information are ineliminable features of scientific research. Researchers often possess expertise that is highly specialized and a comparable proficiency with the specific subject matter of a study may be limited to a relatively small group of experts. Participants and other stakeholders, including the institutional actors who are the ultimate consumers of the information produced by research, may lack comparable scientific expertise. Study participants often fall far below the level of acumen, education, and literacy of other stakeholders, but of researchers in particular. These parties may thus vary in their degree of familiarity with the substance of a research study and in the intellectual and social resources they can bring to bear in order to enrich their understanding. As a result, they are heavily, if not exclusively, dependent on researchers for relevant information and explanation.

Similarly, as discussed in §7.3.3, there are asymmetric costs to preparing protocols and implementing studies that are "cherries." In other words, it takes more time and resources to plan and conduct studies that generate high-quality, socially significant information without exposing participants to unreasonable risk while securing the free and informed consent of an adequate number of participants.

Finally, uncertainty about outcomes is an inherent feature of most research with humans. The "outcomes" here include whether a study will result in serious adverse events and whether it provides a reliable answer to a question of social importance. Participants and other stakeholders will not have this information at the conclusion of a study and if the results are not published they may never have access to them.[11] If the study results are published, many participants may not seek out this information or be able to evaluate scientific publications on their own. Even those who seek out and digest this information will not know whether the results that are published address the question that the trial was designed to answer, or whether the study has been re-described in order to enable the publication of findings that were incidental to the original hypothesis. As a result, participants and other stakeholders in an unregulated environment are largely unable to

[11] For a discussion of cases in which trial data were not published, or were published only years after studies were completed, see Fauber (2012).

assess whether their participation or support contributes to well-designed, socially relevant science.

In an unregulated market, participants are also unlikely to be able to assess "outcomes" that relate to the regard that was shown for their rights or welfare. That is, participants are unlikely to know that they were deceived about the nature of the study, or about what was done to their persons or to their private information. They are unlikely to know that they were exposed to excessive risk, either because bad outcomes don't materialize, or because individual participants are not in a position to ascertain whether their bad outcomes are exceptional cases that happened in the face of reasonable precaution, or an easily foreseeable consequence of the study design or the lack of reasonable precaution and protection.

In this environment, because potential research participants are unable to distinguish researchers who implement high-quality, socially valuable studies that respect participants' rights and welfare from those who do not, they cannot reward the former with participation and penalize the latter by staying away (London, Kimmelman, and Emborg 2010). Participants therefore enroll in both types of studies alike. As a result, low-quality studies flourish and to the extent that they are cheaper to implement, they will gradually crowd out higher-quality studies, which are usually more costly and time intensive. The diversion of resources to such trials, however, represents a poor use of scarce social resources that yields a lower return on investment than would be expected in a market in which protocols are subjected to prospective review before committees of diverse representation (Carpenter 2009).

As participants and the public in general become aware of the differential in quality among studies in an unregulated market, distrust in the market builds. This awareness of differential quality can come about through several routes. One is via a dynamic described in §7.3.5. As ex post revelations of abuse prompt scrutiny into ex ante research decisions, the public becomes aware of the asymmetric nature of their relationship to researchers and the degree to which researchers have taken advantage of the potential for the betrayal of trust latent in that dynamic.

Another dynamic, however, may arise from revelations of the frequency of poor-quality science. When an area of inquiry absorbs public funds and resources but fails to bear significant fruit, it draws public scrutiny. Revelations that studies in this area suffered from methodological flaws that compromised the value of the data they generated feed concerns about the social return on investment from support for the research enterprise and speculation that

researchers are benefitting from such investment without taking due care to ensure that their work advances the common good through high-quality scientific inquiry (London, Kimmelman, and Emborg 2010).

7.5.3 Benefits of Prospective Review

Prospective review before committees of diverse representation can reduce this kind of quality assurance problem. Independent assessment of the study rationale, the relevance of the question to uncertainty in the medical community (see chapter 6), the reasonableness of risks in relation to anticipated benefits, and the steps taken to reduce burdens on participants serve to reduce the frequency of ethically problematic studies. This, in turn, increases the probability that social resources are allocated to studies that reflect respectful treatment with responsible limits on risk.

As a result, even if IRBs do not explicitly evaluate research in terms of their social value, altering researcher incentives in a way that reduces the proportion of low-quality studies submitted for review has the indirect effect of raising the overall quality of research. To the extent that resources that would have been allocated to lower-quality research are instead directed to higher-quality studies, this promotes and improves the value of a community's investment in research.

Again, even if IRBs are not the best venue for ensuring that research is aligned with and advances the health priorities of communities, promoting a more explicit focus on the social value of research during IRB review would more directly promote the overall value of research. Even with an imperfect focus on social value, independent review can improve the average quality of studies available to potential participants and the likelihood that research participation will represent an avenue for contributing to a socially important discovery.

Rather than casting prospective review of research as an intrusion into the private affairs of researchers and participants, grounded in a paternalistic concern for the welfare of the latter, the view I am defending here treats prospective review as a mechanism for resolving coordination problems within an activity that serves a sufficiently important social purpose that there is a social obligation to promote its proper functioning. Resolving these coordination problems contributes to the proper functioning of research by providing a credible social assurance that participating in research offers a

means of advancing the common good without exposing participants to indifference, neglect, abuse, or other forms of domination or unfairness.

The mismatch between the value of prospective review and its public justification or rationale is a source of profound instability at the foundations of research ethics. The system of research oversight instituted in the wake of the National Commission emphasizes protectionist goals grounded in benevolent paternalism. Its most significant value, however, need not be understood in these terms. That is, despite this public rationale, I have argued here that prospective IRB review has the effect of resolving a set of dynamics that give rise to two social dilemmas in an unregulated system. Resolving these problems helps to elevate the quality of research while providing credible public assurance that the institutions of social progress are not also instruments of domination that routinely abrogate the rights and interests of participants. The result of this mismatch is a system that has the effect of preventing tragic outcomes that all stakeholders in this enterprise want to avoid while generating resentment and anger from those same stakeholders in the process.

7.6 The Paradox of Cooperative Resentment

7.6.1 Misalignment between Value and Justification

If the analysis I have presented here is correct, then features of the conceptual ecosystem of orthodox research ethics are responsible for a profound tension at the foundation of the field. On the one hand, orthodox research ethics treats research as a series of optional, private undertakings, disconnected from the larger social purposes of a just social order. As I argued in chapter 2, this view of research fortifies the bulwark of protections for the rights and interests of study participants because of the widespread perception that linking research to morally weighty social goals would invariably justify abrogating the rights and interests of study participants.

On the other hand, I have argued in this chapter that the system of prospective review instituted in the wake of the National Commission has had the effect of creating a system of research that resolves coordination problems that are likely to plague unregulated systems. Telegraphing to researchers that protocols will be assessed by committees of diverse representation who will evaluate the quality of their procedures for securing informed consent,

whether they have eliminated gratuitous risks, and whether remaining risks are reasonable in light of the importance of the information a study is likely to generate, has the indirect and admittedly partial and imperfect effect of improving research quality while providing social assurance to study participants that in contributing to this enterprise they will not be subject to antipathy, exploitation, domination, or abuse. The net effect of these reforms was to create a system of research that could absorb increasing demand for research at the same time that it prohibited researchers from drawing disproportionately on institutionalized populations that had been the primary source of fodder for research in the immediate post-war period.

However, because this system of research oversight operates on terms that are disconnected from the social benefits that it provides, few of the stakeholders who benefit from this system appreciate its value. To the extent that orthodox research ethics frames research as a series of discrete interactions among private parties, the rationale for social interference in their private transactions hinges on the proposition that study participants lack the ability to secure their own interests in this domain. Yet, as researchers and study participants participate in a system that promotes interactions of respect and freedom from domination and abuse, they increasingly see IRB requirements, couched in paternalistic and often protectionist terms, as unwarranted intrusions into private interactions and as unjustified restrictions on individual liberty and academic freedom.

7.6.2 Fostering the Appearance of Arbitrary Interference with Private Purposes

Ironically, perhaps, the success of scientific research has produced a zeal for access to novel therapeutic candidates on the part of patients who suffer from conditions that are not well treated by current methods. When patients and their advocacy groups push for access to novel treatment modalities, paternalistic concerns about the overreaching of researchers seem out of place. If participants are eager to access novel interventions and willing to accept the risks and if researchers are happy to have these intrepid patients as partners in inquiry, the protectionism of IRBs seems self-defeating.

However, the parochial focus on the desires of study participants obscures and eclipses the social role of research in generating information on which a wide range of stakeholders rely to discharge important moral and social

responsibilities (§4.7). Participants seeking access to novel interventions and researchers eager for career advancement may be happy to move forward with research that advances their personal interests. But if such studies do not generate information that subsequent researchers, clinicians, patients, and policy makers need in order to properly evaluate and use novel interventions, then such studies can represent the co-optation of research by stakeholders who advance their parochial interests.

For example, even if participants are willing to face the prospect of serious adverse events, the emergence of serious harms in a trial can derail promising research programs by altering the assessments other stakeholders make about the prospects for success of such a program (London, Kimmelman, and Emborg 2010). If study sponsors view adverse events as limiting the value of an intervention, they may invest their resources elsewhere. Serious adverse events may dampen the interest of subsequent researchers who prefer to investigate strategies that have a more benign adverse event profile. Because research is a stag hunt (§5.9.3), if serious adverse events arise in an early-phase trial then it may be more difficult to recruit sufficient numbers of participants in subsequent studies.

But the most intense animosity for IRB review comes from those who view it as curtailing their academic freedom. To judge from the rash of recent law review articles, it is a miracle that research with human subjects in the United States continues to draw breath under what is portrayed as the asphyxiating heel of the rent-seeking,[12] creativity-stifling,[13] jack-booted bureaucrethics that is the current system of research ethics oversight and review. IRBs have been accused of perpetrating "probably the most widespread violation of the First Amendment in our nation's history," resulting in a "disaster, not only for academics, but for the whole nation" (Columbia Law School 2009). One member of the President's Council on Bioethics went so far as to assert, "There has been no greater damage to academic freedom in the

[12] See Mueller (2007) for the clearest "capture-theoretic" account of research ethics regulation. Mueller argues that the one clear benefit of increased regulation has been "jobs, jobs, jobs" for the research ethics "industry," going so far as to wonder "if there may not be nearly as many ethics reviewers, regulators, and staff as there are researchers," and referring to the research ethics enterprise as a "pyramid scheme" (820–821).

[13] "Trying to unravel the mystery of the social sciences' survival in the face of IRB encroachment is a challenge replete with paradoxes and illusions. The exercise demands that we probe the convergent logics of two mutually exclusive things that must somehow co-exist: creativity and regulation." Later, these authors assert that the survival of any creative research at all must itself be attributed to complicity of researchers with these organs of censorship: "That any creative research at all has survived under the IRB system, distorted as we believe it has become, must be attributed to the dynamics of consensual censorship between investigators and IRBs" (Bledsoe et al. 2007, 597, 628).

United States in my lifetime. And my lifetime encompasses McCarthy and it encompasses political correctness, both" (Schneider 2009). Locked in the bureaucratic "iron cage" of IRB oversight, critics charge that researchers have been transformed into a vulnerable, exposed population, subject to domination (Bledsoe et al. 2007, 608, 610), resulting in a denial of benefit to some study populations that has been likened to "Tuskegee in reverse" (Malone et al. 2006).

Assessing the burdens of IRB review, critics point to a loss of creativity, spontaneity, academic freedom, and squandered time, as well as money and even lives lost (Whitney and Schneider 2011). When it comes to the benefits of research oversight, they simply gape in outraged silence. We are told that "it is clear that the constraints imposed on academic inquiry have not been accompanied by an increase in public benefits" (Mueller 2007, 810) and that "there is no empirical evidence that IRBs have any benefit whatsoever" (Hyman 2007).

If these allegations are true, then we are living in a truly Orwellian dystopia in which "the problem is with the ethics industry, not the researchers" (Mueller 2007, 832). According to critics, IRBs restrict the liberty of researchers and participants, consume scarce social resources, and impede the ability of more nimble and knowledgeable agents to produce important social goods. If research ethics and the mechanisms of regulation and oversight it has spawned have had such disastrous effects on the one social enterprise fundamentally dedicated to seeking truth and producing new knowledge, then we should all grab torches and pitchforks and take to the streets.

What critics would have us do once we have assembled an angry mob, however, is somewhat unclear. Some critics regard IRB review as having a proper place in biomedical research and simply want to rein in what they regard as its uncritical and unnecessary expansion into areas such as the humanities and the social sciences. Others want to overturn the whole regulatory edifice, end the inquisition, and found a social renaissance by returning to the heady days of individual virtue and unsupplemented professional ethics.

Although I believe that radical critics of research regulation in the United States are mistaken, the questions they raise go to the foundations of research ethics and, like the discussion of Wertheimer's principle of permissible exploitation in chapter 3, they reveal a deep tension at the heart of orthodox research ethics. In both of these cases the protectionism of research ethics is

challenged on the ground that it is ineffective at best and counterproductive at worst.

7.6.3 The Egalitarian Research Imperative as a More Stable Foundation

My claim is that the discordance between the beneficial effects of research oversight and the public justification offered on its behalf creates a kind of paradox. All individual researchers prefer the situation in which they have the greatest personal freedom and discretion over their work, but implementing such a system results in an outcome that everyone wants to avoid. Conversely, a regulatory system that avoids the tragic outcome benefits all stakeholders: researchers benefit from continued social support, participants benefit from safer studies that provide an avenue in which to advance the common good, community members benefit from the fruits of sustained scientific inquiry into questions of social significance, and sponsors benefit either by advancing valuable science in accordance with their social mandate or by generating profits through the creation of interventions that improve welfare. Nevertheless, this system produces discontent among these various stakeholders because it is presented as a public intrusion into private interactions to curb individual freedom and discretion in order to protect people who, within this system, chafe at the demeaning allegation that they are in need of protection or that they are bent on turning participants into scientific cannon fodder.

Where the costs associated with this system are clear to many stakeholders, its benefits are far less salient. I have been arguing that this is partly the result of a mismatch between the benefits this system actually produces, and the justification orthodox research ethics offers on its behalf. But this is also due to the fact that those benefits accrue most directly at the *system level* while orthodox research ethics focuses myopically on the discrete interactions of private parties.

To see the benefits of prospective review we must adopt the kind of social perspective I am advocating. This social perspective is essential to a coherent and comprehensive research ethics. The current discussion illustrates this by showing how prospective review resolves fundamentally social problems of coordination among a wide range of actors. Such problems cannot even be articulated within a research ethics that is

myopically focused on the discrete interactions described in individual study protocols.

Moreover, the benefits of prospective review not only accrue at the social level, but they become most clear only in comparison to alternative ways of organizing research as a cooperative social enterprise. Because this aspect of research ethics is, at least in part, an exercise in what economists call *mechanism design* (§3.7, chapters 6 and 8), the only way to assess the merits of one set of institutions and rules for organizing this social activity is to compare it against an alternative set of institutions and rules (see also §7.7).

When research is severed from larger social purposes, and the moral epicenter of the field is located in the private interactions between researchers and participants that are described in individual study protocols, the paternalistic justification for research oversight enflames the sensibilities of political liberals who tend to view liberty as a right to be left alone. Severing research from larger social purposes and treating it as a set of goals and ends that are adopted by individual actors creates a conceptual ecosystem in which the core values of the field—beneficence and respect for persons—can be marshalled against the discipline's own self-conception. In other words, prospective review appears to infringe the rights of both researchers and participants to engage in private transactions for mutual benefit.

I have argued here that prospective review before bodies of diverse representation helps to resolve coordination problems that would plague an unregulated system. Resolving such problems is a legitimate use of state authority when those problems plague institutions that are part of a just social order (Galston 2004, 3, 125). Even if from a traditional liberal perspective we might say that prospective review may represent an infringement on the liberties of the parties whose conduct is regulated, this infringement is justified by its contribution to the proper function and long-term sustainability of the research enterprise and by the importance of that enterprise to a just social order.

This point is easily formulated within the civic republican tradition, where resolving coordination problems is not an instance of domination or illegitimate use of state authority to the extent that that authority tracks the larger interest in advancing the common good (Pettit 1997, vii, 68; 2004). Although the many parties that contribute to the research enterprise may have personal or parochial interests that are frustrated by prospective review (e.g., unfettered discretion over study design, unfettered pursuit of profit, unfettered access to investigational medicines), subordinating the pursuit of those

parochial interests to the common good is not an instance of arbitrary interference because resolving these coordination problems helps the parties to achieve goals that they recognize—it "track[s] their interests according to their ideas" (Pettit 1997, 68). This includes providing credible public assurance that the research enterprise represents a form of social cooperation that will advance the common good. It also includes public safeguards that ensure that stakeholders in this enterprise can advance their parochial interests, but only on terms that are consistent with promoting the common good. This includes prohibitions against subjecting other parties to this scheme of social cooperation to harmful, demeaning, or disrespectful treatment.

Trust in the long-term sustainability of the institutions that ensure the alignment of the parochial interests of various stakeholders with the common good is also important as a means of encouraging individuals to see the research enterprise as an avenue through which they can also pursue some of their own parochial interests on terms that respect the status of others as free and equal. When the public has confidence in the quality of research and feels secure in the expectation that their rights and interests will be respected, they will be more likely to view research participation as a reasonable avenue through which to contribute to the common good.

7.7 Challenges of Measurement

7.7.1 Incentives Affect Which Protocols Are Written

The analysis presented here also explains one reason why it may be difficult to point to empirical evidence of the benefits of IRB review. The benefits of prospective research review before committees of diverse representation accrue at a system level. Instituting the system of regulation and oversight changes the *strategic environment* in which researchers act. In an unregulated environment, researchers might be "rewarded" for attaining a competitive advantage over their peers by pressing the envelope of risk or skimping on research safeguards for participants. In a system in which they must submit protocols for prospective review, researchers face significantly different incentives. The regulatory environment thus shapes which studies are pursued, how studies are designed, and the degree of regard shown for participants. Objectionable studies that would be carried out in the unregulated environment are less likely to be submitted for IRB review because researchers know that they are

less likely to be approved, or that they will require protracted revision. As a consequence, studying the effect of IRB review on protocols that are actually submitted is only capable of capturing the *incremental benefit* (if any) of IRB review on protocols that *already reflect the influence of the regulatory regime*.

As a result, it could be true both that actual IRB review adds little or no (incremental) value to protocols that are reviewed and that the system of prospective review before committees of diverse representation is better for all stakeholders than an unregulated system. Such a situation would occur, for example, if the reason that IRB review adds little *incremental* value is that researchers have become relatively efficient at designing research studies that are likely to meet high ethical standards. This efficiency could come about because researchers internalize the relevant moral norms and act on them or because those who do a better job of simulating what will happen to various versions of a protocol once submitted for IRB review are less likely to face costly delays caused by protracted revisions. Regardless of which of these two mechanisms accounts for this efficiency, it does not follow that it could be preserved if we dispense with IRB review. The reason is that the incentive to become more efficient at designing trials that align with important social values hinges critically on the prospect that protocols will face review before bodies of diverse representation.

Here again, then, is something of a paradox. The prospect of having to submit a protocol for prospective review before a committee of diverse representation creates an incentive for researchers to become highly efficient at designing studies that will pass evaluative muster. In the real world, IRBs have to deal with researchers of varying degrees of experience and competence at navigating IRB review. It is likely that IRBs will spend considerable time attending to protocols submitted by researchers unfamiliar or inexperienced with IRB review. If all researchers were ideally rational and knowledgeable, however, almost all protocols would be submitted in a form that would be acceptable with, at most, minor revisions. In this environment, IRBs would be able to quickly approve most protocols and their actual review would add little incremental value.

Dismantling the system of prospective review, however, would change the incentives that even ideally rational and competent researchers face, and it would result in the production of studies that would be unlikely to pass prospective ethical scrutiny. We will never be able to measure the value of submitting such protocols for IRB review, however, because which protocols are produced itself depends on which system of oversight we implement.

7.7.2 IRBs and the Incentive to Make Work

The last point from the previous section deserves further examination because it may explain a behavior that some critics of IRBs have pointed out. That is, actual IRBs may want to feel like they are adding significant value to the system. But on the model outlined here, the most significant value might come from *the effects on researcher behavior of implementing a system of prospective review* and not necessarily from the incremental benefit of actual IRB review. As a result, IRBs that are fortunate enough to see protocols from experienced, competent, and ethically scrupulous researchers may nevertheless search for increasingly minor issues on which to focus out of a desire to feel like they are making a positive impact. Researchers who have become highly efficient at meeting high scientific and ethical standards in the design and implementation of their research will nevertheless find themselves having to address minor issues in their protocols. A central challenge, then, is to figure out mechanisms by which IRBs can remain sufficiently vigilant to detect significant problems with submitted protocols without becoming hyper-focused on minor details in order to manufacture the perception that they are making a difference.

7.7.3 Strategic Environment and Individual Virtue

If the analysis presented here is correct, then it should also drive a stake through the heart of a view with a long pedigree in research ethics. This is the view that the best way to safeguard the research enterprise is by investing in the character of the individual researcher. Although Beecher was prescient in warning that American medicine was nearing a tipping point, and although he was a proponent of informed consent, he argued that "a far more dependable safeguard than consent is the presence of a truly *responsible* investigator" (1966, 1355). Beecher's claim that "the more reliable safeguard provided by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator" (1966, 1360) was echoed by others. As Louis Lasagna (1971) eloquently puts it:

> I submit that the successful development of such an ethical conscience, combined with professional skill, will protect the patient or experimental subject much more effectively than any laws or regulations.

> I have previously said that for the ethical, experienced investigator no laws are needed and for the unscrupulous incompetent no laws will help, except to allow the injured subjects to obtain compensation or to punish the offending scientists (109).

The impotence of regulation in comparison to the importance of moral virtue (or vice) in individual investigators remains a theme that is echoed in contemporary critics of IRB review.

The arguments I have articulated here are agnostic about the specific motives or dispositions of character of researchers. It is perfectly consistent with the dynamics outlined here that the public reservoir of social trust in the research enterprise could be exhausted by the cumulative activities of benevolent, smart, well-meaning, rational researchers. It is difficult to overstate the importance of this fact, as it illustrates one of the fundamental shortcomings of efforts to preserve the public trust by investing solely or primarily in the character of individual investigators. Namely, not all bad things are done by bad people, and extremely bad consequences (e.g., the exhaustion of public trust) can result from the uncoordinated activities of individual agents rationally perusing activities intended to advance the common good.

7.8 Safeguarding a Unique Public Good: Beyond IRBs

7.8.1 Connecting Research to a Just Social Order

Rejecting the paternalistic focus and justification for research oversight in favor of the framework articulated here has several advantages. First, it promotes a better alignment between the goals of research oversight and the criteria for a just research enterprise. I argued in chapter 4 that the egalitarian research imperative is grounded in the importance of a set of basic interests that all persons share, the role of the basic social institutions in a community in protecting and advancing those interests, and the unique ability of the research enterprise to produce information necessary to bridge gaps between the basic interests of community members and the ability of the basic social institutions in their community to safeguard and advance those interests. Ensuring that the research enterprise produces information that constitutes this public good is thus necessary to ensure the justice of this undertaking. If

this division of labor is to function as a scheme of voluntary cooperation that respects the status of its participants as free and equal, then there must also be concrete and credible social assurance that this undertaking advances the common good without knowingly compromising the basic interests of any stakeholder in the process.

The legitimate role of research regulation and oversight is to provide this credible social assurance in order to secure and promote the kind of broad-based and sustainable social support that is necessary to maintain a voluntary scheme of social cooperation among people who are respected as free and equal. To do this, research ethics must be configured to prevent four types of problems we have seen in this chapter: antipathy, disrespect, lack of social value, or unfair division of social labor.

The current system of research ethics is easily adapted to guard against problems of antipathy and disrespect, at least insofar as these values apply to study participants. Antipathy refers to a manifest lack of concern for the health, welfare, and broader interests of research participants. This includes exposing study participants to risks that are unnecessary or in some other way gratuitous. Disrespect refers to a failure to respond to the moral status of a person by treating him or her as a mere means to the ends of some other decision-maker. Deception, manipulation, coercion, and unfair treatment represent relationships in which some parties deprive others of their right to exercise their agency in the pursuit of their own considered values, free from unwarranted or unjustified interference from others. This includes the ability of study participants to understand the options that are available to them, to make an informed choice from among those options, and to be free from undue influence in the process.

But the value of respect does not apply solely to study participants. It includes the interest of many other parties to the research enterprise in having credible assurance that their support—whether in the form of money, time, effort, institutional space, or their contributions to the scientific evidence base on which research builds—is not being sought under false pretenses or used to support ends that serve only the parochial plans and interests of some other stakeholder.

This aspect of respect is tied to the other failings that research oversight should seek to avoid. When research lacks social value then it is unlikely to make a meaningful contribution to the ability of a community's basic social systems—such as its health care systems—to understand, protect, and

advance the basic interests of community members. When participants, funders, host institutions, and other stakeholders support research as a means of generating valuable information, but that research lacks social value, then their support is misdirected and their efforts and resources are squandered.

Alternatively, an unfair division of social labor occurs when a group of stakeholders contribute to a joint enterprise for the purpose of generating a public good but more advantaged parties are able to co-opt the collaboration so as to advance their personal or parochial interests at the expense of the common good. When stakeholders support research to advance the common good, but that research lacks social value because it has been co-opted to advance the parochial ends of one stakeholder, then it is not merely that other participants are disrespected. The party who co-opts this system acts unjustly, diverting resources and cooperative undertakings away from their legitimate social purposes that are grounded in the prior moral claims of community members (§4.8.2).

7.8.2 Oversight of a Wider Range of Stakeholders

Second, embracing the vision of research oversight that I have outlined here underscores the limited role of IRB review in ensuring that research advances the common good. In particular, IRBs have limited ability to influence how priorities for research are set and for determining whether they create a general portfolio of research that is likely to expand the capacity of a community's basic social structures to advance the basic interests of its members effectively, efficiently, and equitably. They also have limited ability to influence downstream actions that are necessary to ensure that the knowledge produced in research is actually incorporated into the operation of these basic social institutions.

If the argument of the present work is sound, then research ethics should reconceptualize the role of IRB review along the lines I have sketched here and undertake the challenge of identifying new mechanisms for ensuring accountability from the wider range of stakeholders who participate in and influence the conduct of research with humans.

As we will see in the next chapters, the limited scope of IRBs came into stark relief when research began moving in higher volumes into low- and

middle-income countries. In particular, it was ironic that prominent guidance documents stated that international research must be responsive to the health needs and priorities of host communities when research ethics in its domestic incarnation was largely silent on how health priorities should be defined and how research should align with them.