Contemporary research ethics policies started with reflection on the atrocities perpetrated upon concentration camp inmates by Nazi doctors. Apparently, as a consequence of that experience, the policies that now guide human subject research focus on the protection of human subjects by making informed consent the centerpiece of regulatory attention. I take the choice of context for policy design, the initial prioritization of informed consent, and several associated conceptual missteps, to have set research ethics off in the wrong direction. The aim of this paper is to sort out these confusions and their implications and to offer instead a straightforward framework for considering the ethical conduct of human subject research. In the course of this discussion I clarify different senses of autonomy that have been confounded and present more intelligible justifications for informed consent. I also take issue with several of the now accepted dogmas that govern research ethics. These include: the primacy of informed consent, the protection of the vulnerable, the substitution of beneficence for research’s social purpose, and the introduction of an untenable distinction between innovation and research.

INTRODUCTION

Since the end of World War II, when scientists, physicians, and the public turned their attention to ethical issues raised by biomedical research with human subjects, protection has been the focus of policy, and informed consent has been the centerpiece of regulatory attention. I take this initial prioritization and several associated missteps, to have set research ethics off in the wrong direction. As I see it, a few snarls early in the course led, over subsequent decades, to a tangled web of research ethics policies that are sometimes at cross-purposes with the goals that they should actually promote. To set us back on course it is necessary, therefore, to identify and criticize the presumptions and principles of current research policy.

The first set of issues involves starting with the model of malevolent Nazi scientists and their abused subjects and the strange ranking policy makers assigned to the problems in their research practices. Policies have taken a peculiar turn by taking concentration camp research as their instructive example. Instead of focusing attention broadly on the development of reasonable boundaries for the conduct of human subject research, policies have focused narrowly on the protection of human subjects. Even the titles of oversight policies and agencies reflect this narrow aim. In the U.S., the regulations are called “Policy for the Protection of Human Research Subjects,” and the agency for compliance was first the Office for the Protection from Research Risks (OPRR) and now the Office for Human Research Protection (OHRP). Although there is an obvious intuitive appeal in the desire to protect those who are least able to protect themselves, current research policies too often limit research, particularly with individuals who are classified as “vulnerable,” and thereby promote practices that are unethical and unreasonable by being harmful, wasteful, or both. Rather than according a reasonable balance to a range of interrelated issues that affect the moral assessment of various projects (e.g., risk, efficacy, justice, respect), the rules give special weight to the protection of the vulnerable.

The second, but interrelated, set of issues involves scrambling two distinct concepts of autonomy. Policies that confuse the ideal of autonomy (which I shall call the first-person sense of autonomy) with respect for autonomy (which I shall call the second-person sense of autonomy) produce jumbled requirements. In some circumstances, they are disrespectfully paternalistic. In other circumstances they impose incoherent requirements related to informed consent.

The aim of this article is to sort out these confusions and their implications and to offer instead a

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1. Madison Powers identifies this focus on protecting the vulnerable from exploitation in research as an antiliberal Marxist element. He sees it as “[t]he central thrust” in research policy (Powers 1998, 151–152).
straightforward framework for considering the ethical conduct of human subject research and an intelligible justification for informed consent. The demystified perspective that I put forward points to the need for re-prioritization of the ethical issues in human subject research and redirection of our efforts in research oversight. This paper is also intended as a challenge to several of the widely accepted principles for the ethical conduct of human subject research. Because these principles are interconnected and rely upon each other for their validity, discussing them singly would tend to obscure their broad implications and distort judgment on the entire mesh of prevailing rules. My position depends upon a presentation of the network of concepts all together.

This project is obviously complex. I have tried to present my criticisms clearly and to explain how they relate to each other. I beg the reader’s indulgence in having to follow many threads at once and in having to accept mere sketches of solutions instead of a full, detailed account. The research dogmas that I shall contest include: the primacy of informed consent, protection of the vulnerable, the substitution of beneficence for research’s social purpose, and the introduction of an untenable distinction between innovation and research. I begin this long agenda with a very brief review of history in order to explain how distortions entered research policy and how false steps at the beginning confounded the problem.

INFORMED CONSENT FOR RESEARCH

Informed consent has become ensconced as the cornerstone principle of research ethics (Emanuel, Wendler, and Grady, 2002). Yet, prior to World War II, biomedical researchers paid little attention to informed consent as an ethical standard for research with human subjects. According to Paul Appelbaum, Charles Lidz, and Alan Meisel, it wasn’t until the military judges for the trials of Nazi doctors at Nuremberg were outraged by revelations of experiments performed by doctors on human subjects that the concept was formally articulated. The Nuremberg judges asked their expert witnesses, including American physicians Andrew Ivy and Leo Alexander, “to articulate the universal standards of ethical research practices” (Appelbaum, Lidz, and Meisel 1987, 212). The experts produced three principles of research ethics which were endorsed by the American Medical Association. They were elaborated upon and modified by the Nuremberg tribunal into what became the Nuremberg Code. Principle 1 is at issue here. It declared that “[t]he voluntary consent of the person on whom the experiment is to be performed must be obtained.” Reflecting that priority, the elaborated version in the first section of the Nuremberg Code declares that the solution to every problem looks like another group that should be declared “vulnerable.”

6. There were a few notable exceptions: In 1900 Walter Reed obtained informed consent for his yellow fever experiments; 1900 regulations by the Prussian Ministry of Health required informed consent for nontherapeutic experiments; 1931 German regulations required informed consent for new therapy and experimentation. (cf. Jonsen 1998b)

7. Jonsen 1998b refers to 500 journal articles on research ethics written in the decade prior to 1963 (p. 7). Just what is being counted as a relevant paper or when they were published is not clear from Jonsen’s remarks. Nevertheless, it does seem clear that the subject had received little attention before 1960. My own MEDLINE/Pub Med search of English language articles revealed the following numbers of publications:


8. The other two principles are: “(2) The danger of each experiment must have been investigated previously by means of animal experimentation; and (3) The experiment must be performed under proper medical protection and management.” (Appelbaum et al. 1987, 212) These principles were significantly altered and expanded in the Nuremberg Code. The priority of principle 1 was preserved as The Code’s principle #1. A weaker version of principle 2 became The Code’s principle #3. Principle 3’s interest in expertise appears in The Code’s principle #8, but the original concern with oversight seems to disappear entirely.

2. Ezekiel J. Emanuel, D. Wendler, and C. Grady have similarly challenged the primacy of informed consent in current research policy, and they advocate for some of the changes in the research ethics framework that are similar to those that I recommend. Nevertheless, my route to these similar conclusions is significantly different.


4. In several different forums, I have heard speakers describe “research ethics as standing firmly upon two pillars, informed consent and IRB review,” or words to that effect.

5. In a similar vein, Trudo Lemmens asserts, “if you are a North American bioethicist, everything looks like a problem of informed consent.” (Lemmens 2001, 52) I would add that “if you are a North American bioethicist,”
The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent, should be so situated as to be able to exercise free power of choice without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to make an understanding and enlightened decision. [italics added] (Applebaum et al. 1987, 213–214)

This commitment to informed consent as an absolute and primary consideration for the moral acceptability of human subject research was preserved in the World Medical Association’s 1964 expanded statement of Principles for those in Research and Experimentation, the Declaration of Helsinki. For therapeutic clinical research, the Declaration of Helsinki requires that “If at all possible, consistent with patient psychology, the doctor should obtain the patient’s freely given consent after the patient has been given a full explanation.” And it imposes a more stringent requirement on non-therapeutic research, by insisting that “The nature, purpose and the risk of clinical research must be explained to the subject by the doctor,” and that “Clinical research on a human being cannot be undertaken without his free consent after he has been fully informed” [italics added] (Applebaum et al. 1987, 214).

In 1966, the United States Public Health Service, the parent body of the National Institutes of Health (NIH), issued a policy statement to cover all of their funded research programs. They required institutional and prospective assurance review of: (1) the rights and welfare of the individual or individuals involved, (2) the appropriateness of the methods used to secure informed consent, and (3) the risks and potential medical benefits of the investigation. According to Applebaum and colleagues, “[t]his was the first enforceable regulation of the research process, and a giant step beyond the previous NIH policy” that had allowed extramural researchers to be guided by their own professional judgment and controlled by their own ethical standards as well as those of their institutions (Applebaum et al. 1987, 216).

The 1981 Department of Health and Human Services (DHHS) regulations, now referred to as the Common Rule, evolved after the convening of a National Commission of physicians, scientists, theologians, and attorneys in 1974 and the publication of The Belmont Report in 1979. The Common Rule requires that a request for consent to research occur: only under circumstances that provide the prospective subject or the [legally authorized] representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. (Applebaum et al. 1987, 226).

Under the banner of informed consent, the DHHS has increasingly moved its regulatory attention in the direction of protecting human research subjects from coercive pressures or harms, particularly potential subjects who are perceived as especially vulnerable. Presumably, certain groups cannot be expected to understand or appreciate information about proposed research projects, and that makes them vulnerable to exploitation and abuse. OPRR, and the newly created OHRP have reaffirmed protectionist commitments. According to their policies, and those of Institutional Review Boards (IRBs) that introduce additional policies inspired by the regulations, vulnerable groups include: the mentally ill, the mentally handicapped, pregnant women, fetuses, products of in vitro fertilization, children, prisoners, the elderly, people who are in the midst of a medical emergency, and the educationally or economically disadvantaged. That’s a lot of people.

Although the regulations express legitimate concerns about the potential for harm, force, and deception, the efforts to protect the vulnerable are guided by a distorted view of the theoretical underpinnings of informed consent. Because of the underlying misunderstanding, the regulations and guidelines promulgated by OPRR and OHRP and the contortions imposed on researchers

9. Parents should certainly protect their children. But, consider the bicycle-riding policy that parents would adopt if they took protection to be their primary parental responsibility. Children would not be allowed to ride bicycles because it would subject them to risk of harm. Yet, parents who actually allow their children to ride are likely to consider the importance of protection along with the importance of other developmental goals such as: independence, risk management, social interaction, exploration. When a multiplicity of goals is accepted, protection is considered in the context of other critical objectives and other aims will sometimes be overriding.

10. Robert J. Levine takes a similar view of the history of research ethics. He too sees that beginning with a focus on Nazi atrocities has led to viewing research as dangerous and exploitive.

11. Even more vigorous efforts to protect vulnerable subjects of research are urged by non-governmental groups such as the Alliance for Human Research Protection (AHRP).
by well-intentioned IRBs, lead us off the path of ethically sensitive human subject research policy.

CONCEPTUAL CONCERNS

After the Nuremberg Code framers offered their insights on the ethical flaws of Nazi research and their guidance on how such heinous practices could be avoided, and after the 1963 revelation of investigators injecting uninformed elderly patients with live cancer cells at the Jewish Chronic Disease Hospital, and after Henry Beecher’s 1966 expose of questionable American research practices, and after the 1971 revelation of the Tuskegee syphilis study, and after the 1975 U.S. Army acknowledgment of experiments with hallucinogenic drugs on unaware civilians, and after the promulgation of the 1974 Department of Health, Education, and Welfare regulations and the implementation of IRB human subject research oversight, bioethicists began to offer their accounts of the moral foundation of informed consent in research. Their analyses reached the unanimous conclusion that the concept of autonomy explains the centrality of informed consent for the ethical practice of research, both in the history of U.S. and European regulations, in judicial decisions (Veatch 1987, 44), and in moral philosophy (e.g., Faden and Beauchamp 1986; Veatch 1987). It is not surprising that the justifications offered by discussants in legal decisions and in elaborations on regulations point to autonomy. Post World War II was the period of civil rights, women’s rights, and the Americans With Disabilities Act (ADA), all causes that properly champion individual self-determination. But the champions of informed consent for research and the protection of vulnerable subjects often misappropriate the concept of autonomy.

Two distinct points just happen to be historically connected in this issue. One concerns the misidentification of the problems in Nazi research. The other concerns the mishandling of the concept of autonomy in its application to human subject research.

Problems with Nazi Research

If the Nazi doctors’ only ethical failure in their treatment of human subjects involved lack of informed consent, their behavior would have been no worse than that of most of their fellow scientists around the world. Indeed, given the state of ethical insight into research standards in their time, failing to obtain informed consent was no failure at all. Other features of their actions, however, made their research practices monstrously horrific. One profound problem was that they inflicted risks and burdens on people, including pain, disability, death, losses of pleasure and freedom that no reasonable person would accept (Gert, Culver, and Clouser 1997). These practices violated the most basic principle of morality, do not treat another as you would not be treated. Another critical problem was that the Nazis devalued a portion of their population and treated them in a way that they recognized was grossly unacceptable for the rest. This was a violation of the principle of equality or fairness. Also, Nazi research, such as the altitude and hypothermia studies, sacrificed one group (concentration camp inmates) for the benefit of another (military personnel). These were violations of justice. Furthermore, many of the Nazi studies were poorly designed. Unless a study begins with an appropriate research question and unless the study design can answer that question, the use of resources is not justified. Without reasonable expectations that the study can produce knowledge, resources should not be spent, animals should not be sacrificed, and most certainly, humans should not be put at risk of harm.

In the context of constituting gross violations of the negative golden rule, serious inequality, egregious injustice, and worthless study designs, pointing at the failure to obtain informed consent as the ethical downfall of Nazi research seems to miss the target entirely. Whereas requiring researchers to pay attention to informed consent is certainly an important contribution to our evolving moral insight into the appropriate conduct of human subject research, miscasting informed consent as the crime of the Nazis gives it disproportionate weight. This

12. Again, Walter Reed was one of few notable exceptions who obtained informed consent from his research subjects. He also provided a $100 incentive for those enrolled in his yellow fever study and an additional $100 for those who contracted yellow fever as part of the study or a $200 benefit to a beneficiary in case of the subject’s death from yellow fever. Furthermore subjects would forfeit these benefits by leaving the camp during the study period. These considerable inducements and constraints would be considered unethical according to today’s reigning views of research ethics.

Thinking Clearly About Autonomy

Another serious blunder was made by starting with standards and then searching for a justification. History and political philosophy have taught us that it is very hard for politicians and jurists to achieve consensus on theoretical underpinnings, so they frequently skip that step and simply hammer out agreements where they can be achieved. This is not failure but political necessity. The error comes from trying to read a theory back into a political solution and then trying to extrapolate further from incoherent premises.

The concept of autonomy is a useful theoretical tool of moral philosophy, but it is crucial to recognize that the concept is used in a variety of applications with subtle but significantly different senses. In discussions of informed consent for research, “autonomy” is used in at least two distinct senses. When these uses are not acknowledged and distinguished, or when the differences are mistaken as alternative models of the same concept, discussions of informed consent for research are likely to reach muddled and absurd conclusions.

“Autonomy” is employed as a first-person concept, to refer to what Ruth Faden and Tom Beauchamp describe as “a lofty ideal.” In the first-person sense, the concept of autonomy expresses the core content of an individual’s moral obligation, the duty to determine one’s own actions by the moral law, the duty to be a good ruler over oneself. Autonomy, in this sense, is a lofty standard to aim for, the model an individual might strive to achieve in her own action and the criterion that she might use for the self-assessment of her own action. Autonomy in the first-person sense involves a person reflecting on the issues involved in a situation, considering her options in terms of her values and moral commitments, and making a choice that reflects her priorities and the ethical standards she embraces.

“Autonomy” is also used in a second-person sense to reflect the appropriate moral attitude towards others who are capable of autonomous action. In sum, we should respect the autonomy of others. This is a related but distinct concept. Respect for the autonomy of others requires us to presume that others are acting from the values and principles that they embrace and to leave them alone and allow them to live by their own lights. Moral theorists, such as Immanuel Kant and John Stuart Mill, instruct us on how we are to act towards others; we are to respect their choices. For Kant, the capacity for autonomous action marks persons as distinct from other beings. It gives them special status and puts their actions in the moral realm. Beings capable of autonomous action deserve the special attitude of respect, and their autonomous action has moral value.

According to my reading of Kant, we are required to presume that others are acting autonomously (unless we have compelling evidence to the contrary) and to allow them to make their own choices. In other words, respect for autonomy is the ethical default position that we are morally bound to take toward the action of others. For the most part, we cannot know whether some particular other is, in fact, trying to determine a particular choice by the moral law. Nevertheless, we should adopt the hypothetical attitude of assuming that the other is acting autonomously and then treat the person as if that were the case (Kent 1983).

Mill’s discussion of respect for autonomy occurs in his famous essay, On Liberty. There he is arguing to defend individual liberty against government intrusions. According to Mill’s “harm principle,” limitations on liberty are justified only by harm to others. Clearly, interference with the presumed autonomy of another marks a boundary for public policy. Mill’s commitment to safeguarding the scope of liberty and justifying infringements only in terms of the autonomy of others is compatible with Kant’s concept of respect for autonomy as an attitude that we should take towards the acts of others.

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13. E.g., the Universal Declaration of Human Rights, the recommendations of the National Bioethics Advisory Commission in the U.S.
14. There is a long philosophic tradition of discussing “autonomy” along these lines. It begins with Aristotle and the Stoics and continues prominently in Hobbes, Kant, Mill, Berlin. In contemporary literature the concept is commonly discussed in terms such as “higher-order desires,” “higher-order preferences,” or “reflective endorsement.” It is beyond the scope of this discussion to delve further into this rich and nuanced literature. Because Kant’s account is the most frequent point of reference for discussions of autonomy in the bioethics literature, I employ Kantian terms in my account.
CURRENT STANDARDS FOR INFORMED CONSENT IN RESEARCH

The first principle of The Belmont Report, “respect for persons,” requires informed consent out of an appreciation of autonomy. The Report goes on to invoke “respect for persons” and the concept of autonomy to limit the participation of “vulnerable” subjects in research. For example, using the Faden and Beauchamp formulation, we should restrict human subject research to those who (1) intentionally, (2) with understanding, and (3) without controlling influences agree to be subjects (Faden and Beauchamp 1986, 238). And, according to Robert Veatch, “we should not treat people as means without their consent” (Veatch 1987, 56). Pointing to autonomy, these standard accounts constrain the participation in research of classes of people who might, just possibly, have impaired autonomy. They place special limitations on the involvement of individuals who might lack the capacity to consent, except in very restricted cases when, according to Veatch, “the benefit could not possibly be gained by studies on consenting subjects” (Veatch 1987, 56). Kenneth Kipnis goes on to identify different types of vulnerability and the related considerations that might call for special paternalistic protections (Kipnis 2003). Such theorists classify groups as vulnerable and demand that they be protected from researchers.

Although the traditional account of respect for autonomy, what I described as the second-person sense of autonomy, requires people to presume that others can and do make autonomous choices for themselves, the literature on informed consent for research takes the opposite as the default position. It denies the presumption of autonomy to entire classes of individuals who might, possibly, be less than ideally autonomous. Current policies, reports, and guidelines presume that all of those who can be classified as “vulnerable” should be paternalistically protected from researchers irrespective of whether the individuals in those groups consider their participation as a net benefit, whether or not they want to be protected, and regardless of the fact that some, most, or, possibly all of the individuals in the so-called “vulnerable” group actually have the capacity to consent to research participation.

Classification of Research Subjects as Vulnerable

Some groups that are classified as “vulnerable” clearly lack decisional capacity. Research involving children, the profoundly retarded, the seriously mentally ill, the demented, and the unconscious clearly need special oversight. But protecting research subjects from other groups based on their classification as “vulnerable” does not show respect for their autonomy. It is actually a denigration of their autonomy. When policy protects the vulnerable the underlying presumption is that their ability to appreciate and assess risks is inadequate and that the judgment of benefits and burdens by others should override theirs. This is paternalism. It denies people the opportunity to evaluate the costs and benefits of research participation in light of their own priorities, their own goals, and their own values. Instead of trying to respect the autonomy of others by presuming that they are autonomous and trying to see their choices as reasonable from their perspective, classifying people as “vulnerable” denies them respect. The special outlandishness of this approach to groups designated as “vulnerable” becomes glaringly obvious when we stop to notice that pregnant women are presumed to have the capacity to make choices about child bearing, that the mentally ill are frequently allowed to make choices about their living arrangements, and that restrictions on the liberty of the elderly or the educationally or economically disadvantaged in any circumstances other than consent to research would be branded unacceptable discrimination. Although some who can be classified into these groups may lack decisional capacity, evaluation cannot be based on group membership. The determination must be predicated on a demonstration that the individual in question is not entitled to be presumed autonomous (Wikler 1978).

AUTONOMY-RELATED POLICY CONFUSIONS

Respect

One mistake introduced into research ethics policy seems to grow out of a confusion related to the moral requirement for respecting autonomy. It involves a misunderstanding of the Kantian injunction against treating persons as means. A careful reading of Kant’s rule against “using others as a means only” shows that it does permit furthering...
your purposes in your interaction with others so long as the using is also respectful of their autonomy. In other words, there is no moral problem in using the services of doctors, lawyers, teachers, or research subjects, so long as those persons are also treated with respect—that is, so long as they are allowed to determine their own participation in light of their own values and priorities.

**The Non-Autonomous**

Another mistake is the extension of autonomy-regarding moral constraints to the non-autonomous. Respect for autonomy is a rule that applies only to moral persons, beings who are capable of self-determination. Human beings who lack decisional capacity should be treated with beneficence, but respect for something that is absent makes no sense.\(^16\) The idea of respecting the autonomy of those who lack decisional capacity is incoherent. We can act with consideration of the future autonomy of those who may develop the capacity or have it restored (call this the third-person sense of autonomy). In such cases we could have an ethical obligation to promote and nurture future autonomy or to undertake action to regenerate the capacity. Such autonomy-regarding duties, however, are not acts of respect for autonomy. It would be more accurate to refer to them as autonomy-regarding paternalism. The relevant point is that when you limit the research participation of people who lack autonomy you are not protecting their autonomy and you are not respecting their autonomy.\(^17\) A different model is needed to describe the relevant ethical considerations for research with those who actually lack the capacity to consent.

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16. Wendler and Prasad (2001) discuss what they see as "a major failing of the current regulatory reliance on informed consent." They discuss six sets of guidelines that have been put forward to protect those who lack decisional capacity. As they see it, all of these guidelines advocate for making decisions on research participation that are "consistent with their [the subjects'] remaining preferences and interests." As I see it, except for subjects who previously explicitly expressed views on research participation, showing respect for "remaining preferences and interests" is incoherent because these inclinations do not flow from a self-legislating will.

17. A decision on grounds of restoring or promoting autonomy takes the possibility of future autonomy into account where that may be possible. Concern for future autonomy could be a ground for restricting research participation, but it is a very different ground.

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**Coercion**

Another autonomy-related problem with the standard approaches is an overstatement of the problem of coercion, or what The Belmont Report has termed "undue influences." In ordinary usage, "coercion" is an unjust threat of harm. Blackmail, intimidation, extortion, and torture all count as coercion. Discussions in the research ethics literature have stretched the term to include any persuasive experience, incentive, or promise of benefit (Macklin 1981). This exaggerated sense of "coercion" seems to have taken root in Hans Jonas’s widely read paper, "Philosophical Reflections on Experimenting with Human Subjects."\(^18\) In that piece Jonas decries every request for participation in research as coercion. According to him,

\[\text{[t]he mere issuing of the appeal, the calling for volunteers, with the moral and social pressures it inevitably generates, amounts even under the most meticulous rules of consent to a sort of conscripting. (Jonas 1969, 503)}\]

Jonas goes further to proclaim that the sick are to be considered the “least and last” (Jonas 1969, 505) conscriptable because a patient’s

physical state, psychic preoccupation, dependent relation to the doctor, the submissive attitude induced by treatment—everything connected with his condition and situation makes the sick person inherently less of a sovereign person than the healthy one. (Jonas 1969, 505)

Jonas’s denigration of patient autonomy (indeed the denial of autonomy to those outside the “noble” and “elite” society of scientists, the only individuals he values as capable of the “motivation, identification, understanding” necessary for making an uncoerced and informed choice about research participation) should be deeply offensive to anyone committed to equality and respect (Jonas 1969, 503). Instead, Jonas’s concept of “noblesse oblige” and his “descending order” framework, of using first “the most valuable and scarce” elements of society and using the most available and expendable elements last in human subject research, have been implicitly endorsed by the research ethics community (Jonas

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18. Jonas’s influence on contemporary research policy is acknowledged by Albert R. Jonsen. “The easy assumptions about social progress as a rationale to override human rights was thoroughly demolished (a famous essay by philosopher Hans Jonas contributed mightily to its fall)” (Jonsen, 1999b Sourcebook, 9).
1969, 504). Nevertheless, Jonas’s principles show profound disrespect for the moral fabric of most members of society by refusing to acknowledge their fundamental capacity to adopt goals and principles and to act from commitments and for reasons that are other-regarding. For Jonas and those who similarly disparage people outside the elite, the least valuable and most expendable elements of society must all be presumed to be selfish egoists who only pursue personal advantage and who are also profoundly gullible and manipulable. These presumptions are the antithesis of respect and they are deeply repugnant to people who are morally committed to regarding others as moral equals.

Although Jonas and those who accept and endorse his distinctions and criteria see any decision by the classes of people they count as “vulnerable” to be susceptible to coercion, their thinking opposes a long philosphic tradition that has recognized the complexity of human choice. Peoples’ decisions are commonly the conclusions of their consideration of a variety of factors. Our choices reflect the situations in which we find ourselves, the things we like and dislike, the things we consider important, the things we want to achieve or avoid. Long ago Aristotle offered the paradigmatic example of autonomous choice by describing the ship captain who tosses his goods overboard in a storm in order to save himself, his crew, and his ship. No one would imagine that the captain would choose to be in that situation, but given that he finds himself there, it is hard to see why anyone would deny that the captain is making a reasonable choice that reflects his own priorities. It is also hard to see why an analogy to the ship captain should not hold for the sick, the elderly, or the economically or educationally disadvantaged, and so it is hard to see why people in these groups should be discounted as “vulnerable” and be more limited in their choices about research participation than the non-vulnerable (Aristotle 1954).

Situations frequently induce us into choosing paths we would not otherwise choose, but there is nothing morally problematic about such decisions (Taylor 2003). Many of our everyday choices reflect the pressures of daily life—for example, skipping a meal because you are running late, choosing a moderately priced car over the better but pricier one because of limited funds, spending an hour of needed work time on the phone because a friend seems to need the attention. Neither strong emotions (e.g., the captain’s fear of death, his eagerness for financial reward, his devotion to his shipmates, his attachment to his ship) nor strong priorities (e.g., his ranking of self-preservation above other competing considerations) discredits the autonomy of a person’s choice.

Unjustified duress, however, is morally problematic and should not be part of research practice. No prospective research subjects should be threatened with punishment or withholding of treatment to which they would otherwise be entitled.

Research policy must recognize that not all influences are problematic and aim at distinguishing unacceptable coercion from acceptable inducements and influences that are, and must be, part of life. Certainly, people with serious disease and surrogates of individuals with serious disease face difficult choices. They are surely pained by the medical problems they confront and stressed by having to make difficult decisions in the face of uncertainty. But to deny them the presumption of autonomy and to use that as a justification for limiting or denying research participation is, just as clearly, a subversion of morality.

RETHINKING INFORMED CONSENT FOR RESEARCH

With a clarified understanding of these different senses of autonomy and how they relate to informed consent, we can consider how these concepts should inform research policies.

Civil rights, women’s rights, and the ADA all concern allowing individuals to make choices about their own lives in light of their own values. They involve creating a society in which individuals’ autonomy must be respected and barriers to their autonomous action must be removed. But policies that support civil rights, women’s rights, and the ADA are also constraints that we have imposed on ourselves as ideally self-determining beings who create the rules for our own action. And at any subsequent point in time, even when we don’t want to or would choose not to, we are morally constrained to conform our actions with the principles we had previously

19. “We have, or think we have, a more significant luxury, of living in a world understood as a community of moral equals; we want to believe that what people deserve or are owed is determined not by considerations of social position but, at the most basic levels of morality, from a position of equality.” (Williams 2002, 117).

20. The parameters of due and undue inducements is an important topic in research ethics. Saying more here would go beyond the scope of this paper.
autonomously endorsed. Similarly, with respect to human subject participation in biomedical research, we need to ask ourselves, as ideal legislators, what is the policy we should endorse?

Since World War II, we have witnessed a dramatic increase in biomedical knowledge and tremendous progress in creating effective treatments for disease. These are benefits that flow from human subject research. We are also aware that we stand on the brink of a cascade of insights into human genetics and the promise of spectacular related advances in biomedical technology. Furthermore, we would want medicine to be able to provide effective treatment when we or our loved ones should need it. Without human subject research, those treatments are less likely to be available. So, in light of our appreciation of human vulnerability to injury and disease and our appreciation of the value of clinical research, reasonable people should endorse policies that make research participation a social duty.21

In the same way that we have endorsed laws that require us to pay taxes and to serve on juries, reasonable people should accept an obligation to periodic service as research subjects. In an age when it is important to learn about the long-term effects of therapies and the unusual side-effects and complications that may not appear even in Stage-3 trials, and when population studies will be crucial for identifying the genetic component of disease and for improving the efficacy of medical therapy through pharmacogenetics, we need general cooperation in the project of advancing medical science. To withhold endorsement from such a policy would be taking advantage of the kindness of others—that is, being a free-rider on the system and failing to recognize the moral equality of others—hence, unreasonable. (Menzel 2002) In the sense that no reasonable person could withhold agreement without injustice, we should subscribe to a social contract for reasonable research participation when others are willing to commit themselves as well. Even though Jonas pointedly denies the force of such a social contract, the genealogy of developments in medical science makes a compelling case for a duty of research participation (Caplan 1984, 1992).

Certainly, a policy of required service as a research subject would have to be significantly different from plans for paying taxes or jury service. Unlike money, our bodies are not fungible. Some physical requirements will be crucial for some projects (e.g., subjects might be restricted to women, those with glaucoma, or a serious burn). Yet, because everyone suffering from disease or injury can be presumed to want to share in the benefits of medical science, and because no one can be certain about the specific nature of her own or her loved ones’ future medical needs, each should do her part in contributing to the advance of medical science that requires research with human subjects.22

Informed consent would certainly have an important role within such a framework for understanding the ethics of human subject research. Its role, however, would be markedly different from the place it has been given since Nuremberg. Rather than informed consent being the necessary tool for the protection of vulnerable subjects from Nazi-like researchers, in the model I suggest informed consent would have four different and distinct functions.

A NOVEL PROPOSAL

To allow you to vividly appreciate the role that I see for informed consent and the concept of autonomy in research regulation, I put forward a hypothetical policy suggestion on human subject research participation, a novel proposal.23 Imagine that after sharing information (e.g., about actual harms that have been suffered by research subjects since the institution of research regulations, advantages achieved through previous studies, options for improved research oversight, etc.), opportunity for discussion, and a period of lively free and open debate, a social consensus emerges, and with bi-partisan support

21. Gerald Dworkin might classify this account of hypothetical consent to a research participation policy as a “collective decision” justification for hard paternalism (Dworkin 1983).

22. In have presented this argument in the terms of contractarian constructivism that we find in Rawls (1993) and Scanlon (1998). I pointedly employ Rawlsian language and draw on his accounts of “rational” and “reasonable.”

23. This thought experiment is designed to illuminate responsibility for research participation. Issues related to the funding of research and research oversight, as well as the profits that we allow pharmaceutical companies to reap are acknowledged but bracketed. This “novel proposal” should be taken as a hypothetical construction for the sake of illustrating a point. An actual policy would have to take these and other important broad and detailed considerations into account. My novel proposal is far more modest.
our legislature passes a bill that requires every U.S. resident to perform some research service every ten years.24 25 According to the carefully crafted measure, while each of us would be required to serve as a subject in some research study, we would be left the freedom to choose the particular project for our service from among all of the projects listed on a national web-site for which we meet the selection criteria.26

In such a context, the research participation policy would embody our autonomous choice of a principle for ruling our own action in the first-person sense of autonomy. The policy’s allowance for individual decision-making would express the commitment to respect for autonomy in the second-person sense. In this context, informed consent would have to do new kinds of work.

First, informed consent would help to assure the trust and trustworthiness of biomedical research. In an informed consent environment, people would not volunteer to serve as research subjects or endorse and comply with a policy of required research participation unless they could trust biomedical research as an institution and the individual researchers who conducted studies under its auspices. Without subjects’ trust that studies would actually produce valuable information and trust that subjects were unlikely to be significantly harmed or to experience more burdens than they had been given to expect, the research enterprise could not go forward. Developing subject trust and assuring the trustworthiness of biomedical research practices is, therefore, essential for the practice of human subject research.

Medical science’s need for trust and medical researchers’ need for trust provides them with reasons for taking steps to assure the trustworthiness of their practice and to secure the trust of subjects (Rhodes and Strain 2000). For research to be trustworthy, medical science would have to take its fiduciary responsibility seriously and pay significant attention to research oversight (e.g., by IRBs). The commitment would allow subjects to be reasonably confident that studies would impose no unreasonable risks or burdens, that each research project was well designed, properly conducted, and could conceivably produce its promised results (Freedman, Fuks, and Weijer 1993; Fuchs and Westervelt 1996).

Second, we know that the same thing can look very different from different perspectives. From the point of view of a researcher, whose judgment may be colored by self-interest or theoretical commitment (Medawar 1983), or even a relatively objective review body, some risks and burdens could appear quite reasonable. But they might not appear quite so reasonable from the point of view of some potential subjects. Allowing subjects the option of choosing their participation with full disclosure, of at least the usual kinds of information required by current legislative guidelines, would allow their judgment to serve as a check on researcher bias.27

Third, informed and voluntary selection of projects by subject-participants would keep research design to an ethically reasonable standard because researchers would be reluctant to publicly describe procedures that they should not undertake. When subjects are kept in the dark and researchers can conceal the nature of what they are doing behind masks of deception and duplicity, some researchers, as if rendered invisible by the magical powers of the ring of Gyges, could be tempted to do things they otherwise would not. In the light of full disclosure, a well-nurtured sense of shame is likely to inhibit at least non-sociopaths who might be tempted to stretch moral limits. In other words, a publicity condition that makes research proposals transparent to the biomedical research community and to the larger public will inhibit researchers from proposing unreasonable study designs.

Fourth, informed consent in subjects’ selection of projects would be the principal mechanism for assuring respect for subject autonomy, in the second-person sense. It would allow individuals to fulfill their research obligations within a framework of recognition and respect for their other values, goals, and commitments. Family responsibilities, career agendas, personal projects, tastes, attitudes toward risk and pain, and an individual’s comprehensive

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24. Every ten years is just a guesstimate. The number would, of course, be subject to debate based on data about the need for research participation. The frequency of required participation could be more or less frequent.
25. Don Marquis alludes to “an ethics of conscription” in a paper where he wrestles with the incompatible commitments of treatment and research.
26. Surrogates would select the research participation service for those who lacked the capacity to make the selection for themselves (e.g., children, the profoundly retarded).
27. I intend my position to reflect a point that Jay Katz makes. He explains that a “thorough-going commitment to unequivical honesty in making disclosures to the subjects of research” should be coupled with “a willingness to abandon a contemplated research project if too many subjects do not volunteer after all alternatives, risks, and benefits have been explored with them” (Katz 1992, 257).
moral view make some particular project choices reasonable and acceptable to some and different ones reasonable and acceptable to others. For a person who has suffered from schizophrenia and found the burdens associated with current drug regimes very onerous, the risks associated with a drug-free wash out period for a trial of a new drug could be worth taking. For another with a family history of Alzheimer’s disease, the discomfort and inconvenience of a study that could advance the scientific understanding of that particular degenerative process could be worth taking. For someone else, it could be important to find a project that could be done from home or completed in a single day. For another, a study that involved the movement to parameters of acceptable research beyond those set by disinterested “protectors” of research subjects because individuals’ personal values and personal attitudes toward risk vary significantly. That’s precisely the point of respect for autonomy.

To some, a universal policy of required participation in some research project may appear to violate autonomy. But we must take care to avoid a superficial understanding of this complex concept. Protective thinking of the currently prevailing sort misses the point of autonomy as the rule-giving, self-legislating capacity to undertake responsibility and to create influences to control one’s own behavior. Every principle and every policy that a person endorses constrains her own future behavior. That’s what all laws do. Unless every principle, policy, and law violates autonomy, there is no special reason to actually expand the parameters of acceptable research beyond those set by disinterested “protectors” of research subjects because individuals’ personal values and personal attitudes toward risk vary significantly. That’s precisely the point of respect for autonomy.

When those engaged in research oversight in the name of autonomy take the stance of “protector,” they express a willingness to deny genuine respect for autonomy out of fear of possibly allowing someone to make a less than ideally autonomous choice. However, as Mill has taught us, respect for autonomy requires the opposite approach by recognizing the illegitimacy of limitations on personal choice out of concern for the personal safety of others. Yet, research subject protectors seek ever more demanding mechanisms of protection and search out more and more groups that may be less than ideally rational and, so, in need of their protection. I am arguing that these well-meaning efforts are misdirected and counter-productive in that many may do more harm than good in terms of safe-guarding personal autonomy and supporting autonomous choices.

Although my “novel proposal” of periodic required research service is contrived, it was only put forward as an example of how commitments to equality and the importance of research could be implemented. For the most part, people want biomedical science to pursue therapeutic advances, and they are prepared to do their fair share when others do so as well. And, just as other laws apply to those who cannot consent to them, there is no obvious reason why a research participation policy should be different. No groups should be exempt from research participation. People with all sorts of special needs have to be investigated so that researchers can learn about them and so that they, and others who are similarly situated, can benefit from advances in biomedical science. For these reasons, even those incapable of giving consent (e.g., children, the demented) should be considered legitimate research subjects. Modern medical technology carries potentially huge benefits, serious dangers, and immense costs. Wasting opportunities to gather evidence while subjecting people to avoidable hazards associated with unstudied “therapy” benefits no one and is, therefore, an immoral approach to research policy. Because those who cannot consent, as well as others who are classified in vulnerable groups, have been systematically excluded from full research participation, we have an underdeveloped understanding of their medical treatment.

The recent decision to exclude babies—who had a 75% chance of dying from their genetic disease, ornithine transcarbamylase (OTC)—from the University of Pennsylvania/Schering-Plough gene therapy trial and to use, instead, relatively healthy adult volunteers (including Jesse Gelsinger, age 18, now deceased) is a case in point. The researchers put aside the formerly accepted researcher ethic of beginning with those who had the most to gain and the least to lose, and according to a New York Times Magazine article, conformed with the advice of their bioethicist and Federal guidelines (Stolberg 1999). Those recommendations directed the researchers to protect the “vulnerable.” By viewing the situation from the perspective of avoiding participation of the non-autonomous in research with more than a minimal
risk (i.e., the babies) and by eschewing the consent of anyone who might be “coerced” by their situation (i.e., the babies’ parents), the researchers decided against beginning their trials with those who were very likely to die anyway. Instead they subjected relatively healthy people to significant risks for little gain. Whatever more may have been wrong with the execution of this gene therapy protocol, as I see it, the ethical reasoning that supported the design was seriously flawed.

**MEDICAL DECISIONS ON BEHALF OF CHILDREN AND OTHERS WHO LACK DECISIONAL CAPACITY**

Those who lack decisional capacity are like everyone else in sometimes needing medical treatment. Decision making for those who are incapable of making decisions for themselves is, therefore, a common feature of medical practice. Because we have a well-accepted model for surrogate treatment decisions, we can draw on the medical approach to guide research policy for those who lack decisional capacity.

Children, for example, lack the capacity to consent because they lack autonomy. Young children and even infants can express desires, but they lack the ability to conceive of their actions in terms of reasons or principles that they embrace. Older children and adolescents have the ability to make some decisions for themselves, but we do not generally ascribe autonomy to them because their practical reasoning is not fully developed and it deviates significantly from mature judgment. Adolescents are famous for their egocentricity. They also typically undervalue future consequences and overrate immediate consequences; they typically conceptualize situations in terms of good and evil rather than the subtleties and complexities that adults might see; they typically leap to conclusions that mature thinkers would slowly consider; they are typically influenced by peers more than adults are likely to be; and what they do frequently deviates from the conclusions of their own moral reasoning. For these reasons we do not, as a general rule, accept the decisions of children or adolescents about medical treatment or contracts of any sort.  

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28. There is considerable debate about the decisional capacity of mature minors with some taking the position that “those age 14 and older, may have as well developed decisional skills as adults for making informed health care decisions” (American Academy of Pediatrics, Committee on Bioethics, Informed Consent, Parental Permission, and Assent in Pediatric Practice, Pediatrics 1995. Feb; 95(2):314–17). Others, particularly specialists in brain development and developmental psychology, have taken the position that decisional skills are only a piece of maturity and that full mental maturity is not achieved until much later. I tend to side with the latter group.

29. Lainie Friedman Ross (2002) argues for the place of parents in making decisions on behalf of children who are minors.
cannot accept a surrogate’s personal reasons for refusing significantly beneficial treatment for a child.30 Besides those unusual cases, surrogates should be extended the presumption of reasonableness and allowed to make decisions that reflect their values and priorities without physicians delving into their priorities or evaluating their reasons.

**RESEARCH DECISIONS ON BEHALF OF CHILDREN AND OTHERS WHO LACK DECISIONAL CAPACITY**

In the medical treatment model, boundaries for surrogate decisions are (and should be) set by physicians. Clinicians comply with surrogate decisions that are not unreasonable, and because of their fiduciary responsibility to their patients, physicians prevent surrogates from making unreasonable significant decisions. There is no obvious reason to presume that a similar model should not be extended to surrogate decisions for research participation.

Unfortunately, in spite of its more nuanced discussion, *The Belmont Report* drew a sharp distinction between medical practice and research.31 Consequently, according to current interpretations, clinical interventions which are permissible as treatment are sometimes impermissible in the context of research on “vulnerable” subjects. Although justifiable medical innovations are based on an understanding of biomedical science and reflect a hypothesis as to why the novel treatment could be efficacious, *The Belmont Report* declares that, by contrast, “research” designates an activity designed . . . to develop or contribute to generalizable knowledge.” This sharp line continues to allow clinicians and surrogates license to offer patients who lack decisional capacity innovative treatments as they see fit, but research constraints sometimes prevent clinician-scientists from systematically gathering evidence at the same time (Rhodes 2003).

Modeling research policy on our approach to the treatment of patients who lack decisional capacity would allow for involving them in research.32 Just as doctors impose limitations on the decisions of surrogates, regulatory bodies and IRBs can exercise their fiduciary responsibility by imposing reasonable limitations on research participation. IRB members should decide on the ethical acceptability of a proposed study by engaging their moral imaginations to evaluate the risks and burdens of study participation relative to the background considerations of the subject’s condition and the available alternatives (Freedman et al. 1993). Once a study gains their approval, IRBs should provide potential research subjects or their surrogates with a report of the IRB’s assessment of the likelihood and seriousness of research-related risks so that their expert assessment can inform participation decisions.33

As a general rule, IRBs should prohibit everyone from participation in studies that are unreasonably risky or burdensome. So long as this gatekeeper function is seriously addressed, approved studies should involve only acceptable risks so that no subjects are exposed to excessive risks.34 If it would be acceptable for someone who has decisional capacity to participate in a study, it should also be reasonable for a surrogate to enroll a subject who lacks decisional capacity. If the risks and burdens make it unacceptable for someone who has decisional capacity to participate in a study, it should also be unacceptable for a surrogate to enroll a subject who lacks decisional capacity. As a general rule, if it would be acceptable for a capacitated patient to choose, or for a surrogate to authorize or forgo an innovative therapeutic intervention, then it should also be reasonable to enroll a subject who lacks decisional capacity.

30. In emergency situations (e.g., ruptured appendix) physicians override a surrogate’s unreasonable refusal of treatment. In nonemergency situations, the physician may not simply override a surrogate’s unreasonable refusal of treatment. Nevertheless, the physician has the responsibility of identifying a surrogate’s unreasonable treatment refusal and, when the refusal is likely to have a serious impact on well-being, to bring the matter before the courts.

31. Jonsen points out that “[f]rom Hippocrates’ time to the nineteenth century, experimentation was not clearly distinguished from practice.” (Jonsen 1998b, 5). Although the authors of *The Belmont Report* were specifically asked to draw a distinction between the two, the reason for marking the border is not clear. Perhaps those who made the request were following the 1964 Declaration of Helsinki which discusses the importance of allowing doctors to innovate (Principle II, 1) and distinguishes therapeutic from non-therapeutic research (Sections II & III).

32. Although policy separates the issues of research with children from issues of research with other subjects who lack decisional capacity, Brody suggests that these policies should be analogous (Brody 1998, 131).

33. This suggestion has been made in conversation by Daniel A. Moros.

34. Parents who allow their children to ride bicycles may impose limitations that reflect a concern about protection from excessive or likely risks. Parents may restrict riding to bike paths and require children to wear helmets. Similarly, IRBs can impose limits on research or prohibit studies that expose subjects to excessive or likely significant risks.
capacity in a trial of that therapy when research involves only reasonably small additional burdens.

**SOCIAL PURPOSE OR BENEFICENCE**

Another piece of the tangled theoretical foundations of research ethics involves the substitution of beneficence for the social purpose of research. The Nuremberg Code explicitly endorses the social purpose of human subject research. Principle 2 states that “[t]he experiment should be such as to yield fruitful results for the good of society. . . .” Nevertheless, The World Medical Association’s Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, a document written by physicians and for physicians, starts the shift away from that common sense understanding of research. Its introduction declares that “[t]he health of my patient will be my first consideration.” Then, Principle II, 3 maintains that “[i]n any medical study, every patient— including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method.” And, the concluding Principle III, 4 provides that “[i]n research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.”

Moving further away from the research commitment to a common good, The Belmont Report explicitly invokes Claude Bernard’s rejection of social benefit as a justification for human subject research and implicitly follows Hans Jonas’s disavowal of the social contract conceptualization of the biomedical research enterprise. By declaring beneficence as the second principle of research involving human subjects it, in affect, collapses the customary distinction between the goals of medicine and research. Whereas the distinctive feature of the ethics of medicine is physicians’ commitment to the primacy of each patient’s good, or beneficence, research is markedly different (Miller and Brody 2002).

It is not surprising that doctors who participate in clinical research should feel the tension between these two different agendas. A 35-year accumulated literature addresses this discomfort. What remains, however, is the incongruity between the aim of research, which is hypothesis testing, and the aim of medicine, which is the good of the patient. Although clinician-researchers engage in research in order to develop beneficial treatment, they undertake studies precisely because they do not know whether a theoretically promising intervention will be beneficial. A finding that an intervention actually does more good than harm can then be used to benefit patients later on. Nevertheless, the declaration of beneficence as a research aim is incompatible with clinical science and counterproductive.

It is important to recognize that The Belmont Report moves beyond the Declaration of Helsinki’s commitment to provide the “best” to the individual patient/subject and coins new responsibilities to maximization of possible benefits and minimization of possible harms. Although these commitments sound benign or even noble, they implicitly reject the social purpose of research.

It is also important to note that requirements imposed by The Belmont Report go far beyond even the responsibilities of clinical medicine. If keeping with a common reading of its principle of beneficence, research can be criticized for small risks of small harms or for failing to maximize benefits, even when there are only small differences between the benefits of maximal treatment and what the study offers, and even when those maximal benefits would not be otherwise provided. These concerns become especially inhibiting in research with children and other groups classified as “vulnerable” where the standard of acceptable risk is set by regulations. They lead to severe restrictions on non-therapeutic research (Brody 1998, 127) and on therapeutic research with “vulnerable” subjects. The commitment to beneficence supplements IRB protectionism and discourages researchers from studying groups and problems that raise red flags.


36. The 1947 Nuremberg Code does not endorse beneficence. The Nuremberg Code expresses concern for “the good of society” (#2) and “the humanitarian importance” of the research (#6) as well as concern for avoiding “unnecessary . . . suffering and injury” (#4) and protecting subjects “against even remote possibilities of injury, disability, or death” (#7).

37. If this principle of beneficence were applied to medical practice, blood and organ donation would be prohibited on grounds of causing harm without direct benefit to the donor. Furthermore, any physician who provided less than the maximal best treatment for patients, such as those who could not afford the very best or where resources (e.g., beds, equipment, medicine, time, energy) were scarce, would also be in violation of the principle. In other words, clinical medicine that is otherwise considered appropriate can frequently be taken to violate this understanding of the principle of beneficence.
Various study designs implicitly violate The Belmont Report’s sense of “beneficence.” Under a strict interpretation, non-therapeutic research that would subject participants to some small injury (e.g., a small biopsy scar) would not be acceptable because it inflicts harm. Therapeutic studies that would not be expected to offer any direct health benefit and studies that involved a placebo design (e.g., a cheaper treatment for athlete’s foot when an effective but costly one already exists) would violate the principle by failing to maximize benefits. These limitations interfere with the effective conduct of science, and they also frustrate broadly accepted legitimate research goals. Finding treatments that can be made widely available and finding reliable answers to research goals. Finding treatments that can be made widely available and finding reliable answers to research questions quickly can be good reasons for performing certain studies. A narrow, short-sighted view of “beneficence” may often be an inappropriate consideration.

CHILDREN

Out of concerns about informed consent, vulnerability, and beneficence, reigning policies restrict the participation of children in biomedical research. The most obvious consequence of these rules is that pediatricians are frequently left to treat children with no data to support the choice or dosage of prescribed medications. Medications’ dosage formulas are typically developed in studies of adult men. But children are significantly different from adult men, and a reduction in dosage that reflects only the difference in weight may ignore other significant differences between children and adults. Children are, typically, a lot more active than adult men. Their metabolism is different, their diet may be different. Adult bodies are fully developed, but the bodies of children are developing in ways that could be impacted by drugs more or less dramatically depending upon particular stages of child development. Because they are young, children can be expected to live with drug effects longer than adults will, and the long-term toxicity could be significantly different from a shorter effect.

Without information about the effect of a drug on each of these variables, pediatricians are left to develop their idiosyncratic accumulation of guesses and anecdotes. Pediatricians are unable to extrapolate from studies on capacitated similar subjects because there are none. This perpetuation of the status quo leaves each treated child to face otherwise avoidable dangers. It is hard to see how continually subjecting children to the risks of shooting in the dark can be a more ethical approach than developing evidence to guide clinical pediatric practice through research involving children (Kopelman 2000).38

RETHINKING RESEARCH ETHICS

Protective thinking of the currently prevailing sort misses the point of autonomy as the rule-giving, self-legislating capacity to undertake responsibility and to create influences that control one’s own behavior. In research, respect for another as an autonomous being requires allowing the other to make choices about research participation by assessing the personal and societal advantages and disadvantages according to her own priorities.

Lack of autonomy is an excellent reason for refusing to leave decisions about research participation with those who lack decisional capacity. It does not, however, justify a limitation on their research participation. The reason for limiting anyone’s participation in research should relate to the vulnerability that we all share. On the one hand, we are all vulnerable to the emotional effects of a serious illness. Frequently, our judgment and decisions are impacted by the pressures inherent in the situations that we confront. Nevertheless, to the extent that emotional impact allows subjects or surrogates to meet a threshold level of autonomy, they should be allowed to decide for themselves (Oshana 2003). Any sweeping move to limit or usurp self-determination in research decisions based on emotional vulnerability should be recognized as the unjustified paternalism that it is, and expunged from research ethics policies. On the other hand, we are all vulnerable to death, pain, and disability, to the loss of pleasure and freedom. If the likelihood of any of these is a credible consequence of a research study, and if the circumstances make it unreasonable to take the chance, the research community should prevent the study from going forward.

In other words, IRBs should change the focus of their study review from an attitude of protecting the vulnerable from Nazi-like researchers to assuring that the risks and burdens of research are reasonable, that the design is sound, and that the research is conducted with caring and respect: When that is done, a study conforms with the highest ethical standards. In that light, IRBs should examine protocols with an eye toward prohibiting those studies that would impose an unreasonable risk of significant harm and devote attention to oversight of ongoing studies. If

38 Similar arguments can be mounted about the importance of studying medical interventions in the elderly and pregnant women.
IRBs actually embraced these responsibilities, they would permit only research with reasonable risks and burdens to go forward and assure the ethical conduct of human subject research. This new approach should leave neither the decisionally competent nor the decisionally incompetent without protection: Everyone should be protected from unreasonable risks and burdens.39 The worry about accepting the consent of someone who was less than ideally autonomous should also be negligible because there should be no exposure to unreasonable risk.40

TWO CASES

Consider two cases that illustrate my concern about current restrictions on research with vulnerable subjects.

Case 1

John Kirk is a forty-five-year-old man who appeared disheveled and confused when he came to the Emergency Room complaining of chest pain. When he was told that he would be hospitalized for some tests, he became agitated. Saying that he would return the next day, he left the hospital against medical advice. Several days later, Mr. Kirk was brought back to the Emergency Room by his sister and niece. He was experiencing acute chest pain. When diagnostic tests were recommended, he again declared that he wanted to be left alone and that he would return tomorrow. His sister and niece explained that Mr. Kirk had a long history of mental illness, and that he would disappear from their home for weeks at a time to be found living in some shelter. The sister provided documentation showing that she was his legal guardian. Her authorization was accepted for diagnostic procedures. Mr. Kirk violently resisted attempts to perform the studies shouting, “Don’t touch me! Leave me alone! I’ll come back tomorrow.”

39. Limitations on research imposed on everyone by regulations and IRB decisions would protect individuals from unreasonable harms. This paternalism would not be justified by protecting those who lack decisional capacity (i.e., what has been called “soft paternalism”) but by the significant social benefit achieved by preserving the trustworthiness of biomedical science. In other words, this is an imposition on those who should be presumed to be autonomous, hence, “hard paternalism.”

40. The changes in IRB responsibility that I am suggesting would involve additional expertise, training, staffing, and monitoring to provide the appropriate level of review and oversight. The details of how these costs can be met goes beyond the scope of this discussion.

He was sedated for the studies, which revealed that Mr. Kirk had a thoracic aortic aneurysm requiring immediate surgical intervention because of imminent rupture. An open chest operation utilizing cardio-pulmonary bypass was the standard treatment. It would involve a large chest incision to perform the procedure, several days in the Intensive Care Unit (ICU), followed by an additional week or two in the hospital for recovery and rehabilitation.

The cardiac surgeons explained to Mr. Kirk’s sister that they were conducting a clinical trial using a stent to exclude the aneurysm by creating a new channel for blood flow inside the diseased vessel. Mr. Kirk’s condition made him eligible for the study. It involved a far less invasive surgical intervention, with no chest incision, only a day in the ICU, and less than a week of total hospitalization. Of the previous 67 patients who had been informed about the stent study option, 67 had chosen to participate in the clinical trial. To date, there had been no complications. The long-term outcomes of the study were still being evaluated and it was too soon to say whether stent placement or cardio-pulmonary bypass surgery was the better treatment for such aneurysms.

Mr. Kirk’s sister and niece both wanted him to be part of the study. Mr. Kirk kept shouting, “Leave me alone. Don’t touch me. I want to go home. I’ll come back tomorrow.” Because Mr. Kirk would not agree to the experimental procedure, institutional policy and State guidelines prevented him from participating in the study. The doctors and his sister had the authority to impose the far more invasive treatment that was less in keeping with his expressed preference to be left alone and less likely to be effective in his case because of the foreseeable difficulty in achieving his post-operative compliance with rehabilitative therapy. Yet, because Mr. Kirk was mentally ill and, therefore, classified as part of a vulnerable population, he could not be entered into the study when he did not assent. It was clear to everyone that he lacked decisional capacity. Nevertheless, his mere expression of refusal determined his research nonparticipation.

Any policy that leads to this conclusion does not show respect for autonomy; it shows profound confusion.

Case 2

Michael Collins is a fourteen-year-old boy who recently became lethargic and displayed some changes in his appearance, most particularly, droopy eyelids. Michael was somewhat depressed by the social
stigma associated with his altered appearance. Pediatric neurologists diagnosed his condition as myasthenia gravis. This degenerative neurological condition can have a variable course of progressive loss of muscle control. Adult disease is sometimes treated with thymectomy (i.e., surgical removal of the thymus gland) which seems to have no ill effects in adults and sometimes appears to arrest the progress of the symptoms, although the consensus literature reports little evidence of efficacy in adults (Jaretzki et al. 2002). The function of the thymus gland in myasthenia gravis is not well understood, but it is presumed to have a role in immune competence.

Early-onset disease is rare, particularly in boys. Michael’s neurologist and consulted specialists at other institutions speculate that thymectomy in adolescent early-onset cases could be curative. They recommend thymectomy. This is major surgery that will involve surgical risks and a long convalescence. Michael’s loving and attentive parents are very worried about their son. They are concerned about his long-term prognosis and all of its physical and psychosocial implications. They are also appropriately anxious about the risks and efficacy of the proposed surgery. They have reviewed the case reports that neurologists have shared, whatever additional material they could find in the medical library and on the Internet, and they have discussed the plan with the pediatric surgeon who is to perform the procedure. They find no adequate evidence to support a decision for or against the surgery. Ultimately, they decide to trust the neurologists and consent to the surgery. Michael raises no objections.

Michael’s parents, surgeon, and neurologist are free to proceed with thymectomy as treatment, but no study was discussed. Although research rules might allow for a study of this invasive innovative intervention because it offers a possible benefit to the child, no protocol was developed, no study was undertaken, and years later we will have no evidence to guide recommendations of future pediatric neurologists faced with patients who have problems like Michael’s (Jaretzki et al. 2000). There is no animal model of the disease and no supporting research evidence to show that this surgical intervention is likely to provide a benefit.

It seemed as if the physicians saw procurement of IRB approval of an invasive study on children without supporting evidence of benefit as an insurmountable hurdle. Yet without a rigorous multi-institutional study there is no way to answer the efficacy question. This is the case particularly because the number of affected children is small, the expected results would be neither immediate nor dramatic, and the surgery and medical follow-up are neither performed nor monitored in a way that allows adequate comparison of results. This case illustrates an important problem created by protectionist research policies: They have created an atmosphere that inhibits scientific study.

**IMPLICATIONS OF RETHINKING THE ETHICAL CONDUCT OF RESEARCH**

Policies and their associated sanctions and rewards should be designed to promote important goals. Current research policies are counter-productive because they tend to discourage studies that we need for guiding medical practice. In that respect, policies are ethically flawed. Whereas research policy preambles pay lip service to equality, respect, and the importance of studying children,41 the policy focus on protection and beneficence frequently impedes studies that could provide immediate benefit or evidence that could improve the medical treatment of patients later on.

Although individuals today may want to avoid serving as guinea pigs (just as they prefer to avoid jury duty and paying taxes), expanding the use of research would make study service part of the fabric of life. Because we need to learn about the long-term consequences of treatments, their side-effects and complications, we should strive to make research a common component of treatment instead of an unusual exception. This approach has led to amazing advances in pediatric oncology and it should become the reigning standard.

Society may not yet be ready to embrace my novel proposal for compulsory research participation. Yet, the perspective on research that I am urging has several obvious and not so obvious implications that should be given immediate attention. No doubt, most studies that would be prohibited under current policy would also be disallowed under the revised framework I propose. Yet, a model that discards the reigning dogmas and conducts human subject research with assurance of no more than reasonable risk and attention to oversight differs significantly from the current approach. This change

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in perspective should also promote a more just distribution of researcher attention. Some differences associated with forsaking the reigning policies are hard to foresee, others are already apparent. For example:

- Mr. Kirk’s (Case 1) refusal of assent would not have excluded him from research participation. To the extent that they can understand, patients and subjects who lack decisional capacity should be informed about what is being done to them and why in order to encourage their cooperation. If, however, they lack autonomy, their refusal of assent has no moral standing.
- Thymectomy for Michael (Case 2) would have been performed in the context of a study. Because no hard and fast line should be drawn between treatment and research, therapy should be accompanied with study whenever there is a need to learn more about the intervention.
- The classification of vulnerable groups that need special protections from exploitation would be replaced with the recognition that everyone should participate in the advance of biomedical science. When no one is allowed to be a free-rider, everyone becomes a stakeholder with an interest in appropriate standards for studies in which any individual might be called upon to participate.
- Surrogates would have greater authority for approving the participation of subjects who lack decisional capacity while IRBs would have greater responsibility for monitoring the conduct of studies with such subjects.
- Instead of taking incentives as coercive destruction of autonomy, incentives would be allowed to play a role in promoting cooperation and collaboration (Grady 2001; Lemmens and Elliott 1999; Savulescu 2001). Currently shunned incentives for completing studies would become acceptable motivation.
- When the focus on maximizing direct benefits to subjects is replaced with a reasonable balance of considerations in the context of treatment, efforts to develop affordable therapies will be allowed even when more effective but costly treatments exist.
- Study design would be chosen based on a reasonable evaluation of validity and efficiency on the one hand, and risks and harms on the other. So long as no serious or enduring harm could be expected by forgoing an existing therapy, studies that involved washout periods or placebos could be acceptable when well justified by design considerations. The surmise that placebo studies deny benefits to those in the inactive treatment arm would be replaced by an appreciation that those receiving placebos would share in the benefit of knowledge produced by the study while being subject to the least risk of harm if the active arm turned out to be counterproductive or ineffective. Placebo studies would be promoted for their assay sensitivity and efficacy in providing answers to study questions (Levine 2000, 2003; Levine, Carpenter, and Applebaum 2003; Miller and Brody 2002; Temple and Ellenberg 2000; Temple and Meyer 2003).
- Severe constraints on research in situations where it is impossible to obtain subject or surrogate consent would be replaced with a more reasonable approach. Currently, when it would not be feasible to obtain informed consent, studies are only allowed for interventions that might provide direct benefit in life-threatening conditions. Under the proposed framework, when obtaining informed consent is impossible, studies of non-life-threatening conditions and studies that involve no direct benefit but only reasonable risk would also be allowed (Biros 2003).

CONCLUSIONS

Each of us has a stake in the outcomes of biomedical research. This suggests that we should each contribute our fair share and endorse rules and procedures that allow the research agenda to move forward with safety, efficacy, and trust in the scientific community. We now need to face up to the flaws in research policy, use what we have learned about the ethical conduct of human subject research, and start over again to formulate reasonable research policies:

- We need to change our view of researchers and subjects. When we regard them as exploiters and exploited, dedicated scientists are demonized and courageous subjects are devalued. Instead, we should see both as cooperative partners engaged in and committed to socially important collaborative projects constrained within bounds of reasonable risk (Katz 1992).42
- We need to change the focus of IRB review from an attitude of protecting the vulnerable against

42. Jay Katz makes a similar point. He writes, “Whereas such a fundamental reorientation will create formidable problems, it will not destroy the research enterprise. . . . Research subjects will continue to participate in research but they will do so now in a true collaborative spirit” (Katz 1992, 258).
the exploitation of Nazi-like researchers to assuring that research is conducted according to the highest ethical standards. IRBs need to redefine their role and to appreciate their charge as protectors of the trust and trustworthiness of the biomedical research enterprise. This will require increased attention to the evaluation of the scientific merits and conduct of studies, the assessment of potential risks and burdens, and investment into oversight of ongoing projects.

- **No groups should be exempt from research participation.** People with all sorts of special needs have to be investigated so that they can benefit from advances in biomedical science. Even those incapable of giving consent should be considered legitimate research subjects because participation is the rule we should presume them to endorse if they had the requisite capacities.43

- **The judgment of individuals who lack decisional capacity cannot serve the oversight role.** New procedures will have to be developed for monitoring the conduct of research involving individuals who cannot consent for themselves in order to assess and assure the reasonableness of burdens and risks.

- **A health care system that accepts the social contribution of all research subjects without making the benefits available to all is grossly unjust.** The U.S. has tolerated a health care allocation system that leaves approximately 45,000,000 people without any form of medical insurance. Society has turned a blind eye and accepted a situation in which some poor people with chronic disease can only receive drugs by serving as research subjects in the development of treatments for the benefit of the insured (Kolata and Eichenwald 1999). Adopting a system of universal participation in biomedical research would make universal access to health care a conspicuous moral imperative and require research benefits to be distributed along with the burdens.

- **A variety of different reasons justify numerous limitations on research practices.** Research policy should reflect the range of broadly shared reasonable concerns. For example, health, life, and dis-

ability insurance for research participants should be a requisite feature of studies that involve hazards. Most subjects would want to minimize their risks and burdens by having insurance. Yet, unless regulations required it for everyone, it would be very difficult for any individual subject to negotiate that coverage. Providing a benefit that reasonable people would want is a good reason for making it a condition of hazardous research. Notice, however, that this is a “hard paternalism” justification of insurance for subjects, and not the “soft paternalism” justification that follows from declaring them “vulnerable” and denying them the presumption of autonomy. Another example is a limitation on inducements for prisoners. Because the criminal justice system involves meting out punishment (i.e., a morally precarious activity of deliberately inflicting harm, a violation of ordinary rules of morality that requires serious justification) it is important to protect the system from contamination by any outside influences and to safeguard it against avoidable conflicts of interest. Again, the justification does not rely upon any aspersion of prisoner decisional capacity.

Informed consent has been seen as the primary standard for the ethical conduct of research, and protecting groups branded “vulnerable” (e.g., children, the mentally ill, the elderly, prisoners) has been taken as the single easy answer to every vexing question about the proper conduct of human subject research. But different questions require different answers. There is no obvious reason to presume that informed consent is the primary consideration for the ethical conduct of research or that protecting groups classified as “vulnerable” provides the answer to every moral question concerning research.

Ethics is not simple. At this point in our evolving understanding of the moral requirements for the ethical conduct of research, it is crucial that we reexamine and reassess the reigning research dogmas of the primacy of informed consent, protection for the vulnerable, and beneficence constitutes self-righteous, but culpable, moral blindness. Cleaving to the old web of dogmas also subverts the moral standard that requires appropriate and weighty reasons as the justification for policy. Because the

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43. The tradition of contractarian theory, from Hobbes to Rawls and Scanlon, employs hypothetical models of agreement, and not actual consent, to deduce just principles for regulating society. For example, those behind Rawls’s veil of ignorance are hypothetical representatives of hypothetical persons or hypothetical representatives of hypothetical family lines. In this tradition it is legitimate to demonstrate that a principle is just without having actual consent.
unjustified inhibition of research, as well as the misconduct of research, are both ethical catastrophes, unjustified constraints imposed by misguided policy deserve attention as urgent matters of concern.

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The author declares that she has no competing financial interests.

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