The Case for Evidence-Based Rulemaking in Human Subjects Research

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Here I inquire into the status of the rules promulgated in the canonical pronouncements on human subjects research, such as the Declaration of Helsinki and the Belmont Report. The question is whether they are ethical rules or rules of policy. An ethical rule is supposed to accurately reflect the ethical fact (the fact that the action the rule prescribes is ethically obligatory), whereas rules of policy are implemented to achieve a goal. We should be skeptical, I argue, that the actions prescribed by the rules are ethically obligatory, and consequently we should focus our attention on how to craft the rules so as to promote the legitimate goals of human subjects research. Unfortunately, this cannot be done without evidence about the likely effects of various candidate policies—evidence we currently lack. Therefore, we should take the rules as mere starting points, subject to revision as the evidence comes in.

Keywords: Belmont Report, Declaration of Helsinki, Nuremberg Code, rules, research ethics

It is widely accepted that there are various rules that investigators should follow when performing research on human subjects, such as the rule requiring the obtaining of informed consent (in most cases). These rules are familiar because they have been promulgated in a set of canonical codes of conduct: the Nuremberg Code, the Declaration of Helsinki, the Belmont Report, International Ethical Guidelines for Biomedical Research Involving Human Subjects, and Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. One question about these codes that is often overlooked, but is of the utmost importance for reasons to be explained presently, is the following: What were the codes’ authors attempting to accomplish by promulgating a set of rules?

Promulgating a rule serves either of two purposes: reporting an obligation or creating an obligation. To make the distinction evident, let’s look at two paradigm cases. In his famous book Animal Liberation, Peter Singer promulgated a rule proscribing the consumption of meat. Singer, of course, took himself to be reporting an obligation to not eat meat; the obligation was supposed to be preexisting and not contingent on his say-so. Consider, on the other hand, the promulgation of a speed limit. When a legislature prohibits driving in excess of 55 m.p.h., it is in the business of creating an obligation. The obligatory maximum speed is not discovered; it is decreed.

All obligations of the former kind—obligations that are not created through promulgation—are ethical obligations, so the rules that report such obligations are properly called “ethical rules.” There is no obvious label for the latter kind of rule: I will simply designate them “rules of policy,” or, alternatively, “policies.” Given this distinction, it is reasonable to ask whether the rules found in the canonical codes are supposed to be ethical rules or policies.

In other writings, I argue that several of the consen- sus rules—rules promulgated in most of these canonical pronouncements and generally accepted by commentators...
and practitioners—cannot plausibly be defended as ethical rules. Nor could they be rules of policy, strictly speaking. Creating obligations through one’s promulgations requires having authority over those who are obligated.7 (Think of how the speed limit-imposing legislature must have authority over the drivers who are to obey the speed limit.) It is reasonably clear that the authors of the canonical pronouncements do not have authority over researchers. The Nuremberg Military Tribunal, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, and the National Bioethics Advisory Commission (NBAC), authors of the Nuremberg Code, the Belmont Report, and Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries (hereafter referred by the name of its author, NBAC), respectively, do not even exist any more. The World Medical Association (WMA) and the Council for International Organizations of Medical Sciences (CIOMS), authors of the Declaration of Helsinki and International Ethical Guidelines for Biomedical Research Involving Human Subjects (hereafter referred to by the name of its author, CIOMS), respectively, do still exist, but certainly do not have authority over researchers per se. They are membership organizations and therefore any authority they have extends only over their membership, which does not include all people who do research on human subjects. It is not possible, then, for these bodies to be policymakers in the sense we are interested in. However, it is possible for them to issue (or have issued) policy recommendations. What this would mean is that while their promulgations do not themselves create obligations incumbent on researchers, those promulgations might be enacted by the bodies that do have the authority to create such obligations, such as governments, research institutions, and institutional review boards (IRBs).

The question I want to ask, therefore, is whether the consensus rules found in the canonical pronouncements are defensible as policy recommendations. Interestingly, almost no one has offered arguments purporting to defend them as such. With respect to seven of the consensus rules (see Table 1), I will demonstrate that once we envision how such defenses would have to go we will see that there are large gaps in the evidence. We just don’t have robust support at this point for many of the key empirical premises. And while obligations of policy, as I have said, are decreed rather than discovered, what would constitute a good policy in a given arena is something that can be discovered. Consequently, I argue, if we conceive of these seven rules as policy recommendations then it would be wise to take them as starting points, subject to revision as the facts come in. Adopting this stance would constitute a long-overdue reorientation of our approach to rulemaking. It would mean embracing the idea of evidence-based rules in the arena of human subjects research.


THE NORMATIVE DISTINCTION BETWEEN ETHICS AND POLICY

Our first task is to be precise about the similarities and differences between ethical rules and rules of policy. Rules, as I shall understand them, are prescriptions to perform a certain kind of action, and for every (purported) rule there is a corresponding (purported) obligation to perform the prescribed action. Where rules of policy and ethical rules differ is in the source of the obligation’s normativity—its reason-giving force. The normativity of a policy is grounded partly in the mere fact of its being promulgated.8 Consider, again, a 55 m.p.h. speed limit. A legislature might have strong reasons to impose a 55 m.p.h. speed limit, but it is not obligatory per se to drive under 55 m.p.h. until the legislature actually enacts the policy. The normativity of an ethical rule, on the other hand, has nothing to do with its promulgation. Its reason-giving force is grounded entirely in a further fact: the fact that performing the prescribed action is ethically obligatory.9

There is an important lesson to take away from the speed limit example in addition to the point about the source of a policy’s normativity: A policy can have force even if the actions it prescribes are not obligatory independent of the promulgation of the rule prescribing them. Independent of the existence of a speed limit, it is not obligatory to drive under 55 m.p.h. Yet such speed limits have force. Thus, the very notion of having rules of policy rests on the premise that there are sometimes reasons to prescribe an action besides its being ethically obligatory. For instance, many theorists concede that doctors violate no ethical obligation in assisting a terminal patient in committing suicide, but they believe that there are strong reasons to have a policy—in this case, a criminal law—banning the practice: For example, some family members or physicians might otherwise coerce some patients into opting for assisted suicide.10 We can distinguish ethics from policy without insisting that they are entirely separate domains. In particular, we can and should concede that there can be ethical reasons favoring a policy. For instance, we have an ethical reason to behave in ways that are less damaging to the environment, so there is an ethical reason to enact a policy that prohibits drivers from exceeding 55 m.p.h. We should also admit that while legitimate policies can prescribe behavior that there is no preexisting obligation to perform, nevertheless the fact that a legitimate policy prescribes some behavior can make it ethically obligatory to engage in it. Finally, we should recognize that it is possible to enshrine ethical rules as policies, since a single rule can be reason-giving both as an ethical rule and as a rule of policy. The criminal law against killing

8. Frederick Schauer, Playing by the Rules, p. 112.
9. This is identical to the oft-made distinction between ethical rules and laws. It makes sense that the two distinctions should be drawn in the same way, since laws are policies.
10. I thank Margaret Little for this example. For this kind of argument against legalizing physician-assisted suicide, see Ezekiel J. Emanuel, “What is the great benefit of legalizing euthanasia or physician-assisted suicide?,” Ethics 109 (April 1999): 629–642.
Table 1. Seven Rules

<table>
<thead>
<tr>
<th>Name I use to refer to rule</th>
<th>Rule</th>
<th>Source of quote</th>
<th>Other canonical pronouncements that contain a similar rule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valid Design</td>
<td>“...investigators and sponsors must ensure that proposed studies involving human subjects conform to generally accepted scientific principles...”</td>
<td>CIOMS, Guideline 1</td>
<td>Nuremberg Code, Directive 3, Declaration of Helsinki, Principle 12</td>
</tr>
<tr>
<td>Risk Minimization</td>
<td>“Risks should be reduced to those necessary to achieve the research objective.”</td>
<td>Belmont Report, Part C2</td>
<td>CIOMS, Guideline 8, Nuremberg Code, Directive 4</td>
</tr>
<tr>
<td>Post-Trial Access</td>
<td>“At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.”</td>
<td>Declaration of Helsinki, Principle 33</td>
<td>CIOMS, Guideline 10, NBAC, Recommendation 4.1</td>
</tr>
<tr>
<td>Undue Inducement</td>
<td>“...The payments should not be so large...or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment (‘undue inducement’).”</td>
<td>CIOMS, Guideline 7</td>
<td>NBAC, Chapter 3, Belmont Report, Part C1</td>
</tr>
<tr>
<td>Right of Withdrawal</td>
<td>“...the individual...will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would otherwise be entitled...”</td>
<td>CIOMS, Guideline 5</td>
<td>Declaration of Helsinki, Principle 24, Belmont Report, Part C1</td>
</tr>
<tr>
<td>Responsiveness</td>
<td>“...the investigator must make every effort to ensure that...the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out...”</td>
<td>CIOMS, Guideline 10</td>
<td>Declaration of Helsinki, Principle 17, NBAC, Recommendation 4.2</td>
</tr>
<tr>
<td>Reasonable Availability</td>
<td>“Whenever possible...agreements should be negotiated by the relevant parties to make the effective intervention or other research benefits available to the host country after the study is completed.”</td>
<td>NBAC, Recommendation 4.3</td>
<td>Declaration of Helsinki, Principle 17, CIOMS, General Ethical Principles—Justice</td>
</tr>
</tbody>
</table>

people is a good example. Like all criminal laws, it is a policy, but its reason-giving force is not incompatible with the reason-giving force of an ethical rule proscribing killing people. Similarly, in the area of human subjects research, if we believe that it is wrong for investigators to put subjects at risk without the possibility of compensating benefits we are free to formulate a policy prohibiting just that. Thus, rulemaking in human subjects research can serve both a reflective and a prospective purpose: It can codify and add normative force to what are already ethical obligations incumbent on researchers and it can create new obligations.

The normative distinction between ethics and policy gives rise to a distinction in how to defend ethical rules as opposed to policy recommendations. To defend an ethical rule one need only show that it accurately reflects the ethical truth—namely, that performing the prescribed...
Table 2. How the Canonical Pronouncements Contextualize the Rules They Contain

<table>
<thead>
<tr>
<th>Pronouncement</th>
<th>Contextualizing statement</th>
<th>Location of the statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuremberg Code</td>
<td>“The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts.”</td>
<td>Immediately before Directive 1 of the Nuremberg Code in the official record of the Nuremberg trials¹³</td>
</tr>
<tr>
<td>Declaration of Helsinki</td>
<td>“The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.”</td>
<td>First sentence of the Declaration</td>
</tr>
<tr>
<td>CIOMS</td>
<td>“This is the third in the series of international ethical guidelines for biomedical research involving human subjects issued by the Council for International Organizations of Medical Sciences since 1982.”</td>
<td>First sentence of the introduction</td>
</tr>
<tr>
<td>Belmont Report</td>
<td>“Ethical Principles and Guidelines for the protection of human subjects of research”</td>
<td>Subtitle</td>
</tr>
<tr>
<td>NBAC</td>
<td>“This report discusses the ethical issues that arise when research that is subject to U.S. regulation is sponsored or conducted in developing countries…”</td>
<td>First sentence under “Scope of this Report”</td>
</tr>
</tbody>
</table>

action is ethically obligatory. But rules of policy create obligations.¹¹ Like any intentional action, the creation of an obligation has a purpose. Therefore, such rules themselves have a purpose.¹² A defense of a policy recommendation, therefore, should demonstrate at least that the rule serves a legitimate purpose. This distinction should clarify the meaning of my initial claim that several of the rules found in the canonical pronouncements cannot be defended as ethical rules but might be defended as policy recommendations. It means that the actions prescribed by the rules are not ethically obligatory, yet prescribing them might nevertheless effectively promote a legitimate purpose.

**REJECTING THE RULES AS ETHICAL RULES**

In this section I defend my assertion that several of the rules found in the overlap of the canonical pronouncements cannot be defended as ethical rules. First, however, I want to explain why it was ever legitimate to interpret them as such. Admittedly, the canonical pronouncements do not say what the status of their rules is supposed to be. However, most of the evidence indicates that they are supposed to be ethical rules. For one thing, the language of ethics dominates the parts of the canonical pronouncements that are not themselves expressions of the rules—the dicta. Many of the words themselves are blatantly ethical. The word “ethics” and “ethical” appear time and again in them, as does talk of “principles” and “justification.”¹⁴ Furthermore, this sort of language often appears in the most prominent places in these documents: the places where the rules are put into context (Table 2).

Because of this, I consider it reasonable to interpret the rules found in the pronouncements as ethical rules. Consequently, in other writings I call into question the Valid Design, Risk Minimization, Post-Trial Access, Undue Inducement, and Right of Withdrawal rules. My attack is two-pronged. I demonstrate, first, that the purported ethical obligations cannot be grounded in the four canonical principles of bioethics: respect for persons, nonmaleficence, beneficence, and justice.¹⁵ I then argue that the kinds of action that these rules prescribe in the research context are usually not considered obligatory in other contexts that are like human subjects research in all the ethically relevant respects.¹⁶ In what follows, I make my case against those five rules, plus Responsiveness and Reasonable Availability, as ethical rules. My goal is to show that the actions prescribed

¹¹. Schauer says that they create reasons (Playing by the Rules, pp. 5–6, 51–52), and I agree. I simply want to say that they create reasons by way of creating obligations.


¹⁴. In fact the Belmont Report explicitly states which ethical principles are supposed to justify its rules.


by these rules are not obligatory.\textsuperscript{17} My arguments in the case of the first five rules are kept brief since I have already made my case against them elsewhere. My arguments against the latter two rules are more detailed, but not by much. Partly this is because the arguments themselves are simple. More importantly, however, I want to leave space for my primary concern in this article: the question of whether the seven rules are defensible as policy. Therefore, the brevity of the arguments should not be taken to suggest that I consider the cases against these seven rules to be open-and-shut. In particular, I believe that the Valid Design, Risk Minimization, and Undue Inducement rules are each predicated on important ethical concerns. My complaint in those cases is that we have misidentified the precise nature of that concern and consequently crafted rules that fail to accurately pick out the research practices that are unethical.

Valid Design. If Valid Design is an ethical rule, then it must be the case that an investigator’s enrolling a research recruit in a poorly designed study is a violation of an ethical obligation. That is, doing such a thing must be a violation even when the recruit is aware that the study is poorly designed and wants, with good reason, to participate anyway—whether for the chance to receive novel therapy, for the monetary inducement, or for something else—and is compensated fairly for her participation. But it is hard to see how there could be any such ethical obligation. What this suggests is that ensuring valid design is not in itself obligatory, and that the force of our concern for scientific validity is parasitic on the concern, enshrined as a rule in all the canonical codes, that risks to subjects be offset by benefits to subjects and to society at large. When and only when abiding by the latter requirement necessitates designing one’s study in a valid way are researchers ethically required to do it.

Risk Minimization. Risk Minimization requires investigators to reduce, to the extent possible given the goals of the study, the risks their subjects undertake. We can concede that an investigator’s omitting to do so would constitute the violation of an obligation in many cases while still insisting that there might be nothing wrong about such an omission in some instances. If, for instance, the investigator were to offer the recruit sufficiently more expected benefit in exchange for taking on the unnecessary risk, the offer as a whole would appear unimpeachable. We should conclude therefore that the ethical concern that animates Risk Minimization is, like the concern animating Valid Design, parasitic on the concern that risks to subjects should be balanced out by benefits to subjects and society.

Post-Trial Access. In accepting Post-Trial Access as an ethical rule we endorse the idea that investigators violate an ethical obligation when they fail to ensure that everyone who enters their study receives the best treatment available after the conclusion of the study. But do we really believe any such thing? This idea would seem to rely on the claim that if investigators failed to do this then the terms of participation would be unfair. However, on the assumption that the fairness of the terms of a deal is based on how the harms and benefits are distributed, this is implausible. There are any number of ways for investigators to increase the benefits they bestow on their subjects besides providing treatment post-trial.

Undue Inducement. The most compelling argument in favor of the Undue Inducement rule as an ethical rule is that offering a potential subject a large inducement to enroll in a study can constitute a violation of respect for persons. The basic idea would be that such an offer may be an attempt to subvert or circumvent the rational deliberative capacity of the potential subject, such that his/her eventual decision to enroll represents not an autonomous exercise of will but rather an unreasoned succumbing to temptation. This is a valid concern, but it does not imply that all sufficiently large inducements are unethical. Rather, it suggests that such offers can be unethical if not accompanied by other measures intended to engage the rational faculties of the potential subject. Thus, we do not need to ban large inducements; we need to make sure that investigators who make such offers also make good-faith efforts to ensure that potential subjects deliberate thoroughly before accepting them.

Right of Withdrawal. The key premise in the argument for Right of Withdrawal as an ethical rule is that it is a violation of the subject’s autonomy to impose any conditions upon her or his right to withdraw from the study. But imposing such conditions doesn’t seem to constitute the violation of an ethical obligation per se. Surely if such conditions were forced on the subject, we would have grounds for objection. But by declaring null and void any conditions imposed on the subject’s right of withdrawal, the rule even prohibits imposing conditions that the subjects want, perhaps with good reason, to be imposed—for instance, when additional benefit is offered as compensation for the imposing of the condition. The rule, it seems, overreaches.

Responsiveness. The Declaration of Helsinki, CIOMS, and NBAC each endorse Responsiveness as a rule applying only to studies conducted in the developing world. The rule requires investigators conducting such studies to ensure that they address a question that is important to the host community. The rule arose as a response to the infamous 10/90 gap: the finding of the Global Forum for Health Research that just 10% of global health research funds are spent studying the diseases that are of primary concern for 90% of the world’s population.\textsuperscript{18} This fact strikes many as an enormous injustice. Responsiveness addresses this injustice by imposing a constraint on investigators. Yet we might question whether investigators are the ones violating an obligation here. One would think, on the contrary, that the transgressors are the entities that control the allocation of research funds. Furthermore, even if some investigators share in the guilt, Responsiveness surely misidentifies that

\textsuperscript{17} Rule-based obligations, or the reasons they ground, can range from weak to absolute (Schauer, Playing by the Rules, pp. 113–118). My arguments are intended to be effective no matter how strong the obligations are purported to be.

\textsuperscript{18} For an example of a defense of Responsiveness motivated in this way, see Alex John London, “Responsiveness to host community health needs,” in Ezekiel J. Emanuel et al., eds., The Oxford Textbook of Clinical Research Ethics (New York: Oxford University Press, 2008), pp. 737–744.
set of investigators. If it is ethically obligatory for investigators to dedicate more resources to conducting research on matters of concern to people in the developing world, then the transgressors would be every investigator who conducts research on matters of importance to members of the developed world but not the developing world, not just those who conduct this kind of research in the developing world. Yet Responsiveness constrains only the latter set of investigators. Why not, instead, make it a condition on the approval of a study conducted anywhere that the research team find ways to generate knowledge relevant to a developing community somewhere?

**Reasonable Availability.** Like Responsiveness, Reasonable Availability is generally held to apply only to those studies that are conducted in developing communities (the Declaration of Helsinki is an exception here in that it imposes the rule on all studies). The concern to which Reasonable Availability responds is that in drawing research subjects from already-disadvantaged communities, investigators exploit those communities unless they guarantee something in return.¹⁹ That something, according to Reasonable Availability, should be “the effective intervention or other research benefits,” to be made available to the members of the community afflicted with the condition being studied. Note, however, that sometimes the very conducting of the study is of benefit to the host community. This benefit can take various forms: the spread of previously unknown information about the disease being studied, the return to the workforce of those who were sick but are now healthy after having received treatment as part of their participation in the study, the added money pumped into the community’s economy due to the distribution of monetary inducements, etc. This is not to say that there is no risk of exploitation here. Rather, it is to suggest that exploitation will occur only when these other benefits are not beneficial enough to constitute a fair or proportional reward for the host community’s sacrifice. The Reasonable Availability rule requires the conferring of additional benefit no matter what, and is therefore an exaggerated response to the exploitation worry.

**HOW TO DEFEND THE RULES AS POLICY RECOMMENDATIONS**

If I am right that there is little hope for defending the seven rules as ethical rules, it would be worth our while to consider whether they are defensible as policy recommendations. I said in the second section that to defend a policy recommendation one must show that the policy would likely do a good job of promoting a legitimate policy goal. Therefore, we first need to identify a legitimate purpose of human subjects research policy.

One would hope that for answers we could look to the authors of these (what we are now interpreting to be) policy recommendations: the Nuremberg Military Tribunals, the World Medical Association, CIOMS, the National Commission, and NBAC. However, as I revealed in the previous section, these bodies seem to conceive of themselves as engaged in reporting the ethical facts. Not surprisingly, therefore, none of them enunciates a policy objective.

Fair enough. At what objectives may human subjects research policy aim? This question is too fraught to be given a precise answer here, so I will settle for a vague one about which everyone will most likely agree. Human subjects research policy should protect and promote the interests of those who have a stake in the endeavor: subjects’ interests in being able to contribute to the generation of medical knowledge and being protected from unscrupulous researchers and dangerous studies; physician-researchers’ interests in being able to do their job effectively; community members’ interests in not having medical research be a drain on the community’s resources; taxpayers’ interests in gaining a good return on their investment; and future patients’ interests in having access to quality health care.²⁰ And it bears repeating that policies can and often should be designed to serve ethical purposes as well. Again, it is a controversial question which ethical purposes human subjects research policies should aim to serve, and I will not try to settle that dispute here. For the sake of illustration, however, I offer distributive justice as a possible ethical objective. It is often noted that a disproportionate number of research subjects are poor, and that an ever-increasing proportion of studies are being conducted in poor communities abroad. We might, therefore, see an opportunity to use human subjects research as a vehicle for promoting distributive justice. If we adopt this view, then all else being equal we would want our policies to require that more of the benefits of research be conferred on subjects and community members. It would then appear that ethical concerns would favor placing greater weight on the interests of subjects and community members and lesser weight on the other interests listed earlier.

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²⁰. At this point, one might begin to doubt whether the process of defending a rule as a policy recommendation really does differ from the process of defending it as an ethical rule. It may seem that in seeking a list of rules for the sake of promoting the interests of those affected by them, we are seeing the ethical rules that would fall out of a particular normative ethical theory—rule-utilitarianism. But this impression would be mistaken. While both rule-utilitarians and policy-creators are in the business of promulgating the optimal set of rules, only rule-utilitarians say that those rules would be obligatory even if no one had ever promulgated them.
ARE THE RULES DEFENSIBLE AS POLICY RECOMMENDATIONS?

In the previous section I asserted that human subjects research policy should serve the interests of those affected by such research. Given my earlier argument that a defense of a policy recommendation must make evident how that policy would effectively promote the legitimate policy objective, we now know what it would take to defend the seven rules as policy recommendations. We must exhibit that implementing these rules would likely do a good job of protecting and promoting the interests of those affected by human subjects research.21 In what follows I investigate whether this can be done, once again taking the rules one by one. In each case except one (Undue Inducement), I conclude that at present we simply don’t know. I do not take this to suggest that IRBs should stop enforcing these rules (except Undue Inducement); rather, I take this to suggest that we should consider the rules subject to revision as the facts come in and that we should actively search for those facts.

Valid Design. There are two considerations favoring a prohibition on the enrollment of human subjects in scientifically invalid studies. Feinstein and Lichtenstein posit that scientifically invalid research will lead to worse clinical practice.22 While this will not be true in all cases, we might reasonably claim that scientifically invalid research will fail to improve clinical practice.23 Meanwhile, Emanuel, Wendler, and Grady raise the obvious concern that poorly designed research is a waste of resources.24

The latter point is contingent on the former. If somehow scientifically invalid research could lead to better treatment of patients, then taxpayer money expended on it wouldn’t be a waste, though it might remain the case that it would be better used on scientifically valid research. Whether invalid research will lead to better treatment of patients depends on in what way and to what extent the research is invalid. Consider one criterion of validity: power. We typically say that a study is sufficiently powered if and only if it has at least an 80% chance of detecting a certain level of association between a predictor and an outcome if the association really exists. But there’s nothing magical about 80%. Talk of “sufficient power,” full stop, is a fiction; the truth is that power is incremental. Since power is incremental, ipso facto scientific validity is too.25 And when it costs more money to run a study in a more scientifically valid way, increments of validity have a cost. This being the case, we need to discover both the marginal utility and cost of increments of validity, and then find out whether money spent on increments of validity could be more efficiently used elsewhere. Only then will we know which particular version of a scientific validity requirement best serves the interests of future patients and taxpayers most effectively.

Risk Minimization. All else being equal, it is certainly in subjects’ interests to be exposed to less risk. However, all else is not always equal. Whether Risk Minimization will actually work in favor of subjects depends on whether investigators, given the freedom to expose subjects to unnecessary risks, would offer them compensating benefits in order to induce them to take those risks. We do not know the answer to this question.

Supposing Risk Minimization did turn out to serve the interests of subjects, there would still be the issue of its apparent failure to serve the interests of future patients. Minimizing risks often is costly in terms of time and money, and of course it is in the interest of future patients that studies face as few of these obstacles as possible. If Risk Minimization benefits subjects but works to the detriment of future patients, then we need to investigate the ethical question of how to weigh the interests of the members of these groups.

Post-Trial Access. The Post-Trial Access rule works in favor of subjects who because of the rule retain access to treatment after the study is completed. This, undeniably, constitutes a reason to require investigators to provide such treatment. However, it will usually be more expensive, all else being equal, to conduct a study while adhering to this rule. Consequently, the rule might serve to discourage drug companies and other potential research sponsors from undertaking research in the first place.26 This in most cases would work to the detriment of future patients who might benefit from the knowledge gained. It would also work to the detriment of potential subjects. The people who would otherwise have the opportunity to participate in a study, and thereby possibly receive free treatment, information about their condition, diagnostic exams, and any other benefits of participation, will obviously miss out on them if the study is never carried out.

This is another case, then, where we need to know how the interests of subjects and future patients compare, and it also presents the new question of how to balance the interests of subjects against the interests of potential subjects. Also, we need empirical evidence on how often studies are

21. It is entirely possible that we should hold these candidate policies to a higher standard: that we should demand more of human subjects research policy than its effective promotion of a legitimate goal. Even so, it is worthwhile to inquire whether the recommendations at hand pass even this test.
25. This is consistent with the claim that there is both a lower and an upper limit to how (in)valid a study can be.
foregone because the rule is in place. No one has ever tried to answer that question.

**Undue Inducement.** Various commentators support the Undue Inducement rule on the grounds that the practice of paying research subjects leads to a situation in which the poor are made to shoulder most of the burden of human subjects research.27 There are two ways to interpret this concern: It is either a concern for how well off the poor are or a concern for the equal distribution of research-related health risk. These are not identical concerns; equality is not about how well off people are but rather about how well off people are compared to other people.28

If we are concerned for the plight of the poor, then imposing the Undue Inducement rule is counterproductive. We should want them to be paid more money for their participation, not less. If, on the other hand, we are concerned about equal distribution of health risks, then our concern is too narrow. There is no reason to be concerned specifically about equality in the distribution of health risks; the distribution of health risks is just one element of the distribution of welfare, and that is what we should care about. Notice that the distribution of money is also an element of the distribution of welfare. So the Undue Inducement rule, by prohibiting investigators from offering the poor quantities of money that more than compensate for their undertaking certain research risks, actually makes the poor less well off overall and thereby exacerbates the inequality that we should care about.

**Right of Withdrawal.** Right of Withdrawal as a policy has all the same strengths and weaknesses as Risk Minimization. First, it might or might not work to the benefit of subjects. If investigators, given the latitude to impose conditions on the subject’s right to withdraw, would offer compensating benefits in exchange for imposing those conditions, then allowing them to do so would work to the benefit of subjects. If not, then subjects would be harmed. Since we don’t know what investigators would do with this freedom, we don’t know whether Right of Withdrawal benefits subjects. Second, Right of Withdrawal is probably not best for medical science and thus for future patients. Subject withdrawals can severely damage the quality of a study’s data and can make it more expensive to run a study, thereby inhibiting the production of medical knowledge. Thus, we do not know whether Right of Withdrawal is justified on policy grounds. To figure this out, we need to know first what investigators would do with their freedom, and second, how to weight the interests of subjects against those of future patients.

**Responsiveness.** In light of the 10/90 gap, it makes sense to have a rule requiring investigators to conduct more studies on matters of concern to members of developing communities and fewer studies on other topics. Notice, however, that Responsiveness doesn’t require either of these things. What Responsiveness does is prohibit studies that take place in a developing community but do not address a question of importance to the members of that community. Consequently, whether holding investigators to a Responsiveness rule does anyone any good depends on what sort of research ends up being undertaken by investigators when they are prohibited by Responsiveness from doing the research they would like to do (“unresponsive research”).29 If they instead do research in developing communities on topics that are important to those communities—“responsive research”—then the rule promotes the intended goal. If instead they do research in developed communities, then the rule is counterproductive. It would be better that investigators should do unresponsive research, in which case members of developing communities at least have the opportunity to enroll in a study and obtain benefits such as medical attention and monetary inducements, than that they should do research in developed communities and thereby confer those benefits on people who need them less. The data that would identify the actual effect of the Responsiveness rule are unfortunately nowhere to be found.

**Reasonable Availability.** The obvious benefit of Reasonable Availability is that it guarantees “the effective intervention or other research benefits” to members of developing communities in which treatment studies are conducted. The obvious risk, as with Post-Trial Access, is that because of the added cost of providing such interventions some studies will become financially unfeasible and thus will not be carried out.30 Any time that happens, everyone who would have benefited from the study—the subjects, the investigator, future patients—loses out on that benefit.31 Another risk, as with Responsiveness, is that investigators from developed countries will carry out their research domestically instead. To determine whether Reasonable Availability is overall a beneficial rule, we need to study its effect on investigators’ and sponsors’ decision making about which


28. This point was originally made by Joel Feinberg, “Noncomparative justice,” Philosophical Review 83(3) (July 1974): 297–338, and is now widely accepted among political theorists and moral philosophers.


31. This undermines NBAC’s point that it is irrelevant if Reasonable Availability deters the carrying out of studies since studies that don’t abide by Reasonable Availability are of no benefit to host communities anyway (NBAC, p. 68).
studies to conduct and where. Once again the needed studies have not been undertaken.32

With respect to six of the rules (Undue Inducement being the exception), it would appear that enforcing the rule will in general effectively promote the interests of some of those affected by human subjects research, while setting back the interests of others. Furthermore, how good a job it does of promoting the relevant interests will vary based on the details of the particular study to which it is applied. This, on its own, is not an indictment of the rules as policy recommendations. Although the correct set of ethical rules prohibits all and only actions that are unethical, a good set of policy rules can prohibit actions that it would be better to allow and allow actions that it would be better to prohibit.33

This is because rules of policy are promulgated ahead of time and even the best policymakers cannot possibly anticipate every situation that might come up.34 Nevertheless, it is possible that we can do better—that we can make the rules more nuanced so as to ensure that they come closer to prohibiting all and only the research practices that it would be good to prohibit. Rules of policy, unlike ethical rules, are ours to create, and we can make them as nuanced as we want.

At the extreme, we might decide that the best rule with respect to some issues is no rule at all, and thus we might consider allowing decisions about validity, risk minimization, post-trial access, etc., to be made on a protocol-by-protocol basis by IRBs.35 While this might seem like a scary proposition, consider that IRBs are already entrusted to make case-by-case determinations about other important matters. For instance, IRBs are charged with determining, for each study, whether the benefits of that study for subjects and for society in general balance out the risks to subjects. This is often a very delicate matter, requiring the exercise of scientific judgment in assessing what the likely result of the study will be and also ethical judgment in assessing how the interests of future patients should be weighed against the interests of subjects. IRBs also have the task of deciding when to modify or waive the informed consent requirement. This, too, is a judgment call, requiring the IRB to render a verdict about the importance of the project and the possible harm that could accrue to subjects on account of the modification or waiver. Even for some of the seven rules discussed here it is inevitable that IRBs should have to exercise judgment. For instance, determining whether risks to subjects have been minimized relative to the aim of the study is not often a straightforward matter.

In any event, instructing IRBs to make decisions on matters currently covered by the seven rules would indeed constitute a great exercise of faith in the ability of IRBs to make good judgments. Perhaps such faith is unwarranted. But how would we know that? This, too, is a hypothesis that would seem to admit of empirical confirmation or disconfirmation.36

I do not mean to suggest that having no rules at all on these matters would be a panacea. There are at least four kinds of benefit to be had from instituting a system of rules—consistency, reliance, efficiency, and risk avoidance37—each of which is available in the human subjects research context: First, the less discretion we give IRBs, the more consistency there will likely be among them. Consistency might be seen as fairer in itself38 and it also might discourage IRB shopping. Second, good rules can be effective as guides to deliberation and action, and one might worry that we give investigators too little to work with if we rescind the rules. If researchers cannot rely on their protocol being held to a certain standard, they might not be willing to expend the energy developing one. Consequently, eliminating the rules might cause a chilling effect. Third, it is more efficient to have decisions on risk minimization, scientific validity, etc. made just once, by a rule-promulgating body, than to have them made again and again by IRBs. And fourth, as already mentioned, allowing IRBs to make judgments involves accepting the risk that they could make some very bad ones. Whether these advantages of rules outweigh the disadvantages is, like so many other questions in this area, something that requires a kind of research that has never been undertaken. (Though the general question about the wisdom of delegating decision-making authority instead of promulgating rules is surely one that has been researched in some other context at some point. Perhaps that research is applicable to the human subjects research context.)

32. This has not stopped some commentators from stating that imposing the Reasonable Availability rule will work to the benefit of citizens of developing countries. See, for instance, Peter Lurie and Sidney M. Wolfe, “The developing world as the ‘answer’ to the dreams of pharmaceutical companies: The Surfaxin story,” in James V. Lavery et al., eds., Ethical Issues in International Biomedical Research: A Casebook (New York: Oxford University Press, 2007), pp. 159–170 at 166.
33. Schauer, Playing by the Rules, chap. 3 and pp. 100 and 135.
34. Ibid., pp. 83–84.
35. Strictly speaking, “no rule at all” isn’t really an option. Empowering IRBs to make decisions about certain matters requires putting in place jurisdictional rules, which are quite different from the rules we have been discussing but are rules nonetheless. See Schauer, Playing by the Rules, pp. 167–174.
36. In order to know whether skepticism is called for, we should monitor IRBs’ attempts to exercise good judgment on the matters about which they currently do exercise their judgment. We might study whether IRBs do a good job of making these determinations. If we had data on this, and if we reached some conclusions about how we might extrapolate our findings to the question of how well IRBs could be expected to exercise their judgment on the matters covered by the seven rules, then, and only then, could we be justified in saying that there should or should not be policies regarding matters such as scientific validity, post-trial access, and responsiveness. Alternatively, we might study the question prospectively, allowing a handful of IRBs to make determinations on these matters on a probationary basis and then reviewing the results.
37. Schauer, Playing by the Rules, chap. 7.
38. For some doubts about this, see ibid., pp. 136–137.
MOVING FORWARD IN A POLICY-ORIENTED FRAMEWORK

In the previous section I gave reasons to doubt whether the seven rules constitute good policy recommendations. But policies are our creations and can therefore be altered until we hit on the right one. Moving forward, I believe we should adopt this flexible posture toward the rules. Taking up a policy-oriented approach is more reasonable than maintaining a dogmatic adherence to the rules as currently written.

What is involved in taking up the policy-oriented approach to human subjects research rulemaking? Four things.

(1) It requires attending to the difference between an ethical violation and a violation of a policy. Whether a rule is an ethical rule or policy has implications for who has grounds for complaint when the rule is broken. When a rule is a policy and not an ethical rule, no one has special standing with respect to it unless the policy explicitly gives someone such standing. That is why violations of the criminal law are prosecuted by the state. So if our rules are policies, then when they are broken subjects and community members do not have any special grounds for complaint or standing to demand redress unless the rulemakers declare that they (the subjects or community members) have it. 39

(2) The policy-oriented approach has implications for whose policy recommendations we should heed. The reason-giving force of ethical rules, as I have emphasized, has nothing to do with who promulgates them (or with whether they are promulgated at all). Their force is contingent on their accurately reflecting the ethical truth, something that everyone who possesses ethical concepts is in a position to discover. But rules of policy are crafted to achieve some end, and some people are more knowledgeable than others about how to achieve certain ends. This suggests that there is expertise in rulemaking, and that therefore only the recommendations of the experts should be heeded. On the other hand, human subjects research policy has effects on a wide range of people, which suggests that policy recommendations in this area should be the result of a deliberative process in which all interested parties are represented. How to balance the need for expertise with the need for representation in human subjects research rulemaking is a topic that deserves more attention than it has been given. Tentatively, however, I would assert that we do not have any special reason to take the recommendations of WMA and CIOMS seriously, despite WMA's claim to the contrary, 40 since they are only narrowly representative bodies (representing physicians and biomedical scientists, respectively), nor are they composed of experts on the likely effects of various possible rules.

(3) If we take the policy-oriented approach to rulemaking, we should be careful about how we express the rules. Taking care involves three things. First, the rules should be contextualized in the right way; they should not be introduced as "ethical guidelines," for instance. Second, if we take up the policy-oriented approach to rulemaking, then our canonical pronouncements should clearly enunciate a policy objective. That the canonical pronouncements as written fail on these two counts is a point for which I have already argued (see the third and fourth sections).

Third, the rules themselves would have to be rewritten so as to clearly mark them out as rules of policy. Now one might worry that if we opted for the language of policy instead of the language of ethics the rules would lose much of their polemic force. It seems that prescriptions expressed in ethical language are more likely to motivate compliance than similar prescriptions expressed in policy language.

This concern, however, can be met. In redrafting our pronouncements, we might take as our model the Geneva Conventions of 1949, which are unabashedly clear that the rules they contain are rules of policy, not ethical rules. Words like "should," "ought," "duty," "obligated," and "obliged" almost never appear in the Geneva Conventions, while mentions of ethics and morality are completely absent. That the documents are called "conventions" also helps make it clear that the rules they contain are not supposed to describe pre-existing truth, as conventions are by definition human creations. All the same, the Geneva Conventions carry great weight and are taken extremely seriously (recent U.S. foreign policy notwithstanding).

One might also worry that in reformulating our pronouncements as policy documents, we will inevitably mischaracterize certain ethical rules, such as the rule requiring the obtaining of informed consent, as rules of policy. This worry, however, is misplaced. As I explained in the second section, the enshrining of a rule as policy should not be construed as an implicit denial that that same rule is reason-giving as a matter of ethics. In fact, if we want our pronouncements to contain justifications for their rules (the Belmont Report, CIOMS, and NBAC already do this), then we can offer ethical justifications for the rules that admit of such justification. 41

(4) Most obviously, given what I have been at pains to argue in this paper, taking up the policy-oriented

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39. Should the rulemakers grant such status? This is a difficult question to which I cannot do justice here, but my inclination is to say that it depends on the rule. If part of the point of the rule is to confer a benefit on subjects or community members, then yes. When such rules are broken, it makes sense that subjects or community members should be granted the standing to demand some compensation for not having received the benefit that conformity to the rule would have conferred on them.


41. Thus, I am not proposing that all ethical language be removed from the pronouncements.
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approach to rulemaking requires doing the research necessary to determine which rules will serve our ends. There is a saying in legal theory that hard cases make bad law, and I think that this lesson applies to human subjects research rulemaking as well. Historically the promulgation of rules governing the conduct of human subjects research has been not evidence driven but scandal driven. With each new object of disapproval—the Nazi experiments, Tuskegee, short-course AZT—has come an additional set of rules. Unfortunately, the enforcement of rules can come at the cost of discouraging or making impossible the carrying out of potentially valuable medical research, as I illustrated in the fifth section. Thus, in trying to avert certain sorts of disaster, we may be creating a disaster of a different kind. This would be the disaster of missing out on the benefits we-know-not-which of research that never occurred, but it would be a disaster all the same. Thus, we should not be complacent about the task of determining which rules will promote our goals. Though it might seem as if, despite their drawbacks, our current set of rules is serving us rather well, this might be merely an illusion caused by the invisibility of our current misfortune.

This is not to deny that we should be vigilant about preventing the next Tuskegee. Unethical studies have been proposed before and will be proposed in the future, and we should enshrine as policy and vigorously enforce the ethical rules that proscribe those studies. But we should also acknowledge that some research practices that we are justified in prohibiting are not unethical. We should then do the research necessary in order to undertake this justification. For starters, we need to establish a policy objective. Since there can be ethical reasons supporting policy objectives, ethical research will be necessary here. To a large extent, however, justifying our chosen policies will be a scientific exercise in which we endeavor to establish causal connections between the enacting of a policy and the production of some benefit for an interested party. The basic point is that in human subjects research regulation, the policy-oriented approach is the scientific approach, and we should hope that the research community will embrace the scientific approach to regulation as wholeheartedly as they already embrace the scientific approach to medicine. I have listed here some of the scientific questions that need to be answered. Until we have the answers, our rules remain unproven.

43. This way of conceiving of the problem was suggested to me as I read Cass Sunstein’s book Worst-Case Scenarios (Cambridge, MA: Harvard University Press, 2007).
44. What kind of research should we undertake? If we are really ambitious we might want to undertake prospective trials in which researchers and their protocols are randomized to IRBs enforcing differing sets of rules. To carry this out, however, we would have to allow the rules to be broken; this might be unpalatable to the research community. In any event, it’s not clear to me that all the other variables could be silenced. A more feasible, albeit less satisfying, kind of research would be a set of surveys aiming to solicit from investigators, potential subjects, and community members information regarding how they would behave if the rules were different.