

# Research with Decisionally Incapacitated Human Subjects: An Argument for a Systemic Approach to Risk-Benefit Assessment

CARL H. COLEMAN\*

*The amount of medical research with persons who lack decision-making capacity is rapidly increasing, but in most states it takes place without clear legal authority. In addition to creating significant liability risks for researchers and persons who provide consent on behalf of incapacitated subjects, the lack of explicit legal standards means that few, if any, safeguards exist to protect incapacitated persons' rights and welfare. Previous efforts to close the gap between clinical reality and legal requirements have failed in part because they have not provided a coherent or persuasive ethical justification for permitting this research. This Article seeks to fill that void by proposing a new way of thinking about the ethics of research with incapacitated persons, grounded in a long-term, systemic approach to risk-benefit assessment. This approach explains why it is ultimately in incapacitated persons' best interests to be governed by a policy that permits them to be enrolled in research without their personal authorization—even if such a policy puts them at risk of participating in studies that, when viewed in isolation, may involve more burdens than benefits. Unlike other approaches, the framework developed here does not depend on false analogies between participating in research and receiving medical treatment, or dubious claims about family members' inherent authority or incapacitated persons' obligations to society. Because the proposed framework directly responds to the criticism that research with incapacitated persons is a form of exploitation, it may increase the likelihood that proposals to authorize this research will actually be adopted. It also has important implications for both how laws governing research with incapacitated persons should be structured, and the roles and responsibilities of surrogate decision makers.*

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\* Professor of Law and Director, Health Law & Policy Program, Seton Hall Law School. B.S.F.S., Georgetown University; A.M., J.D., Harvard University. For helpful comments on drafts of this Article, I thank Martin Coleman, Gaia Bernstein, Kathleen Boozang, Rachel Godsil, Tristin Green, Edward Hartnett, Thomas Healy, Erik Lillquist, Solangel Maldonado, Michael Malinowski, Jon Romberg, and Charles Sullivan. For invaluable help with the research, I thank Ami Doshi and Brian Scibetta.

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## INTRODUCTION

Medical research with persons who lack decision-making capacity is in a state of crisis. More research involving persons with Alzheimer's, schizophrenia, and other capacity-impairing conditions is being conducted than ever before,<sup>1</sup> but in most states, it takes place without any clear regulation.<sup>2</sup> As a result, few, if any, safeguards exist to protect the rights and welfare of incapacitated research subjects, and surrogates who are asked to provide consent on behalf of incapacitated persons have no meaningful standards to help them determine whether they are making the right choice. Moreover, the lack of legal authorization for this research means that those responsible for the studies—both the researchers and the surrogates who provide consent—risk substantial liability when, as will inevitably occur, an incapacitated subject suffers injury and a lawsuit results.

In the late 1990s, a series of government commissions issued comprehensive proposals to correct the gulf between current practice and legal requirements,<sup>3</sup> but none of these proposals was adopted.<sup>4</sup> Some critics of the proposals reacted harshly to the idea of giving formal legal approval to research involving persons who are incapable of consenting; a few charged that such research was tantamount to the Nazis' experimentation on concentration camp prisoners.<sup>5</sup> At the same time, many researchers complained that the proposals were overly strict and would stifle scientific progress.<sup>6</sup> While a few states have since managed to achieve consensus on legislation authorizing surrogate consent to research, these states remain in the minority.

Federal regulators have now decided to reopen the discussion. The Department of Health and Human Services (DHHS) has sought comments on the necessity of developing new regulations governing research with incapacitated persons.<sup>7</sup> Its Secretary's Advisory Committee for Human Research Protections formed a subcommittee to develop recommendations on this category of research.<sup>8</sup> Legislation

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1. See *infra* text accompanying notes 29–30.

2. See Carol B. Stocking, Gavin W. Hougham, Aliza R. Baron, & Greg A. Sachs, *Are the Rules for Research with Subjects with Dementia Changing?* 61 *NEUROLOGY* 1649, 1651 (2003) (“[T]he process [of surrogate selection] appears to be unsystematic in most settings.”).

3. See *infra* Part II.B.

4. See *infra* note 85.

5. See *infra* text accompanying note 117.

6. See *infra* text accompanying note 118.

7. See Jeannie Baumann, *OHRP Asks for Comments on Protections for Decisionally Impaired Research Subjects*, 6 *MED. RES. L. & POL'Y REP.*, Sept. 19, 2007, at 482.

8. Jeannie Baumann, *Panel Leans Toward Guidance, Not Rules to Protect Decisionally Impaired Subjects*, 5 *MED. RES. L. & POL'Y REP.*, Nov. 15, 2006, at 733.

has also been proposed in the House of Representatives that would require DHHS “to promulgate rules to enhance protections for human subjects with diminished decisionmaking capacity.”<sup>9</sup>

Given the reactions to the previous commissions’ efforts, these new policy initiatives clearly face an uphill battle. To succeed, they will have to respond to two very different groups of critics: those who believe that using incapacitated persons as research subjects is inherently unethical, and those who believe that researchers should be allowed to do what they want without significant limitations. Responding to both groups will be impossible unless proposals to change the law are grounded in a more persuasive ethical framework than those that have been advanced so far—a framework that explains why a policy authorizing limited forms of research with incapacitated persons is ethically preferable to either an outright prohibition or a more *laissez-faire* approach.

The purpose of this Article is to provide such a framework. I begin by examining, and rejecting, the conventional ethical arguments. First, I look at the framework underlying the unsuccessful proposals of the federal, New York, and Maryland commissions. Those proposals suggested that public policies authorizing research with incapacitated persons could be justified by the same principles governing surrogate consent to medical treatment—promoting the incapacitated person’s wishes or best interests. This claim, I argue, ignores critical distinctions between consenting to research and consenting to medical care.

I then turn to several arguments raised in the academic literature. These include the claims that (1) in the absence of knowledge to the contrary, we can presume that incapacitated people would altruistically accept sacrifices for the benefit of other people; (2) communitarian values of family autonomy justify deference to family members’ decisions to permit research with their incapacitated relatives; and (3) incapacitated persons have an obligation to be research subjects as compensation for the care-giving benefits that society has provided them. I argue that each of these claims rests on either dubious empirical assumptions or ethical positions that are incompatible with the basic premises of a liberal society.

After rejecting these approaches, I then develop an alternative way of thinking about the ethics of public policies on research with incapacitated persons. The framework I propose is based on two seemingly incompatible propositions. The first is that participating in research often involves more burdens than benefits; this is one of the fundamental differences between being a research subject and being a patient. The second is that, despite the fact that participating in research is often undesirable, a *policy* permitting research with incapacitated persons may nonetheless be in such persons’ long-term best interests. The reason that it may be in their best interests is that such policies make it possible for scientists to conduct more types of research on capacity-impairing conditions than would otherwise be permissible. Incapacitated persons may receive substantial benefits from this additional research—not only from the studies in which they personally participate, but also from studies involving other incapacitated people that could not have been conducted unless the policy existed.

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9. Jeannie Baumann, *House Measure Would Apply Common Rule Consistently to All Human Subject Research*, 5 MED. RES. L. & POL’Y REP., Jun. 21, 2006, at 422.

These two propositions suggest the following standard for determining whether a policy permitting research with incapacitated persons is ethically acceptable: the risks incapacitated persons will face from the policy (i.e., the risk of being enrolled in burdensome research without their personal authorization) must be outweighed by the benefits they can expect from the additional research related to their conditions that the policy facilitates. In other words, at the level of public policy, the question is whether the balance of burdens and benefits is fair to incapacitated persons from a long-term, systemic perspective—not whether individuals will receive net benefits from each and every study in which they are personally enrolled.

This long-term, systemic approach to risk-benefit assessment is consistent with many of the specific policy recommendations proposed in the past. However, grounding those recommendations in a different ethical framework has important implications. First, on a practical level, it increases the likelihood that proposals to authorize research with incapacitated persons will actually be adopted. Unlike other approaches, the framework I develop does not claim that it is acceptable to impose burdens on incapacitated persons solely for the benefit of others in the future. Instead, it requires that any burdens placed upon incapacitated persons be outweighed by potential systemic benefits to *those same persons*. It therefore directly responds to the claim that permitting research with incapacitated persons is a form of exploitation, one of the primary arguments that has stymied previous reform efforts.

Second, the ethical framework developed in this Article explains why the handful of research consent statutes that currently exist, which authorize surrogate consent to research with few substantive limitations, are largely inadequate. While the framework I propose does not dispense with surrogates, it does not rely on surrogate consent as the primary justification for enrolling incapacitated persons in research. Instead, the acceptability of research with incapacitated persons depends more on the nature of the study—specifically, whether it fits within a policy that provides a net benefit to incapacitated people—than on the fact that a surrogate is willing to consent to it. By de-emphasizing the surrogate's moral authority, this approach underscores the importance of subjecting research with incapacitated persons to heightened regulatory oversight.

Third, grounding public policies in a long-term, systemic approach to risk-benefit assessment shows that, from an ethical perspective, limiting the risks faced by incapacitated persons participating in research addresses only half the picture. At least as important is facilitating incapacitated persons' abilities to reap the benefits of all research related to their conditions—including studies involving other incapacitated subjects. Thus, the framework demonstrates the necessity of linking policies on surrogate consent to research to measures to promote incapacitated persons' access to medical care—an issue not addressed by previous proposals.

Finally, the suggested approach has important implications for the process of surrogate decision making. Because it does not pretend that decisions to enroll an incapacitated person in research can usually be justified by the prospective subject's wishes or best interests, it avoids misleading surrogates into believing that consenting to research is no different from consenting to medical treatment. By making clear that the benefits to incapacitated people come from the overall *system* of research—rather than from participating in any particular study—it gives surrogates a more realistic understanding of what they are being asked to decide.

Part I of this Article provides general background on the concept of decision-making capacity and the types of research performed with incapacitated subjects. Part

II explores the current legal regime governing this research and describes the unsuccessful attempts by previous governmental commissions to change the law. Part III critiques the standard ethical arguments that have been offered to justify laws permitting research with incapacitated persons. Part IV proposes an alternative ethical framework grounded in a long-term, systemic risk-benefit analysis, and explains the implications of this framework for law and public policy.

## I. MEDICAL BACKGROUND

### *A. Mental Impairments and Decision-Making Capacity*

Numerous medical conditions can impair individuals' cognitive abilities. Some, such as mental retardation, affect people for their entire lives.<sup>10</sup> Others develop later in life, either suddenly (for example, a traumatic brain injury resulting from a car accident)<sup>11</sup> or gradually (for example, Alzheimer's disease).<sup>12</sup> Some conditions, such as persistent vegetative state, result in a permanent and total loss of ability to make any decisions.<sup>13</sup> Others, including many mental illnesses, wax and wane over a person's lifetime, sometimes causing profound impairment and other times having little or no impact on cognitive function.<sup>14</sup>

In the past, many persons with mental impairments were deemed legally "incompetent," a judgment that rendered them powerless to make virtually any important decisions on their own behalf.<sup>15</sup> Over the past several decades, however, the law has moved away from global determinations of "competence" and "incompetence" towards more nuanced judgments about an individual's capacity to make particular choices.<sup>16</sup> The contemporary approach to decision-making capacity is closely related to the doctrine of informed consent: a person has the capacity to make a decision when she can understand and appreciate the risks and benefits of the available options and use that information as the basis for making an informed choice.<sup>17</sup>

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10. See AMERICAN PSYCHIATRIC ASSOCIATION, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS 39–40 (4th ed. 1994).

11. See Eija Jumisko, Jan Lexell & Siv Söderberg, *The Meaning of Living with Traumatic Brain Injury in People with Moderate or Severe Traumatic Brain Injury*, J. NEUROSCIENCE NURSING, Feb. 2005 at 42.

12. See ALZHEIMER'S DISEASE EDUCATION AND REFERRAL (ADEAR) CENTER, ALZHEIMER'S DISEASE FACT SHEET (July 2006), available at <http://www.nia.nih.gov> (follow "Alzheimer's Disease Information" hyperlink; then follow "general information" hyperlink; then follow "AD Fact Sheet" hyperlink).

13. See AMERICAN ACADEMY OF NEUROLOGY, POSITION OF THE AMERICAN ACADEMY OF NEUROLOGY ON CERTAIN ASPECTS OF THE CARE AND MANAGEMENT OF THE PERSISTENT VEGETATIVE STATE PATIENT (1989).

14. See THOMAS GRISSO & PAUL S. APPELBAUM, ASSESSING COMPETENCE TO CONSENT TO TREATMENT: A GUIDE FOR PHYSICIANS AND OTHER HEALTH PROFESSIONALS 1637 (1998).

15. See Lawrence A. Frolik, *Plenary Guardianship: An Analysis, a Critique and a Proposal for Reform*, 23 ARIZ. L. REV. 599, 601 (1981).

16. JESSICA W. BERG, PAUL S. APPELBAUM, LISA S. PARKER & CHARLES W. LIDZ, INFORMED CONSENT: LEGAL THEORY AND CLINICAL PRACTICE 96 (2d ed. 2001).

17. See, e.g., *In re Farrell*, 529 A.2d 404, 413 n.7 (N.J. 1987) ("A competent patient has a clear understanding of the nature of his or her illness and prognosis, and of the risks and benefits

This “decision-specific” approach to capacity means that it is possible for a person to have the capacity to make some choices but not others. For example, a person in the early stages of dementia may have the capacity to provide informed consent to participate in a focus group discussion about her daily activities, but she may lack the capacity to give informed consent to a more complicated placebo-controlled study of an investigational drug. Similarly, a person’s capacity to make particular decisions may fluctuate over time, even over the course of a single day, depending on her ability to understand and process information.<sup>18</sup> The relationship between capacity and understanding also means that persons who initially appear to lack decision-making capacity can sometimes be rendered capable through education. In one study of cognitively impaired patients with schizophrenia, for example, the patients initially scored lower than a control group on a test of decisional capacity, but after an educational intervention, the difference between the two groups virtually disappeared.<sup>19</sup>

In some cases, determining that an individual lacks decision-making capacity is simple and uncontroversial. For example, no one would dispute that a comatose patient lacks the capacity to make any decisions. In less straightforward situations, however, capacity determinations raise a host of vexing dilemmas. At bottom, the concept of decision-making capacity raises a basic epistemological question about the possibility of truly knowing what is going on inside another person’s head. Although this question is not unique to capacity determinations,<sup>20</sup> it is especially salient in this context, given that the entire process rests on judgments about the quality of other people’s thought processes. When definitive judgments are impossible, we must determine how much evidence of understanding should be required before a person is considered to lack the capacity to make a particular decision.

Underlying this determination are value judgments about the relative importance of autonomy and protection. A low threshold for determining capacity—under which individuals would be free to make any decision, no matter how risky, unless it is manifestly clear that they lack even a rudimentary understanding of the consequences—promotes the value of autonomy at the potential expense of individuals’ welfare. Setting the threshold for capacity high raises the opposite problem, as it paternalistically limits individuals’ abilities to decide which risks they want to assume.<sup>21</sup>

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of the proposed treatment, and has the capacity to reason and make judgments about that information.”).

18. See Paul S. Appelbaum & Loren H. Roth, *Clinical Issues in the Assessment of Competency*, 138 AM. J. PSYCHIATRY 1462, 1465 (1981).

19. See Joan Stephenson, *Probing Informed Consent in Schizophrenia Research*, 281 J. AM. MED. ASS’N 2273 (1999).

20. For example, it also arises when juries are asked to determine whether a witness is credible.

21. As Allen Buchanan and Dan Brock explain:

In the conflict between the values of self-determination and patient well-being, a tradeoff between avoiding two kinds of errors should be sought. The first error is that of failing to protect a person from the harmful consequences of his or her decision when the decision is the result of serious defects in the capacity to decide. The second error is failing to permit someone to make a decision and turning the decision over to another, when the patient is able to make the decision him- or herself. With a stricter or higher standard for competence, more people will be

Further complicating these questions is the fact that, even when mental impairments do not affect individuals' abilities to understand and process information, they can profoundly alter a person's emotions and attitudes, leading to choices that "are so different that we might ask whether [a person's] decisions are truly his."<sup>22</sup> For example, a severely depressed person may fully understand the risks associated with a nontherapeutic experiment, but she may not care about the dangers because she no longer places any value on being alive.

In light of this possibility, some scholars have argued that, in addition to assessing a person's ability to understand information, it also is important to ask whether her decisions are "stable over time and consistent with her values and goals."<sup>23</sup> Yet, while there may be good reasons to question a person's decisions when they are wildly out of character, part of being autonomous is having the right to change one's mind. The challenge is distinguishing between situations where a person's judgment is clouded to the point that she is no longer acting "authentically,"<sup>24</sup> and other situations where her behavior has changed so radically that she is essentially a different person.

In practice, these questions are usually dealt with through a sliding-scale approach to capacity determinations. Thus, if an individual is making a decision that appears to be consistent with her best interests, little evidence of her ability to appreciate the risks, benefits, and alternatives will be required. However, if her decision appears to be objectively unreasonable—for example, if she is refusing a minimally risky life-saving intervention—her capacity is likely to be called into question.<sup>25</sup>

In part, this approach can be explained on efficiency grounds: if someone is making a clearly reasonable decision, it will make little difference whether she actually has decision-making capacity, since if it is determined that she lacks capacity and a surrogate decision maker is appointed, the surrogate will almost certainly go along with the clearly reasonable choice.<sup>26</sup> At the same time, the approach reveals that capacity determinations, in practice, are more about protecting people from harm than promoting their autonomy. Allen Buchanan and Dan Brock, two of the leading

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found incompetent, and the first error will be minimized at the cost of increasing the second sort of error. With a looser or more minimal standard for competence, fewer persons will be found incompetent, and the second sort of error is more likely to be minimized at the cost of increasing the first.

Allen Buchanan & Dan W. Brock, *Deciding for Others*, 64 MILBANK Q. 17, 30–31 (1986).

22. Carl Elliott, *Caring About Risks: Are Severely Depressed Patients Competent to Consent to Research?*, 54 ARCHIVES GEN. PSYCHIATRY 113, 115 (1997); see also Marsha Garrison, *The Empire of Illness: Competence and Coercion in Health-Care Decision Making*, 49 WM. & MARY L. REV. 781, 829 (2007) ("[I]t seems likely that depression acts as a coercive influence that interferes with the patient's capacity to recognize her genuine treatment preferences.").

23. Bernard Lo, *Assessing Decision-Making Capacity*, 18 L. MED. & HEALTH CARE 193, 195 (1990); see also 1 PRESIDENT'S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS IN MEDICINE AND BIOMEDICAL AND BEHAVIORAL RESEARCH, MAKING HEALTH CARE DECISIONS: THE ETHICAL AND LEGAL IMPLICATIONS OF INFORMED CONSENT IN THE PATIENT-PRACTITIONER RELATIONSHIP 171 (1982) (emphasizing the importance of "consistency between the person's choice and that individual's underlying values").

24. Elliott, *supra* note 22.

25. See Buchanan & Brock, *supra* note 21, at 30–31.

26. Indeed, the surrogate may be legally required to do this. See *infra* text accompanying notes 141–146.

theorists in this area, defend the sliding-scale approach on just this basis: “[A] finding of incompetence is more likely in precisely those instances in which the case for paternalism is strongest—cases in which great harm can be easily avoided by taking the decision out of the individual’s hands.”<sup>27</sup>

The purpose of this Article is not to determine whether the concept of decision-making capacity is coherent or justifiable. For present purposes, it is sufficient to note that, under the prevailing approach to capacity determinations, at least some persons with mental impairments will be deemed to lack the capacity to provide informed consent to at least some types of research. Moreover, the fact that, in practice, capacity is most likely to be called into question when individuals are making decisions that do not appear to be consistent with their objective best interests suggests that questions about capacity are likely to arise frequently in research. To understand why this is the case, it is necessary to explore the risks and benefits of being a research subject, which is the focus of the next section of this Article.

### *B. Types of Research with Decisionally Impaired Subjects*

Persons with mental impairments are used as subjects in many types of medical research.<sup>28</sup> For example, in 2005, Alzheimer’s patients were recruited to participate in 100 different clinical trials, representing a “significant growth in clinical testing of new approaches to treatment, prevention and diagnosis” of the disease.<sup>29</sup> In addition, since the 1990s, large-scale clinical research on schizophrenia, depression, and other mental illnesses has burgeoned, leading to the development of new classes of drugs that “have proved to be impressive moneymakers for the pharmaceutical industry.”<sup>30</sup>

This Part divides medical research with mentally impaired persons into two general categories—studies involving a prospect of a direct benefit to the subjects (“direct-benefit studies”), and studies in which no direct benefits to subjects are expected (“no-direct-benefit studies”). The studies described in this Part are offered as examples because they all involve conditions that can impair decision-making capacity. It is not possible to tell from the published reports of these studies whether all of the subjects were in fact decisionally incapacitated. In some of the studies, such as those involving moderate depression, it is likely that many of the subjects had the capacity to make their own decisions about whether to participate. However, in other studies, such as those involving severe Alzheimer’s, it is reasonable to assume that none of the subjects had the capacity to consent on their own behalf.

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27. Buchanan & Brock, *supra* note 21, at 40.

28. This Article focuses on studies involving drugs, medical devices, and other medical procedures, because those are the studies where the potential for harm is the greatest. Examples of other types of research that might involve incapacitated subjects include observational studies in which no interventions are provided, and studies in which the sole interventions consist of interviews or questionnaires.

29. ALZHEIMER’S ASSOCIATION, 2006: THE YEAR IN ALZHEIMER SCIENCE, [http://www.alz.org/alzheimers\\_disease\\_research\\_ad.asp](http://www.alz.org/alzheimers_disease_research_ad.asp).

30. Erica Goode, *Leading Drugs for Psychosis Come Under New Scrutiny*, N.Y. TIMES, May 20, 2003, at A1.



## 1. “Direct-Benefit” Studies

The first category of research involves studies in which subjects are given potentially therapeutic medical interventions. Examples include clinical trials of new drugs after early-phase safety testing has already been completed, or studies comparing two treatments already used in clinical practice to see whether one of them is superior to the other.

Subjects in these studies may receive direct medical benefits as a result of their participation. For example, in one study, investigators sought to evaluate the use of memantine in patients with moderate-to-severe Alzheimer’s, a condition for which few treatment options currently exist.<sup>31</sup> Subjects in the study were randomly assigned to receive either memantine or a placebo. The researchers found that the subjects receiving the memantine showed significantly less clinical deterioration than those receiving the placebo.<sup>32</sup> For those subjects, enrolling in the study appears to have provided a direct medical benefit—a reduction in symptoms that had not previously been achievable.

However, while subjects may receive therapeutic benefits from participating in these types of studies, it is important to remember that providing direct benefits to subjects is not the *purpose* of the research. Instead, as with all research, the primary goal is to develop generalized knowledge that may ultimately translate into beneficial treatments for patients in the future.<sup>33</sup> In order to make the results of a study generalizable, researchers rely on a variety of methodological features that can create risks that do not exist when a person receives individualized medical treatment outside of a study.<sup>34</sup>

For example, research protocols typically specify the precise dosages and timing of drugs and other interventions; deviations to accommodate the idiosyncratic needs of individual subjects are usually not allowed.<sup>35</sup> Research subjects also may be required to do a variety of things that are not necessary for their own health care, but that are helpful to the scientific project. Many of these things involve only minimal burdens, such as staying in the hospital longer for observation or having blood drawn more frequently. Others, however, can be much more significant. For example, subjects may have to undergo invasive diagnostic procedures, including lumbar punctures (spinal taps)—a procedure that, while usually safe, is known to carry a risk of “serious neurological sequelae.”<sup>36</sup> Some studies also involve periods of medication “washouts,”

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31. Barry Reisberg, Rachele Doody, Albrecht Stöffler, Frederick Schmitt, Steven Ferris & Hans Jörg Möbius, *Memantine in Moderate-to-Severe Alzheimer’s Disease*, 348 *NEW ENG. J. MED.* 1333 (2003).

32. *See id.*

33. 45 C.F.R. § 46.102(d) (2008) (defining “research” as a “systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge”).

34. *See generally* Carl H. Coleman, *Duties to Subjects in Clinical Research*, 58 *VAND. L. REV.* 387, 396–402 (2005).

35. E. Haavi Morreim, *Litigation in Clinical Research: Malpractice Doctrine Versus Research Realities*, 32 *J.L. MED. & ETHICS* 474, 475 (2004).

36. A. Strachan & J. Train, Letter to the Editor, *Lumbar Puncture and Headache: Aspirating Cerebrospinal Fluid Speeds Up Procedure*, 316 *BRIT. MED. J.* 1015, 1018 (1998).

in which subjects' regular medications are replaced with placebos, to ensure that subjects' reactions during the study are not being caused by their previous medications.<sup>37</sup>

The process of randomization, in which subjects are randomly assigned to receive either the investigational intervention, standard treatment, or, in some cases, a placebo, also can pose risks to research subjects. Subjects randomized into a placebo control group forego all possibility of benefiting from the experimental intervention,<sup>38</sup> but they will nonetheless be exposed to the risks associated with the nontherapeutic aspects of the study. Subjects assigned to an active arm of the study do not face this problem, but they still forego the benefit of individualized diagnosis and treatment.

It is sometimes argued that randomization cannot harm subjects because clinical trials are conducted only in the face of "clinical equipoise"—that is, when there is "an honest, professional disagreement among expert clinicians" about the relative merits of the investigational intervention and the available alternatives.<sup>39</sup> However, equipoise assessments are based on the expected benefits and burdens of the interventions for the

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37. See generally CARL H. COLEMAN, JERRY A. MENIKOFF, JESSE A. GOLDNER & NANCY NEVELOFF DUBLER, *THE ETHICS AND REGULATION OF RESEARCH WITH HUMAN SUBJECTS* 271 (2005). Not all medication washouts are nontherapeutic. In one study conducted at UCLA, researchers sought to identify factors that could help doctors determine which schizophrenic patients could safely be taken off their medications without experiencing relapses. Subjects were given medications for one year, following which they were either continued on their medications or given a placebo. The study generated controversy when one subject in the placebo group relapsed and committed suicide. Yet, while there were problems with the way in which the study was conducted, it would not be accurate to characterize the study as nontherapeutic. Subjects who were able to go off their medications without negative consequences were freed of an unnecessary medication that can have intolerable side effects—a clear benefit in the view of both schizophrenic patients and physicians. Indeed, the point of the study was to determine whether medication washouts could be offered to some categories of patients as a standard treatment. The study was therefore different from those in which taking subjects off their medications is not expected to have any therapeutic benefit. *Id.* at 271–78.

38. Sometimes, however, studies are designed so that subjects who initially receive the placebo will receive the experimental intervention later in the trial. See, e.g., Sarah A. Eagger, R. Levy & Barbara J. Sahakian, *Tacrine in Alzheimer's Disease*, 337 LANCET 989 (1991). In other cases, subjects in the placebo group are given the option of receiving the experimental intervention after the study is over, assuming the experimental intervention is shown to be effective. See, e.g., Martin R. Farlow, *NMDA Receptor Antagonists: A New Therapeutic Approach for Alzheimer's Disease*, GERIATRICS, June 2004, at 22.

39. Benjamin Freedman, *Equipoise and the Ethics of Clinical Research*, 317 NEW ENG. J. MED. 141, 144 (1987). The principle of clinical equipoise, if applied strictly, means that "placebo-controlled trials are appropriate only when no effective treatment exists for a particular condition, or when the treatments that exist are inadequate for a particular subset of patients." COLEMAN ET AL., *supra* note 37, at 262. However, the World Medical Association has determined that placebo-controlled trials can be acceptable "even if proven therapy is available," if there are "compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a proposed prophylactic, diagnostic or therapeutic method," or if the study involves "a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm." WORLD MEDICAL ASSOCIATION, NOTE OF CLARIFICATION ON PARAGRAPH 29 OF THE WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI (2002).

overall patient population. Even when equipoise exists on a population level, particular individuals may have unique characteristics or preferences that would make a particular arm of the study a better option for them.<sup>40</sup>

In addition, it is important to remember that clinical trials are conducted because it is unknown whether the investigational intervention is safe and effective. If it were clear that the investigational intervention worked, there would be no point in conducting the study. In a state of clinical equipoise, an investigational intervention may prove to be superior, equal to, or even worse than existing alternatives.<sup>41</sup> For example, in one recent study, nursing home residents who had been diagnosed with both Alzheimer's and psychosis were randomly assigned to receive either risperidone or a placebo.<sup>42</sup> The study was conducted because previous reports had suggested that risperidone might be effective in treating Alzheimer's-related psychosis. Ultimately, the researchers found no statistically significant differences between the risperidone and placebo groups in the study's primary outcome measures, but the risperidone group experienced a significantly higher rate of adverse events. Indeed, outside the area of mental impairments, there are numerous examples of much-hyped interventions that were shown to be ineffective or harmful in controlled clinical trials, including high-dose chemotherapy combined with bone marrow transplantation for breast cancer,<sup>43</sup> arthroscopic surgery for osteoarthritis of the knee,<sup>44</sup> and fetal tissue transplantation for Parkinson's patients.<sup>45</sup>

For some people, the risks of exposure to an unproven intervention may be offset by the potential benefits that the intervention offers, especially if there are no good standard treatments available. In many cases, however, enrolling in research is not the only way to obtain the potential direct benefits associated with an investigational drug or procedure. In general, physicians are free to offer investigational interventions to their patients outside of a research study, provided they have a reasonable basis for believing that the intervention will help the patient.<sup>46</sup> The one exception relates to treatments that require approval from the Food and Drug Administration (FDA)—that

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40. See Coleman, *supra* note 34, at 397–98.

41. See Lester M. Crawford, Acting Commissioner of the FDA, Speech before the Mayo Alliance for Clinical Trials Conference (August 26, 2004), available at <http://www.fda.gov/oc/speeches/2004/mayo0826.html> (“We’re currently seeing a 50 percent failure rate among products in late-stage Phase 3 trials. 50 percent!”).

42. Jacobo Mintzer, Andrew Greenspan, Ivo Caers, Ilse Van Hove, Stuart Kushner, Myron Weiner, Georges Gharabawi & Lon S. Schneider, *Risperidone in the Treatment of Psychosis of Alzheimer Disease: Results from a Prospective Clinical Trial*, 14 AM. J. GERIATRIC PSYCHIATRY 280, 280 (2006).

43. Jonas Bergh, Commentary, *Where Next with Stem-Cell-Supported High-Dose Therapy for Breast Cancer?*, 355 LANCET 944 (2000).

44. See J. Bruce Moseley, Kimberly O’Malley, Nancy J. Petersen, Terri J. Menke, Baruch A. Brody, David H. Kuykendall, John C. Hollingsworth, Carol M. Ashton & Nelda P. Wray, *A Controlled Trial of Arthroscopic Surgery for Osteoarthritis of the Knee*, 347 NEW ENG. J. MED. 81 (2002).

45. See Gina Kolata, *Parkinson’s Research Is Set Back by Failure of Fetal Cell Implants*, N.Y. TIMES, March 8, 2001, at A1.

46. See Jerry Menikoff, *The Hidden Alternative: Getting Investigational Treatments Off-Study*, 361 LANCET 63, 63 (2003).

is, drugs, certain medical devices, and biologics (such as vaccines).<sup>47</sup> As long as the FDA has approved the use of the product for at least one purpose, physicians are free to prescribe it to their patients for any other indication, assuming they have a reasonable medical basis for doing so.<sup>48</sup> However, if the product has not been approved for any purpose—for example, a new drug being tested in order to provide data for a future approval application—physicians cannot prescribe it outside of a clinical trial unless they get special approval from the FDA. Such approvals (commonly known as “compassionate use” exemptions) are generally limited to drugs intended to treat “serious and life-threatening illnesses for which there are no satisfactory alternative treatments.”<sup>49</sup>

Yet studies involving unapproved drugs for which no compassionate use exemption is available represent only a small fraction of human subject research currently being conducted. As Jerry Menikoff points out, “[h]undreds, if not thousands of research studies” involve investigational treatments that are “available not only in a randomised research trial, but also as a treatment provided directly by a patient’s doctor, independent of a research study.”<sup>50</sup> In these situations, persons interested in receiving the experimental intervention could do so in the context of an individualized physician-patient relationship, without assuming the inherent risks that being a research subject entails.

## 2. “No-Direct-Benefit” Studies

In contrast to the studies described above, other types of research involve no potential direct benefits to the subjects. In these studies, the sole goal is to develop knowledge that may lead to improved treatments for future patients. Studies that fall into this category include early-phase drug studies designed to learn how a drug is metabolized or to identify side effects as well as basic physiological research about the mechanisms of disease.

One type of no-direct-benefit research is the so-called “challenge study,” in which researchers expose the subjects to symptom-provoking stimuli in order to evaluate the subjects’ responses in a controlled clinical environment. In one study, for example, researchers administered amphetamines to a small group of schizophrenic subjects and

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47. See generally Patricia C. Kuszler, *Financing Clinical Research and Experimental Therapies: Payment Due, but from Whom?*, 3 DEPAUL J. HEALTH CARE L. 441, 446–53 (2000) (describing the FDA approval process).

48. See Menikoff, *supra* note 46, at 63.

49. COLEMAN ET AL., *supra* note 37, at 147. In *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 445 F.3d 470 (D.C. Cir. 2006), a D.C. Circuit panel held that terminally ill individuals had a constitutional right to access to unapproved drugs that had passed early-phase safety testing, thereby calling into question the validity of the FDA’s compassionate use regulations. However, the decision was reversed en banc, 495 F.3d 695 (D.C. Cir. 2007) (en banc), and the Supreme Court denied certiorari, 128 S. Ct. 1069 (2008). Prompted in part by the panel’s decision, the FDA has undertaken efforts to clarify its compassionate use rules. See Mark Barnes, Clinton D. Hermes, Katherine Jaral & Ellen Moskowitz, *Looking Back at 2006, Looking Ahead to 2007: ‘Expanded Access,’ Research Billing, International Research, Grants Accounting, Catalona, Gene Therapy, and Central IRBs*, 6 MED. RES. L. & POL’Y REP., Jan. 3, 2007, at 14.

50. Menikoff, *supra* note 46, at 63.

normal controls to see whether they would produce symptoms of spontaneous dyskinesia (a type of spasmodic motion disorder).<sup>51</sup> The amphetamines offered no potential medical benefits to the subjects; they were given solely to help the researchers better understand the relationship between schizophrenia and dyskinesia. Similarly, in another study, researchers administered carbon dioxide—a substance known to trigger panic attacks in susceptible persons—to subjects with a variety of mental disorders, including major depression. Here, the researchers' goal was to better understand "the mechanism of action and the neurobiological significance" of carbon dioxide-induced panic attacks.<sup>52</sup>

Some no-direct-benefit studies involve significant periods of medication washouts. For example, in one study, researchers sought to better understand the brain chemistry of subjects with chronic schizophrenia. As part of the study, they administered lumbar punctures to subjects who had been treated with the drug haloperidol for at least three months. Then, the researchers replaced the haloperidol with a placebo and repeated the lumbar punctures six weeks later.<sup>53</sup> The drug-free period enabled the researchers to differentiate between activities attributable to the subjects' medications from those associated with the underlying pathophysiology of schizophrenia. In a particularly controversial example of a medication washout and challenge study, researchers at Mount Sinai Medical Center in New York took schizophrenic patients off their medications and gave them a drug known to provoke psychotic symptoms. All of the patients experienced relapses, and some of the patients became violent or suicidal.<sup>54</sup>

No-direct-benefit studies involving lumbar punctures, as in the schizophrenia study described above, are relatively common in brain-related research. In one study of subjects with Down's Syndrome and Alzheimer's disease, for example, the researchers performed multiple lumbar punctures on the subjects in order to better understand the mechanisms of certain chemical processes related to the subjects' illnesses.<sup>55</sup> In

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51. Shawn L. Cassady, Helene Adami, Marianne Moran, Rick Kunkel, & Guntav K. Thaker, *Spontaneous Dyskinesia in Subjects with Schizophrenic Spectrum Personality*, 155 *AM. J. PSYCHIATRY* 70 (1998).

52. Jack M. Gorman, Justine Kent, Jose Martinez, Susan Browne, Jeremy Coplan, & Laszlo A. Papp, *Physiological Changes During Carbon Dioxide Inhalation in Patients with Panic Disorder, Major Depression, and Premenstrual Dysphoric Disorder: Evidence for a Central Fear Mechanism*, 58 *ARCHIVES OF GEN. PSYCHIATRY* 125, 125 (2005). In another example of a challenge study, subjects with major depression who had recently attempted suicide were given the drug fenfluramine in order to identify differences in brain activity between "high-lethality" and "low-lethality" suicide attempters. See Maria A. Oquendo, Giovanni P. A. Placidi, Kevin M. Malone, Carl Campbell, John Keilp, Beth Brodsky, Lawrence S. Kegeles, Thomas B. Cooper, Ramin V. Parsey, Ronald L. Van Heertum, & J. John Mann, *Positron Emission Tomography of Regional Brain Metabolic Responses to a Serotonergic Challenge and Lethality of Suicide Attempts in Major Depression*, 60 *ARCHIVES OF GEN. PSYCHIATRY* 14 (2003).

53. Peter M. Thompson, Mary Kelley, Jeffrey Yao, Guochuan Tsai, & Daniel P. van Kammen, *Elevated Cerebrospinal Fluid SNAP-25 in Schizophrenia*, 53 *BIOLOGICAL PSYCHIATRY* 1132, 1133 (2003).

54. See Dolores Kong, *Study Harmed Mentally Ill, Agency Reports*, *BOSTON GLOBE*, Feb. 9, 1999, at A8 (reporting the National Institute of Health's Office for Protection from Research Risks' criticism of the Mount Sinai study).

55. John R. Atack & Mark B. Schapiro, *Inositol Monophosphatase Activity in Normal, Down Syndrome and Dementia of the Alzheimer Type CSF*, 23 *NEUROBIOLOGY OF AGING* 389

another study, the researchers administered lumbar punctures to subjects with Alzheimer's disease for the sole purpose of evaluating the stress associated with receiving a lumbar puncture. The published report of that study noted that similar efforts have been made to evaluate the stress associated with lumbar punctures in persons with depression and schizophrenia.<sup>56</sup>

The extent of no-direct-benefit research with subjects who lack decision-making capacity is difficult to determine. In an effort to gauge the prevalence of this research, the National Bioethics Advisory Commission (NBAC) surveyed all studies published in medical journals in the United States from 1995 to 1998 that met the following criteria:

the research was recently conducted in the United States; it appeared to present greater than minimal risk, and did not hold out the prospect of direct medical benefit to subjects; the subjects were persons with mental disorders that may affect decisionmaking capacity; and the research design included at least one of the following: washout, placebo, or symptom provocation.<sup>57</sup>

The survey uncovered sixty studies meeting all of these criteria, suggesting that risky, no-direct-benefit studies are not an infrequent phenomenon.

NBAC also concluded that developing better treatments for capacity-impairing conditions sometimes requires enrolling incapacitated persons in no-direct-benefit studies. "[W]hen disease processes themselves are under study," NBAC observed, "the absence of animal models for most psychiatric and many neurologic syndromes means that research on both the underlying dynamics of disease and promising treatments must, at some stage, involve human subjects."<sup>58</sup> NBAC specifically noted the usefulness of brain imaging techniques to "help identify the anatomic location of brain areas involved in cognitive and affective functions,"<sup>59</sup> procedures that offer no direct benefits to the subjects and that some commentators have characterized as involving more than minimal risk.<sup>60</sup>

Individuals, or those who decide on their behalf, often have reasons for enrolling in research that, in their view, outweigh the risks inherent in being a research subject. For example, physicians may see research subjects more regularly, research subjects may receive diagnostic tests that reveal important medical information, and, in some cases,

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(2002).

56. Alan J. Lerner, Robert C. Elston, Chien Hsiun Chen, & Robert P. Friedland, *Response of the Hypothalamic-Pituitary-Adrenal Axis to Lumbar Puncture-Induced Stress*, 2 J. ALZHEIMER'S DISEASE 193 (2000).

57. 1 NATIONAL BIOETHICS ADVISORY COMMISSION, RESEARCH INVOLVING PERSONS WITH MENTAL DISORDERS THAT MAY AFFECT DECISION-MAKING CAPACITY 13 (1998) [hereinafter NBAC REPORT].

58. *Id.* at 4.

59. *Id.* (quoting Nancy C. Andreasen, Daniel S. O'Leary & Stephan Arndt, *Neuroimaging and Clinical Neuroscience: Basic Issues and Principles*, in 12 AMERICAN PSYCHIATRIC PRESS REVIEW OF PSYCHIATRY, (John M. Oldham, Michelle B. Riba & Allan Tasman eds., 1993)).

60. See Rebecca Dresser, *Research Involving Persons with Mental Disabilities: A Review of Policy Issues and Proposals*, 2 NATIONAL BIOETHICS ADVISORY COMMISSION, RESEARCH INVOLVING PERSONS WITH MENTAL DISORDERS THAT MAY AFFECT DECISIONMAKING CAPACITY 23 (1999).

they might receive payment.<sup>61</sup> For persons without health insurance, enrolling in a medical research study may be the only way to obtain any medical attention.<sup>62</sup> Moreover, for some people, an important motivation for enrolling in a medical research study is an altruistic desire to contribute to scientific progress.<sup>63</sup> However, while these reasons may explain why some people choose to become research subjects, they do not change the fact that research involves exposing people to risks that are not therapeutically necessary, solely to obtain information that may help others in the future. This is the conflict inherent in human subject research, and the primary reason that medical research is subject to more extensive oversight than ordinary medical care.

## II. THE LEGAL FRAMEWORK

### A. *The Existing Legal Framework Governing Research with Incapacitated Subjects*

Most medical research conducted in this country is subject to federal human subject protection regulations—either a set of regulations known as the Common Rule<sup>64</sup> (so named because it has been promulgated in identical form by seventeen federal agencies) or separate, but very similar, regulations promulgated by the FDA.<sup>65</sup> These regulations require that multidisciplinary committees called “institutional review boards” (IRBs) review and approve human subject research. As part of this review, IRBs must determine that the “risks to subjects are reasonable in relation to anticipated benefits”<sup>66</sup> and that, with the limited exceptions described below,<sup>67</sup> the researchers have made adequate plans for obtaining the subjects’ informed consent.<sup>68</sup>

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61. See Nancy M. P. King, *Defining and Describing Benefit Appropriately in Clinical Trials*, 28 J.L. MED. & ETHICS 332, 333 (2000).

62. See REBECCA DRESSER, *WHEN SCIENCE OFFERS SALVATION: PATIENT ADVOCACY AND RESEARCH ETHICS* 65 (2001) (“If opportunities to enroll in clinical trials increase, and the number of people with adequate health coverage decreases, research will become a more enticing means for low-income people to obtain a modicum of clinical attention.”).

63. See Nancy E. Kass, Jeremy Sugarman, Ruth Faden & Monica Schoch-Spana, *Trust: The Fragile Foundation of Contemporary Biomedical Research*, 26 HASTINGS CENTER REP. 25, 27 (1996).

64. 45 C.F.R. pt. 46. The Common Rule applies to all research conducted or supported by the federal agencies that have adopted the rule. 45 C.F.R. § 46.101(a) (2008). In addition, many institutions that conduct federally-funded research have contractually agreed to comply with the Common Rule in all their human subject research, regardless of the source of funding. See COLEMAN ET AL., *supra* note 37, at 107.

65. 21 C.F.R. § 56.102 (2008). The FDA regulations apply to all “clinical investigations” related to drugs, biologic products, or medical devices that are intended for “human use.” 21 C.F.R. § 56.102(c), (l) (2008). Some research, such as federally-funded drug studies, are covered by both the Common Rule and the FDA regulations. Other studies escape all federal regulation, because they (1) are not conducted or supported by federal agencies; (2) are not conducted in institutions that have agreed to apply the Common Rule to all their human subject research; and (3) do not involve an FDA-regulated product.

66. 45 C.F.R. § 46.111(a)(2) (2008); 21 C.F.R. § 56.111(a)(2) (2008).

67. See *infra* text accompanying notes 77–80.

68. 45 C.F.R. § 46.111(a)(4) (2008); 21 C.F.R. § 56.111(a)(4) (2008). IRBs also must determine that risks to subjects are minimized, that the selection of subjects are equitable, and

The centrality of informed consent to the oversight of human subject research has both historical and theoretical explanations. As a historical matter, the contemporary human subject protection system was created largely in response to egregious instances of nonconsensual research. The most notorious examples, of course, were the sadistic medical experiments conducted in concentration camps in Nazi Germany.<sup>69</sup> In reaction to these atrocities, an American military tribunal set forth ten “basic principles” to govern human experimentation, known as the Nuremberg Code. The Code’s first principle declares that “[t]he voluntary consent of the human subject is absolutely essential.”<sup>70</sup>

In the United States, scandals involving nonconsensual research were among the primary motivations for the enactment of the National Research Act of 1974,<sup>71</sup> which provides the statutory basis for the current human subject protection regulations.<sup>72</sup> These scandals included the U.S. Public Health Service’s decades-long study of syphilis among unsuspecting African-American men in Tuskegee, Alabama,<sup>73</sup> as well as other cases in which patients were enrolled in dangerous medical experiments without their knowledge or consent.<sup>74</sup>

Theoretically, the emphasis on informed consent reflects the Kantian influences underlying the contemporary system of human subject protection. For a Kantian, research with human subjects is deeply problematic, as it involves the use of persons not as ends in themselves, but as the means of developing knowledge for the benefit of others. Thus, on its face, research with human subjects appears to violate Kant’s categorical imperative, which directs us never to treat people as simply a means to another person’s ends.<sup>75</sup> Writing shortly before Congress enacted the National Research Act, the philosopher Hans Jonas argued that the way around this dilemma was to ensure that subjects were sufficiently invested in the study so that the goals of the study became the subject’s own goals. This solution requires that the subject have “such authentic identification with the cause that it is the subject’s, as well as the researcher’s cause—whereby his role in its service is not just permitted by him, but

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that appropriate measures are in place to monitor the research and to protect subjects’ confidentiality. See 45 C.F.R. § 46.111 (2008); 21 C.F.R. § 56.111 (2008).

69. See generally ROBERT JAY LIFTON, *THE NAZI DOCTORS: MEDICAL KILLING AND THE PSYCHOLOGY OF GENOCIDE* (1986).

70. THE NUREMBERG CODE ¶ 1, reprinted in COLEMAN ET AL. ET AL., *supra* note 37, at 27.

71. Pub. L. No. 93-348, 88 Stat. 342 (1974).

72. See ALBERT R. JONSEN, *THE BIRTH OF BIOETHICS* 142–48 (1998).

73. The Tuskegee study was designed to “document the natural history” of untreated syphilis. The subjects in the study were poor African-American sharecroppers, and “government officials went to extreme lengths to ensure that they received no therapy from any source.” TUSKEGEE SYPHILIS STUDY LEGACY COMMITTEE, *FINAL REPORT OF THE TUSKEGEE SYPHILIS STUDY LEGACY COMMITTEE* (1996), available at [http://www.healthsystem.virginia.edu/internet/library/historical/medical\\_history/bad\\_blood/report.cfm](http://www.healthsystem.virginia.edu/internet/library/historical/medical_history/bad_blood/report.cfm).

74. See Henry K. Beecher, *Ethics and Clinical Research*, 274 *NEW ENG. J. MED.* 1354 (1966). In one of the studies Beecher described, researchers injected live cancer cells into indigent, elderly patients at the Brooklyn Jewish Chronic Disease Hospital. *Id.* at 1358. In another study, children at a state facility for “mentally defective persons” were deliberately infected with hepatitis. COLEMAN ET AL., *supra* note 37, at 39–40.

75. See TOM L. BEAUCHAMP & JAMES F. CHILDRESS, *PRINCIPLES OF BIOMEDICAL ETHICS* 350–51 (5th ed. 2001).



willed.”<sup>76</sup> This situation is only possible if the subject genuinely understands the risks and the potential benefits of the research and decides that the value to society justifies the personal risk to herself.<sup>77</sup>

Yet, unlike the absolutist language of the Nuremberg Code’s first principle, the federal regulations recognize that conducting medical research without first obtaining the subjects’ informed consent can sometimes be acceptable. First, in some cases, the regulations permit IRBs to waive the usual informed consent requirements. Most waivers of informed consent fall into one of two categories.<sup>78</sup> The first category involves minimal-risk studies where the research could not “practicably be carried out” without the waiver.<sup>79</sup> For example, if researchers wanted to review the medical records of the patients who were admitted to a particular hospital during the past year, obtaining the subjects’ informed consent would require them to track down and contact thousands of people—an extremely costly and perhaps impossible task. If the IRB determines that the risks of this study are minimal, it may waive the requirement of obtaining informed consent.<sup>80</sup>

The second category involves research during emergencies, where the subjects lack the capacity to provide informed consent and the surrogate decision makers cannot be located in time. The regulations permit IRBs to waive the informed consent requirement in these situations if certain criteria are satisfied, including that “subjects are facing a life-threatening situation that necessitates intervention,” that available treatments are “unproven or unsatisfactory,” and that the experimental intervention offers the subjects a potential direct benefit with a “reasonable” amount of risk.<sup>81</sup>

The focus of this Article, however, is not situations in which informed consent is unnecessary, but rather studies in which informed consent is important, but the subjects lack the capacity to provide it. In these situations, the federal regulations direct the researchers to obtain informed consent from the subjects’ “legally authorized representative.”<sup>82</sup> The regulations define “legally authorized representative” as “an

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76. Hans Jonas, *Philosophical Reflections on Experimenting with Human Subjects*, 98 DAEDALUS 219 (1969), reprinted in JAY KATZ, EXPERIMENTATION WITH HUMAN BEINGS: THE AUTHORITY OF THE INVESTIGATOR, SUBJECT, PROFESSIONS AND STATE IN THE HUMAN EXPERIMENTATION PROCESS 668 (1972).

77. *See id.*

78. In addition to the two categories described in the text, waivers of informed consent are also available in certain studies of public benefit programs. *See* 45 C.F.R. § 46.116(c) (2008).

79. *Id.* at § 46.116(d).

80. Another way to conduct such a study would be for the researchers to record only non-identifying information from the medical records, which would make the study exempt from the Common Rule. *Id.* at § 101(b)(4) (exempting studies involving the review of existing records “if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects”).

81. 21 C.F.R. § 50.24 (2008).

82. 45 C.F.R. § 46.116 (2008); 21 C.F.R. § 50.20 (2008). In addition to the provisions on legally authorized representatives, the regulations contain three other references to mentally disabled subjects. First, they provide that, if an IRB regularly reviews research involving vulnerable populations, including mentally disabled subjects, “consideration shall be given to the inclusion [on the IRB] of one or more individuals who are knowledgeable about and experienced in working with these subjects.” 45 C.F.R. § 46.107(a) (2008). Second, in determining whether the “selection of subjects is equitable,” the IRB “should be particularly

individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research."<sup>83</sup> Because consent to medical procedures is largely governed by state law,<sup>84</sup> this definition has the effect of delegating the authority to identify the "legally authorized representative" to the law of the state in which a study is being conducted. The federal regulations are silent on the substantive standards the legally authorized representative must apply in deciding whether to consent to research on behalf of an incapacitated person. Presumably, the state law from which the legally authorized representative derives his or her authority would govern this issue.<sup>85</sup>

Yet only a handful of states have laws that unambiguously identify who has legal authority to consent to research with incapacitated persons.<sup>86</sup> One example of such a law is a California statute on medical experimentation, which was enacted at the urging of the research community in 2002.<sup>87</sup> The California statute provides a priority list of potential surrogates, starting with a person empowered to make health care decisions pursuant to an advance health care directive, moving to a court-appointed guardian, and then turning to a spouse, domestic partner, or other relative.<sup>88</sup> Aside from California and a few other states, however, most state laws that directly relate to research with incapacitated persons are designed to *limit*, not facilitate, researchers' ability to rely on surrogate consent. Some states, for example, prohibit or sharply restrict research with decisionally incapacitated persons who reside in state mental health facilities.<sup>89</sup> Other states provide that court-appointed guardians may not consent

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cognizant of the special problems of research involving vulnerable populations," including mentally disabled subjects. 45 C.F.R. § 46.111(a)(3) (2008). Third, IRBs should ensure that, "[w]hen some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as . . . mentally disabled persons . . . additional safeguards have been included in the study to protect the rights and welfare of these subjects." 45 C.F.R. § 46.111(b) (2008).

83. 45 C.F.R. § 46.102(c) (2008); 21 C.F.R. § 50.3(l) (2008).

84. *See Gonzalez v. Oregon*, 546 U.S. 243, 270–72 (2006).

85. In at least one situation, however, federal law provides additional substantive restrictions. *See* 10 U.S.C. § 980(a)(2) (2000) (providing that funds appropriated by the Department of Defense may not be used for research with incapacitated subjects unless the research is "intended to be beneficial to the subject" and "the informed consent of the subject or a legal representative of the subject is obtained in advance").

86. *See* CAL. HEALTH & SAFETY CODE § 24178 (2007); KAN. STAT. ANN. § 65-4974 (2006); N.J. STAT. § 26:14-1 (2008); VA. CODE ANN. § 32.1-162.18(B) (2008), 12 VA. ADMIN. CODE § 5-20-40 (2007); OKLA. STAT. ANN. tit. 63, § 3102A (2007); WYO. STAT. ANN. § 25-5-132(d)(iii) (2007). Some states have statutes authorizing surrogate consent to "experimental treatment" for certain incapacitated patients. *See, e.g.*, FLA. STAT. ANN. § 393.13(4)(c)(6) (2007). However, these statutes would probably exclude studies that do not offer a prospect of direct medical benefit, as such studies could not plausibly be considered a form of treatment.

87. CAL. HEALTH & SAFETY CODE § 24178; *see also* COLEMAN ET AL., *supra* note 37, at 608–09 (discussing the history behind the California statute).

88. CAL. HEALTH & SAFETY CODE § 24178(c).

89. *See* ALASKA STAT. § 47.30.830 (2008) (stating that "experimental treatments involving any significant risk of physical or psychological harm may not be administered to a patient" in a state mental health facility); DEL. CODE ANN. tit. 16, § 5175(f) (2008) ("No [resident of a state mental hospital] shall be approached to participate in pharmaceutical research if patient is incapable of understanding the nature and consequences of patient's consent."); MO. ANN. STAT. § 630.192 (West 2007) (prohibiting research in state-funded or licensed mental health facilities "unless such research is intended to alleviate or prevent the disabling conditions or is reasonably

to research on behalf of an incapacitated person without express court approval.<sup>90</sup> Many of these statutes require the court to determine that participating in research would be in the incapacitated person's best interests.<sup>91</sup>

Most states, however, neither authorize nor prohibit surrogate consent to research. Instead, the law is simply silent on the issue. In these states, the only health care surrogacy laws that exist apply to medical treatment. For example, court-appointed guardians can make decisions about medical treatment for incapacitated patients.<sup>92</sup> In addition, competent individuals can execute "health care proxies," in which they designate another person to make medical decisions for them in the event of a future loss of decision-making capacity.<sup>93</sup> Most states also permit family members, and sometimes close friends, to make at least some types of medical decisions for incapacitated persons who have not created health care proxies or left clear instructions about their treatment wishes.<sup>94</sup> In general, surrogate decision makers must make decisions according to the patient's wishes or, if the patient's wishes are unknown and cannot be determined, according to the patient's best interests.<sup>95</sup>

It is unclear, however, whether laws that authorize surrogate decision making about medical treatment provide a sufficient basis for designating a "legally authorized representative" under the federal regulations. As noted above, a "legally authorized representative" is defined as a person authorized "to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research."<sup>96</sup> This definition is susceptible to two different interpretations, depending on how the phrase "the procedure(s) involved in the research" is construed. On the one hand, if "procedure(s)" refers to discrete interventions, regardless of their purpose—for example, the administration of drugs, or surgical procedures—then anyone with the legal authority to make medical decisions for an incapacitated person could be

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expected to be of direct therapeutic benefit to the participants," and further providing that no research may be performed on involuntarily committed persons without a court order).

90. See ARK. CODE ANN. § 28-65-302 (2008); N.H. REV. STAT. ANN. § 464-A:25(I)(c) (2008); 405 ILL. COMP. STAT. ANN. 5/2-110 (West 2008); CONN. GEN. STAT. § 45a-677(e)(6) (2007) (requiring that research be approved by an IRB and the patient's primary physician and endorsed by the state Department of Mental Retardation).

91. See, e.g., 405 ILL. COMP. STAT. ANN. 5/2-110 (West 2008).

92. See generally Joan L. O'Sullivan, *Role of the Attorney for the Alleged Incapacitated Person*, 31 STETSON L. REV. 687, 689–94 (2002) (discussing the history and powers of guardianship).

93. See CHARLES P. SABATINO, ABA COMMISSION ON LAW AND AGING, 10 LEGAL MYTHS ABOUT ADVANCE MEDICAL DIRECTIVES 5, available at <http://www.abanet.org/aging/publications/docs/10legalmythsarticle.pdf>.

94. See generally ALAN MEISEL, THE RIGHT TO DIE §§ 5.17–.21 (2d ed. 1995). For a summary of state statutes, see ABA COMMISSION ON LAW AND AGING, SURROGATE CONSENT IN THE ABSENCE OF AN ADVANCE DIRECTIVE, available at [http://www.abanet.org/aging/legislativeupdates/docs/Famcon\\_05-07.pdf](http://www.abanet.org/aging/legislativeupdates/docs/Famcon_05-07.pdf) [hereinafter ABA COMMISSION, SURROGATE CONSENT].

95. See MEISEL, *supra* note 94, at § 7.3 (describing a continuum of standards, ranging from a "subjective standard" based on "knowledge of the patient's actual ('subjective') wishes," to a "substituted judgment" standard, in which the patient's wishes are "inferred from the patient's statements and conduct," to a pure "best interests" standard, which "reflects and seeks to implement the value of welfare or well-being, rather than self-determination or autonomy") (emphases omitted).

96. 45 C.F.R. § 46.102(c) (2008).

considered a “legally authorized representative” for purposes of research. This interpretation would even apply to studies where the “procedures” to be employed are unrelated to the subjects’ medical needs. On the other hand, if “the procedure(s) involved in the research” refers more narrowly to *experimental* procedures, or to other unique features of research like randomized treatment assignments or the use of placebo controls, simply having the authority to consent to ordinary medical treatment would not be sufficient. Instead, the law would have to “not only identify an individual who can consent to medical treatment on behalf of a patient, but . . . also an individual who can consent specifically to treatment delivered in the context of research.”<sup>97</sup>

So far, the federal Office for Human Research Protections (OHRP), which oversees research conducted or supported by DHHS, has let research institutions decide for themselves whether state surrogate decision-making laws provide a sufficient basis for appointing a “legally authorized representative” under the federal regulations. For example, in an investigation of a study involving the use of ventilators for incapacitated persons with severe lung injuries, OHRP requested information from Duke University about surrogates’ legal authority to provide informed consent under North Carolina law. Duke’s response was that it interpreted a North Carolina statute authorizing surrogate decision making about “health care” as a sufficient basis for allowing surrogate consent to the ventilator study. OHRP neither endorsed nor rejected Duke’s interpretation of the North Carolina law, but simply “acknowledged” the information provided by Duke and took no further action.<sup>98</sup> Yet, while this acknowledgment suggests that OHRP did not object to Duke’s reliance on the North Carolina statute, it is far from an unequivocal endorsement of the applicability of medical surrogacy statutes to all decisions about research, particularly studies not involving a prospect of direct benefit. Moreover, because it does not reflect an official agency interpretation of the regulatory language, it is unlikely that it would receive deference if the issue came before a court.<sup>99</sup>

No court has yet decided whether state laws governing surrogate consent to treatment can be extended to decisions about research. However, courts’ reactions to previous cases involving research with persons incapable of consenting suggest that judges may be skeptical of efforts to interpret the scope of surrogates’ authority broadly. In *T.D. v. New York State Office of Mental Health*,<sup>100</sup> for example, a New York state court struck down regulations permitting surrogate consent to no-direct-benefit research involving more than minimal risk in facilities run by the state Office of Mental Health. While the decision ultimately turned on the fact that the regulations had been promulgated by the wrong administrative agency, five appellate judges also

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97. Michele Russell-Einhorn & Thomas Puglisi, *Three Exceptions to the Requirement to Obtain Informed Consent in Research*, 1 MED. RES. L. & POL’Y REP., Nov. 6, 2002, at 514.

98. See Letter from Leslie K. Ball, Compliance Oversight Coordinator, OHRP, to Ralph Snyderman, President, Duke University Health System (Feb. 1, 2002), available at [http://www.hhs.gov/ohrp/detrm\\_ltr/YR02/feb02a.pdf](http://www.hhs.gov/ohrp/detrm_ltr/YR02/feb02a.pdf).

99. See *United States v. Mead Corp.*, 533 U.S. 218, 228 (2001) (“The weight [accorded to an administrative] judgment in a particular case will depend upon the thoroughness evident in its consideration, the validity of its reasoning, its consistency with earlier and later pronouncements, and all those factors which give it power to persuade, if lacking power to control.”) (alteration in original) (quoting *Skidmore v. Swift*, 323 U.S. 134, 140 (1944)).

100. 650 N.Y.S.2d 173 (App. Div. 1996), *appeal dismissed*, 690 N.E.2d 1259 (N.Y. 1997).

found that the regulations violated incapacitated persons' constitutional right to procedural due process and "the common law right to personal autonomy."<sup>101</sup> In addition, in a 2001 decision involving pediatric research, the Maryland Court of Appeals concluded that parents lacked the authority under state law to enroll their children in nontherapeutic studies involving more than "any articulable risk beyond the minimal kind of risk that is inherent in any endeavor."<sup>102</sup> As explained below, parents' authority to make decisions for their minor children stands on much stronger legal footing than the authority of surrogates to make decisions on behalf of incapacitated adults.<sup>103</sup> Thus, while the Maryland decision applied only to parental decisions for children, it is reasonable to assume that the court would be equally critical of surrogate consent to research with incapacitated adults, particularly in the absence of explicit legislative authorization for the practice.

### B. Law Reform Proposals

Efforts to reform the law governing research with incapacitated persons date back to the early 1970s, when the Department of Health, Education, and Welfare (DHEW, the predecessor of DHHS) formed a committee to develop recommendations on research with "mentally infirm" subjects.<sup>104</sup> Shortly after this process began, Congress enacted the National Research Act, which established the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research. One of the tasks with which the Commission was charged was to develop recommendations for policies regarding research on subjects "institutionalized as mentally infirm."<sup>105</sup> DHEW put its project on hold pending the receipt of the National Commission's recommendations. After those recommendations were issued in 1978, DHEW released its final regulatory proposal, which would have authorized research with incapacitated persons subject to certain limitations. For example, the regulations would have required the approval of a national ethics committee before no-direct-benefit studies involving more than a "minor increase above minimal risk" could be conducted with institutionalized incapacitated subjects.<sup>106</sup> They also would have required the use of

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101. *Id.* at 176. The New York Court of Appeals ultimately concluded that it was unnecessary to reach the constitutional and common law questions, and it therefore vacated those portions of the intermediate appellate court's decision. *See* T.D., 690 N.E.2d at 1260.

102. *Grimes v. Kennedy Krieger Inst.*, 782 A.2d 807, 862 (Md. 2001); *see also id.* at 814 ("[P]arents . . . have no more right to intentionally and unnecessarily place children in potentially hazardous nontherapeutic research surroundings . . . than do researchers. In such cases, parental consent, no matter how informed, is insufficient."). The *Grimes* decision placed greater restrictions on research with children than the federal regulations, which permit no-direct-benefit research involving more than minimal risks in limited circumstances. 45 C.F.R. §§ 46.406–.407 (2008).

103. *See infra* text accompanying notes 175–81.

104. Diane E. Hoffmann, Jack Schwartz & Evan G. DeRenzo, *Regulating Research with Decisionally Impaired Individuals: Are We Making Progress?*, 3 DEPAUL J. HEALTH CARE L. 547, 551–52 (2000).

105. *Id.* at 551–55.

106. *Id.* at 565. Existing regulations on research with children contain a similar requirement. *See* 45 C.F.R. § 46.407 (2008).

“consent auditors” in many types of research.<sup>107</sup> The DHEW proposal was never adopted, in large part because the research community found the proposed limitations overly burdensome.<sup>108</sup>

Over the next two decades, despite the increasing amount of research being conducted with incapacitated subjects, “there were no new significant efforts to regulate research with the decisionally impaired population.”<sup>109</sup> This situation changed in the late 1990s. In response to the *T.D.* decision,<sup>110</sup> the New York State Department of Health convened an Advisory Work Group on Research Involving the Protected Classes (NYSAWG) to develop a new set of regulations authorizing research with decisionally incapacitated subjects.<sup>111</sup> Coincidentally, NBAC, whose mandate included issues related to human subject research, was also turning its attention to research with incapacitated persons.<sup>112</sup> In addition, the Maryland Attorney General’s office, which has long been at the forefront of bioethics-related policy initiatives, had created a committee to develop recommendations on the same issue.<sup>113</sup>

While there were some differences among the three commissions’ proposals, in general they echoed the overall conclusions of the 1978 DHEW recommendations. All of the commissions agreed that surrogates should be permitted to consent to direct-benefit research for incapacitated persons, as well as to no-direct-benefit research involving minimal risk.<sup>114</sup> They also agreed that no-direct-benefit studies involving more than minimal risks should be permissible under some circumstances, although they disagreed on the specific rules that should govern this category of research.<sup>115</sup> In

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107. Hoffmann et al., *supra* note 104, at 563–64.

108. *See id.* at 568.

109. *Id.* at 569.

110. *See supra* text accompanying notes 100–101.

111. ADVISORY WORK GROUP ON HUMAN SUBJECT RESEARCH INVOLVING THE PROTECTED CLASSES, N.Y. STATE DEPARTMENT OF HEALTH, RECOMMENDATIONS ON THE OVERSIGHT OF HUMAN SUBJECT RESEARCH INVOLVING THE PROTECTED CLASSES 26 (1998) [hereinafter NYSAWG REPORT]. The author of this Article served as a staff member to the NYSAWG.

112. NBAC REPORT, *supra* note 57.

113. *See* Diane E. Hoffmann & Jack Schwartz, *Proxy Consent to Participation of the Decisionally Impaired on Medical Research—Maryland’s Policy Initiative*, 1 J. HEALTH CARE L. & POL’Y 123, 140–46 (1998).

114. *See* NYSAWG REPORT, *supra* note 111, at 26; NBAC REPORT, *supra* note 57, at 60–62; Hoffmann & Schwartz, *supra* note 113, at 140–46.

115. NBAC recommended that surrogate consent to such research be permitted only if the study receives approval from a national ethics panel. *See* NBAC REPORT, *supra* note 57, at 58–60. The NYSAWG, by contrast, concluded that surrogates should be permitted to consent to no-direct-benefit research involving a “minor increase over minimal risk” without special national approval. However, the NYSAWG recommendations limited no-direct-benefit studies involving more than a minor increase over minimal risk to persons who had expressly authorized such research before losing capacity. NYSAWG REPORT, *supra* note 111, at 25, 32–33. The Maryland commission fell somewhere between these two approaches: It concluded that decision-makers appointed by the prospective subject through a health care proxy (i.e., “health care agents”) should be permitted to consent to no-direct-benefit research involving a minor increase over minimal risk, but that surrogates not appointed by the prospective subject should not have this authority. Like the NYSAWG, the Maryland commission would have limited no-direct-benefit research involving more than a minor increase over minimal risk to persons who had expressly authorized such research while competent. *See* Hoffmann & Schwartz, *supra* note

addition to setting forth categories of permissible research, the reports addressed issues such as the process of capacity assessment, the involvement of incapacitated subjects in the decision-making process, and the monitoring of ongoing research.

The proposals were not uniformly well received. On the one hand, some critics argued that allowing research with incapacitated persons would “open[] the door to exploitation of vulnerable people.”<sup>116</sup> The recommendations to authorize some forms of no-direct-benefit research were especially controversial. Criticizing the NYSAWG proposal on this basis, John Cardinal O’Connor, then the Archbishop of New York, stated that “every one of us perhaps could profit by a periodic reminder that much of what was done under the Nazi regime under Hitler began long before with the experiments of psychiatrists and other medical persons on people who are psychologically incapacitated.”<sup>117</sup> On the other hand, the research community argued that the proposals would stifle valuable medical studies.<sup>118</sup> Researchers appeared to prefer conducting their work without clear legal authority to a system that would authorize their activities but subject them to more stringent regulation.

In the years since the commission proposals were rejected, a few states have passed laws authorizing research with incapacitated persons.<sup>119</sup> The fact that these laws were enacted shows that achieving consensus on research with incapacitated persons is not impossible. However, the existing statutes are not nearly as comprehensive as the rejected commission proposals; in essence, they simply authorize surrogate consent to research without any significant safeguards. Moreover, these laws are isolated exceptions. In the vast majority of states, research with incapacitated persons continues to operate in the shadow of the law.

### III. THE UNDERLYING ETHICAL DILEMMA: SEARCHING FOR A JUSTIFICATION FOR RESEARCH WITH INCAPACITATED SUBJECTS

As explained above, the amount of research with incapacitated persons is growing, but in most states, it takes place without clear legal authority. Yet many previous proposals to change the law have met with considerable resistance, both from those who believe the proposals are too permissive and from researchers who consider the same proposals too restrictive. One reason for this stalemate is that efforts to change the law have not been supported by a coherent ethical framework. The initial question that must be answered is *why* laws authorizing limited forms of research with incapacitated persons are ethically preferable to either prohibiting such research or maintaining the status quo.

In this Part, I explain the problems with the standard ethical arguments that have been offered in support of laws permitting research with incapacitated persons. I begin with the argument that research with incapacitated persons can be justified by the principles governing surrogate consent to medical treatment. After explaining why the analogy to medical treatment cannot be supported, I examine alternative justifications

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113, at 141–46.

116. Hoffmann et al., *supra* note 104, at 592.

117. Naomi Toy & Gregg Birnbaum, *O’Connor: No-Consent Testing Recalls Nazis*, N.Y. POST, Jan. 18, 1999, at 5.

118. Hoffmann et al., *supra* note 104, at 592.

119. *See supra* note 86.

for research with incapacitated persons offered in the academic literature. These approaches also do not provide an adequate foundation for policy reform.

### A. The Medical Treatment Analogy

All states recognize at least some forms of surrogate decision making for medical treatment.<sup>120</sup> The general standard for surrogate decisions about treatment is that the decisions must promote the wishes or best interests of the incapacitated person.<sup>121</sup> Previous proposals to authorize surrogate consent to medical research have directly appealed to this wishes/best interest framework. The NBAC, for example, argued that surrogates should base their decisions on “a best estimation of what the subject would have chosen if capable of making a decision” or, if the surrogate is unable to identify “any evidence about the person’s values and preferences,” on “judgments about that person’s ‘best interests.’”<sup>122</sup> The language of wishes and best interests also appears in the NYSAWG and Maryland commission reports,<sup>123</sup> and it is the standard underlying California’s statute on “medical experimentation.”<sup>124</sup>

This Section argues that the principles governing surrogate consent to treatment do not provide an adequate foundation for authorizing surrogates to enroll incapacitated persons in research. First, unlike treatment decisions, decisions to enroll incapacitated persons in research usually cannot be justified by appealing to those persons’ wishes or best interests. Second, the reasons we defer to surrogates’ assessment of incapacitated persons’ wishes and best interests in the treatment context do not necessarily apply to medical research.

#### 1. The Wishes/Best Interests Framework

The standards applicable to surrogate decisions about medical treatment—promoting the wishes or best interests of the incapacitated person—cannot always be reconciled with the realities of medical research. First, it is difficult enough for surrogates to determine what decisions incapacitated persons would have made about

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120. See *supra* text accompanying notes 92–93.

121. See *supra* note 95 and accompanying text.

122. NBAC REPORT, *supra* note 57, at 62.

123. NYSAWG REPORT, *supra* note 111, at 32–33; Hoffmann & Schwartz, *supra* note 113, at 140.

124. See CAL. HEALTH & SAFETY CODE § 24178(g) (West 2006) (requiring surrogates to make decisions “in accordance with the person’s individual health care instructions, if any, and other wishes, to the extent known to the surrogate decisionmaker,” or if those wishes are not known, “in accordance with the person’s best interests”). By contrast, the New Jersey statute provides that, if the incapacitated person’s wishes are not known, the surrogate “shall make a decision in accordance with the subject’s personal values and his best estimation of what the subject would have chosen if he were capable of making a decision.” N.J. STAT. § 26:14-5.d. The statute does not incorporate the best interests standard. Other research consent statutes state only that the surrogate may not make decisions that contravene what is known about the patient’s wishes or values. See KAN. STAT. ANN. § 65-4974 (2006); OKLA. STAT. ANN. tit. 63 § 3102A (West 2004); VA. CODE ANN. § 32.1-162.18(B) (2004). Under these statutes, if the patient’s prior wishes cannot be determined, the surrogate would appear to have unlimited authority to consent to any IRB-approved study.



ordinary medical treatment.<sup>125</sup> Those difficulties are significantly greater when surrogates attempt to assess incapacitated persons' wishes about medical research. When surrogates make treatment decisions, they can draw on a variety of sources of information, even in the absence of clear instructions by the patient. For example, because most people undergo numerous medical interventions throughout their lives, surrogates may be able to infer incapacitated persons' preferences about medical treatment from the patient's reactions to prior experiences. Similarly, many people reveal their preferences about medical treatment in the course of discussing the experiences of family members, friends, or people in the news.<sup>126</sup> Because far fewer people will have had any experiences related to medical research, these sources of information are less likely to be available when surrogates are considering enrolling an incapacitated person in a study.

Moreover, even when some evidence of an incapacitated person's preferences about research exists, that evidence often will not provide reliable information about what the person would have decided after being fully informed about the risks and benefits of enrolling in a particular study. For example, some people may have expressed a desire to participate in research because they thought that doing so would give them access to "cutting-edge" experimental therapies. They may not have been aware of the fact that being a research subject also involves inherent risks, such as randomized treatment assignments (including the possibility of being randomly assigned to a placebo-control arm), inflexible treatment protocols, and the use of risky, nontherapeutic interventions.<sup>127</sup> In addition, people generally do not realize that the experimental interventions offered in clinical trials can often be obtained from a physician without enrolling in a study.<sup>128</sup> Thus, the fact that someone has expressed a desire to "pursue experimental therapies," or even to "participate in a clinical trial," does not necessarily mean that she would have agreed to be a research subject once the risks and benefits were made clear. Such evidence certainly does not mean that the person would have agreed to be a subject in a study that does not offer any potential direct benefit, such as the symptom-provoking challenge studies described in Part I.<sup>129</sup>

Finally, for studies related to certain medical conditions, it will never be possible to rely on evidence of the prospective subject's prior wishes about research, because persons suffering from those conditions have lacked decision-making capacity for their entire lives. This would be true, for example, in a study designed to test a new treatment for severe mental retardation, in which all of the prospective subjects have the mental age of a young child. Because none of these persons ever had the ability to provide informed consent to any medical interventions, surrogates cannot base their

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125. See *infra* text accompanying note 152.

126. See, e.g., *In re Gardner*, 534 A.2d 947, 953 (Me. 1987) (noting that the patient "had specifically observed friends and neighbors in desperate medical straits and had declared that he did not want to be kept alive artificially if he ever came into that condition"); *In re Eichner*, 420 N.E.2d 64, 68, 72 (N.Y. 1981) (finding clear and convincing evidence of the patient's prior decision to refuse a respirator, in part based on the patient's comments about the Karen Ann Quinlan case).

127. See *supra* text accompanying notes 34–40.

128. See *supra* text accompanying note 50.

129. See *supra* text accompanying notes 51–52.

decisions on what the prospective subjects would have chosen for themselves if they were fully informed.

The difficulty of determining incapacitated persons' wishes means that, if the standards applicable to treatment decisions are extended to medical research, decisions about research enrollment will usually have to be based on the surrogate's assessment of the prospective subject's best interests. However, as explained in Part I, participating in a study is often *not* the best choice from the perspective of an individual's medical interests. Even studies that offer a prospect of direct medical benefit involve additional risks not present when patients undergo individualized medical treatment.<sup>130</sup> There are also risks associated with the fact that the experimental intervention has never been proven to work.<sup>131</sup> Moreover, even when the experimental intervention offered in a study looks especially promising as compared to existing therapeutic options, it will often be possible to obtain that intervention outside of research, either by finding a doctor willing to prescribe an approved drug off-label or seeking a compassionate use exemption to permit the non-research use of an unapproved drug.<sup>132</sup> If the potential direct benefits of a study can be obtained without assuming the added risks of research, it is difficult to see how exposing an incapacitated person to those risks can be justified under a best interests analysis.

That is not to say that there are no situations in which enrolling in a clinical trial can genuinely be said to represent the best therapeutic option for a particular patient. Patients suffering from serious conditions for which no effective treatments exist, or patients who have tried all available treatments and failed to respond, may welcome the opportunity to try an unproven intervention despite the uncertain benefits. Under such circumstances, if a promising experimental intervention exists that is not available outside of a clinical trial, it might be in the best interests of the patient to pursue it, despite the risks and uncertainty involved. However, situations in which enrolling in a study are the best therapeutic option for a patient are the exception, not the norm.

A possible response to the foregoing analysis is that it rests on an overly exacting interpretation of the meaning of "best interests." Norman Cantor, for example, rejects "[t]he typical understanding . . . that a best-interests judgment requires maximizing the helpless ward's interest or determining 'the highest benefit . . . among available options.'"<sup>133</sup> Instead, he argues, in some cases the decision need only be "reasonably consistent with the interests of the disabled person," while in other cases, all that is required is that "the determination not be abusive in the sense of subjecting the dependent person to serious risk of harm."<sup>134</sup> Under such a framework it might be acceptable for a surrogate to enroll an incapacitated person in research as long as the study offers a reasonable possibility of providing some direct medical benefits, the risks are not substantially greater than pursuing individualized treatment outside of the study, and other methods of treating the patient's condition would involve additional costs or burdens that the surrogate is unwilling to undertake.<sup>135</sup>

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130. *See supra* text accompanying notes 34–40.

131. *See supra* text accompanying notes 41–45.

132. *See supra* text accompanying notes 46–50.

133. NORMAN L. CANTOR, MAKING MEDICAL DECISIONS FOR THE PROFOUNDLY MENTALLY DISABLED 127 (2005).

134. *Id.* at 127–28.

135. *See id.*

However, the cases Cantor cites do not demonstrate that courts are willing to interpret the “best interests” standard flexibly; rather, they are situations in which the best interests standard does not apply. Specifically, all of the cases involve parents making medical decisions for their minor children. As discussed below,<sup>136</sup> parents have a constitutional and common-law right to raise their children without state interference, as long as they do not engage in conduct that constitutes abuse or neglect.<sup>137</sup> Thus, it is the abuse and neglect laws that define the outer limits of parents’ authority to make decisions for their minor children, not the wishes/best interests standards that govern surrogate decisions about medical treatment for incapacitated adults.

In addition, it is important to remember that the reason participating in research sometimes appears to be in an individual’s best interests is that the optimal alternative—obtaining individualized medical attention from a treating physician—may be practically unavailable to persons without adequate access to health care. In other words, the “benefit” of being a research subject depends to a large extent on the fact that we have an inequitable health care system in which many people face significant financial and other barriers to obtaining basic medical care. As a matter of public policy, it is hypocritical to claim that a system that forces surrogates to rely on research as the only effective means of obtaining medical attention can be justified by a commitment to promoting the “best interests” of incapacitated persons.<sup>138</sup>

Of course, in our health care system as it exists today, it is hard to fault a surrogate for wanting to enroll an incapacitated person in a study if doing so is the only practical way of obtaining access to health care. However, even under an expansive interpretation of the best interests standard, it would be difficult to justify enrolling an incapacitated person in research when other alternatives would be significantly less risky or offer significantly greater benefits. And no matter how far the concept of best interests is stretched, it would still leave out the entire category of no-direct-benefit studies. While such studies may indirectly contribute to improved treatments in the future, they have no therapeutic justification from the perspective of the subjects’ own

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136. See *infra* text accompanying notes 176–79.

137. As the Supreme Court has observed, the best interests of the child is not the legal standard that governs parents’ or guardians’ exercise of their custody: So long as certain minimum requirements of child care are met, the interests of the child may be subordinated to the interests of other children, or indeed even to the interests of the parents or guardians themselves.

*Reno v. Flores*, 507 U.S. 292, 304 (1993).

138. The use of best interests rhetoric to justify decisions that are actually based on other factors is not limited to decisions about medical research. In family law, for example, scholars have recognized that appeals to the “best interests of the child” mask the fact that decisions about children’s welfare are often made on an arbitrary basis. Robert Mnookin has suggested that instead of claiming that custody decisions are based on the child’s best interests, “[w]e would more frankly acknowledge both our ignorance and the presumed equality of the natural parents were we to flip a coin.” Robert H. Mnookin, *Child-Custody Adjudication: Judicial Functions in the Face of Indeterminacy*, 39 *LAW & CONTEMP. PROBS.* 226, 289 (1975). However, there is a difference between using best interests language when all of the options are equally acceptable, as in the custody example, and using it when a surrogate is making decisions that are *inconsistent* with the incapacitated person’s welfare.

medical interests. Accordingly, if surrogate decisions about medical research must conform to the wishes/best interests framework applicable to ordinary medical treatment, the only persons who could be enrolled in no-direct-benefit studies would be those whose wishes to enroll in this type of research were known. For the reasons discussed above, it is unlikely that there will be many persons who have left reliable evidence of their desire to be exposed to risks without any possibility of receiving direct medical benefits. Moreover, for conditions associated with lifelong capacity impairments, evidence of the prospective subjects' wishes will never exist.

## 2. The Justification for Deferring to Surrogates

A second problem with the analogy to medical treatment is that, even in the treatment context, the law's willingness to defer to surrogates' assessment of patients' wishes and best interests is subject to significant limitations. Surrogates are not free to make any decision they want as long as they claim that they are promoting the incapacitated person's wishes or best interests. Instead, surrogates have the discretion to interpret the incapacitated person's wishes and best interests only within a relatively narrow range of permissible choices. These limitations are grounded in the underlying justification for surrogate decision making—a justification that does not apply to most decisions about medical research.

At the outset, it is important to distinguish between two different types of surrogate decision makers—those chosen by the patient while competent (that is, decision makers appointed via health care proxies) and those empowered to make decisions for the patient by operation of law. Proxy decision makers (often called “health care agents”) generally have the authority to make any health care decision for an incapacitated patient that the patient would have been permitted to make if she retained decision-making capacity.<sup>139</sup> While the agent's decisions must be consistent with the wishes or best interests of the incapacitated person, health care proxy statutes effectively put the burden on those challenging the agent's decision to show that the agent did not apply those standards accurately.

Thus, it is fair to say that this first category of decision makers enjoys considerable discretion in interpreting the wishes and best interests of the incapacitated person. This discretion is justified by the fact that the patient voluntarily gave the agent unrestricted authority to make decisions on her behalf. However, health care proxy statutes authorize agents to make decisions about medical treatment, not research. It would be possible, of course, to amend those laws so that individuals could also delegate the authority to make decisions about research, and to give “research agents” the same degree of deference that health care agents currently enjoy.<sup>140</sup> The reality, however, is

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139. See Steven I. Friedland, *The Health Care Proxy and the Narrative of Death*, 10 J.L. & HEALTH 95, 135 (1995/1996).

140. In fact, both NYSAWG and the Maryland commission recommended that states enact legislation authorizing the appointment of “research agents.” See NYSAWG REPORT, *supra* note 111, at 25; MARYLAND GENERAL ASSEMBLY S.B. BILL 307 (1999), at § 20.701(W). Similarly, NBAC proposed “an amendment to the Common Rule that would define the term ‘legally authorized representative’ to include those who, under the law of the state where the research is conducted, may serve as proxy decision makers for clinical care.” NBAC REPORT, *supra* note 57, at 63. However, under all of these proposals, agents would have the authority to consent to

that most people do not have health care proxies,<sup>141</sup> and even fewer people are likely to be interested in authorizing agents to make decisions about medical research. People simply do not like to think about the possibility of losing capacity, and those who make plans for such a possibility generally do not have decisions about research participation at the forefront of their minds.

The more important category of decision makers, therefore, are persons whose decision-making authority exists by operation of law, whether as a result of a guardianship proceeding or pursuant to statutes or case law authorizing surrogate consent. The authority of decision makers in this second category is far more circumscribed than that of decision makers appointed by the patient. For example, in most states, surrogates not appointed by the patient are permitted to refuse life-sustaining treatment only if the patient meets specific medical criteria, such as being terminally ill or permanently unconscious.<sup>142</sup> In some states, there must also be medical evidence that the burdens of continued treatment would outweigh the benefits for the patient.<sup>143</sup> In many jurisdictions, certain sensitive medical decisions cannot be made by surrogates without judicial authorization, including decisions about electroconvulsive therapy, abortion, or sterilization.<sup>144</sup>

In general, the areas where surrogates are given the greatest deference are those in which no single decision can be considered objectively reasonable in all circumstances. For example, the risks and benefits of keeping a debilitated, terminally ill patient on a ventilator or feeding tube are often difficult to determine; their assessment depends as much on the patient's values and preferences as on objective medical facts.<sup>145</sup> The rationale for deferring to surrogates in these situations is that someone with a personal connection to the patient is most likely to be able to make the decision that is best for the patient in light of her individual characteristics.<sup>146</sup>

The situation is different when there is less uncertainty about what would constitute an objectively reasonable decision. For example, if an otherwise healthy woman experiences excessive bleeding following childbirth and requires a transfusion, it is unlikely that a surrogate would be permitted to refuse the transfusion on the woman's behalf in the absence of very strong evidence that the woman, if competent, would have refused the transfusion herself.<sup>147</sup> Unlike a decision about providing a ventilator

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high-risk, no-direct-benefit research only if the incapacitated person had expressly indicated her willingness to participate in such research while competent. See NYSAWG REPORT, *supra* note 111, at 25, 32–33; MARYLAND GENERAL ASSEMBLY S.B. BILL 307 (1999), at § 20.745(A)(1)(I); NBAC REPORT, *supra* note 57, at 63.

141. See Bernard Lo & Robert Steinbrook, *Resuscitating Advance Directives*, 164 ARCHIVES INTERNAL MED. 1501 (2004).

142. See ABA COMMISSION, SURROGATE CONSENT, *supra* note 94.

143. *E.g.*, *In re Conroy*, 486 A.2d 1209, 1232 (1985).

144. *E.g.*, D.C. CODE § 21-2211 (2001).

145. Norman L. Cantor, *Déjà Vu All Over Again: The False Dichotomy Between Sanctity of Life and Quality of Life*, 35 STETSON L. REV. 81, 85 (2005) (noting that patients must rely on “personal values and preferences” to decide “whether the prospective preservable state would be so intolerably painful or degrading as to make treatment unwanted”).

146. See *In re Jobes*, 529 A.2d 434, 444–45 (1987).

147. The most likely reason a surrogate would seek to do this would be for religious reasons. See, *e.g.*, Kent Greenawalt, *Objections in Conscience to Medical Procedures: Does Religion Make a Difference?*, 2006 U. ILL. L. REV. 799, 803 (2006) (noting that Jehovah's Witnesses “believe that God's will is that they not accept transfers of blood”).

or feeding tube to a terminally ill patient, in the case of the transfusion, the objectively reasonable decision is clear: the blood should be provided because it will save an otherwise healthy patient's life. State surrogacy statutes recognize this distinction by limiting surrogates' authority to refuse life-sustaining treatment to situations, such as terminal illness, where the appropriateness of providing treatment is a matter about which reasonable people can disagree.<sup>148</sup>

These limitations reveal an important fact about the purpose of surrogate decision making. While competent persons have broad authority to refuse medical treatment, even when doing so appears to be objectively unreasonable,<sup>149</sup> surrogates are generally limited to making choices among reasonable options in situations where identifying the most appropriate option for the patient requires value judgments about which reasonable people can differ.<sup>150</sup> As in the obstetric example, a surrogate's unsubstantiated claims about what the patient would have wanted are insufficient to justify decisions that are clearly inconsistent with the patient's best interests. Instead, such decisions will be authorized only if there is specific evidence of the patient's own prior decision.<sup>151</sup> In other words, the reason for deferring to surrogates is not to promote the patient's right to engage in behavior that is clearly contrary to an objective assessment of her welfare. Instead, even when surrogates base decisions on the "wishes" of the incapacitated person, the best interests standard lurks in the background, limiting the range of options from which surrogates may choose.<sup>152</sup>

Cases involving the use of incapacitated persons as live organ donors support this interpretation. Every court that has addressed the issue has rejected efforts to use

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148. See *supra* text accompanying notes 145–46.

149. E.g., *Fosmire v. Nicoleau*, 551 N.E.2d 77 (N.Y. 1990) (upholding the right of a Jehovah's Witness patient to refuse a life-saving blood transfusion).

150. See generally Rosamond Rhodes & Ian R. Holzman, *The Not Unreasonable Standard for Assessment of Surrogates and Surrogate Decisions*, 25 THEORETICAL MED. & BIOETHICS 367 (2004) (arguing that physicians should not accede to surrogates' unreasonable decisions).

151. Requiring specific evidence of the patient's prior decision is not simply a form of surrogate decision making with a higher evidentiary standard; it is an entirely different approach. With surrogate decision making, the surrogate is not required to make any particular decision; she has the discretion to interpret the patient's wishes and best interests in light of the circumstances. When there is specific evidence of the patient's prior decision, by contrast, the surrogate no longer has any discretion; the prior evidence is controlling, and the surrogate has no more authority than anyone else to override what the patient has decided. This distinction is recognized in most states' surrogacy statutes, which provide that surrogates may not override instructions the patient set forth in a living will. E.g., 755 ILL. COMP. STAT. 40/15 (2007).

152. Indeed, it is often the case that policies ostensibly motivated by respect for individual autonomy are constrained by societal assumptions about what is objectively reasonable. For example, proponents of physician-assisted suicide frequently ground their arguments in claims about individuals' autonomous right to make life-and-death decisions, but at the same time, most of them emphasize that they would legalize assisted suicide only for terminally ill patients. See generally Charles H. Baron, Clyde Bergstresser, Dan W. Brock, Garrick F. Cole, Nancy S. Dorfman, Judith A. Johnson, Lowell E. Schnipper, James Vorenberg & Sidney H. Wanzer, *A Model State Act to Authorize and Regulate Physician-Assisted Suicide*, 33 HARV. J. ON LEGIS. 1 (1996). Thus, they are not prepared to recognize all autonomous decisions to commit suicide; their support is limited to decisions that fall within parameters they consider to be objectively reasonable.

incapacitated persons as organ donors in the absence of evidence that the donation would be in the best interests of the incapacitated person—for example, by saving the life of a close relative on whom the incapacitated person depends.<sup>153</sup> Without an accompanying benefit to the incapacitated person, the desire to benefit others—even to save another person’s life—does not justify performing an invasive procedure on a person without his or her consent.<sup>154</sup>

The reason for these constraints on the scope of surrogates’ authority is that surrogate decision making is not a risk-free endeavor. Numerous studies have shown that even close relatives and friends often do a poor job of predicting the type of treatments their loved ones would want in hypothetical medical scenarios,<sup>155</sup> thus undermining the reliability of surrogates’ assessments of the wishes of incapacitated patients. In addition, there is always a danger that giving surrogates discretion will allow them to consider factors other than the patient’s wishes and best interests—for example, the surrogate’s own interest in saving money on health care costs—or that surrogates will be motivated by unconscious biases against persons who are elderly or disabled.<sup>156</sup>

We allow surrogates to make decisions for incapacitated patients despite these inherent dangers because relying on surrogates is the least problematic alternative when decisions must be made for incapacitated patients and no single solution is clearly objectively preferable. For many years, it was hoped that people could be encouraged to formalize their wishes about medical treatment in a “living will,” but despite decades of effort,<sup>157</sup> the percentage of the population with living wills remains small.<sup>158</sup> Moreover, physicians and bioethicists are increasingly recognizing that living

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153. *Strunk v. Strunk*, 445 S.W.2d 145, 146 (Ky. 1969) (finding that the donation would be beneficial to the incapacitated person because he “was greatly dependent upon [his brother], emotionally and psychologically, and that his well-being would be jeopardized more severely by the loss of his brother than by the removal of a kidney”). See generally CANTOR, *supra* note 133, at 75–78.

154. Similar constraints apply outside the area of medical decision making. For example, courts have held that guardians may not use the assets of their wards to make charitable contributions unless the ward “manifested [a] commitment to such charity” before losing capacity or the donation would be in the incapacitated person’s best interests. In re: Erna Marx Probate Court, 18 QUINNIPIAC PROB. L.J. 35, 40–41 (2004).

155. See generally David I. Shalowitz, Elizabeth Garrett-Mayer & David Wendler, 166 ARCHIVES INTERNAL MED. 493 (2006).

156. CANTOR, *supra* note 133, at 37 (noting that some advocates for people with disabilities “fear substituted judgment as a cover for exploitation based on prejudice and stereotyped views of the quality of life experienced by the profoundly disabled”).

157. One such effort is the federal Patient Self-Determination Act (PSDA), which requires health care facilities to ask patients upon admission if they have advance directives, to document the existence of any such directives in the patient’s record, and to provide notice to patients without advance directives of their rights to create advance directives and the facility’s policies with respect to such directives. See 42 U.S.C. §§ 1395cc, 1396a (2000 & Supp. IV 2004). The PSDA appears to have had little impact. Carl E. Schneider & Lee E. Teitelbaum, *Life’s Golden Tree: Empirical Scholarship and American Law*, 2006 UTAH L. REV. 53, 95 (2006).

158. Will Lester, *Poll: More Americans Have Living Wills*, ASSOCIATED PRESS, Jan. 5, 2006 (reporting that twenty-nine percent of the population claims to have a living will).

wills have significant limitations. For example, they typically contain broad pronouncements about the patient's wishes that are insufficiently flexible to deal with the ambiguities of real clinical decisions.<sup>159</sup> In addition, living wills are based on people's predictions about how they will react to hypothetical situations that may occur far in the future. Research has shown that people often respond to real-world medical situations very differently than they might have anticipated from the standpoint of good health.<sup>160</sup>

Other approaches to making treatment decisions for incapacitated patients also have serious limitations. Theoretically, the law could require judicial approval of all medical decisions for incapacitated patients. However, in addition to the expense and delay such an approach would entail, it is doubtful that judicial review would change the outcome of decisions when no one is disputing the appropriateness of what the surrogate wants to do. Requiring all potentially life-prolonging treatment to be provided in the absence of clear and convincing evidence of the patient's wish to the contrary, an approach used in a few states,<sup>161</sup> ignores the fact that most people do not discuss their wishes about medical treatment with the level of specificity that the clear and convincing evidence standard demands. As a result, this approach forces many people to receive burdensome interventions that they almost certainly would have refused if they had been competent to do so.<sup>162</sup>

In summary, the reason the law defers to surrogates in the context of medical treatment is that there are situations in which *somebody* must exercise individualized judgment to determine what treatments are appropriate for an incapacitated patient, and relying on surrogate decision makers is the least worst alternative. These

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159. See, e.g., JOSEPH J. FINS, A PALLIATIVE ETHIC OF CARE: CLINICAL WISDOM AT LIFE'S END 125 (2006) (arguing that "[l]iving wills have limited utility in the clinical context" because they may be "too vague," "ambiguous," or "too specific").

160. Rebecca Dresser, *Precommitment: A Misguided Strategy for Securing Death with Dignity*, 81 TEX. L. REV. 1823, 1823 (2003) (citing the difficulty of predicting future treatment preferences as a reason that advance directives are an "inferior strategy for making end-of-life decisions"). See generally Terri R. Fried, Amy L. Byers, Williams T. Gallo, Peter H. Van Ness, Virginia R. Towle, John R. O'Leary & Joel A. Dubin, *Prospective Study of Health Status Preferences and Changes in Preferences Over Time in Older Adults*, 166 ARCHIVES INTERNAL MED. 890 (2006); Nina A. Kohn & Jeremy A. Blumenthal, *Designating Health Care Decision-Makers for Patients Without Advance Directives: A Psychological Critique*, [http://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=1008494](http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1008494) (showing that individuals often do a poor job of predicting their future treatment preferences).

161. E.g., *In re Westchester County Med. Ctr.*, 531 N.E.2d 607 (N.Y. 1988) (holding that the hospital was authorized to insert a feeding tube into the incapacitated patient in the absence of clear and convincing evidence that the patient's wishes were otherwise).

162. Norman L. Cantor, *Discarding Substituted Judgment and Best Interests: Toward a Constructive Preference Standard for Dying, Previously Competent Patients Without Advance Instructions*, 48 RUTGERS L. REV. 1193, 1245 (1996) (arguing that requiring evidence of the patient's desire to refuse life-sustaining treatment ignores the fact that "the vast majority of competent people do not wish to be preserved in a demented, gravely debilitated, and helpless state"); see also *Cruzan v. Dir., Mo. Dep't of Health*, 497 U.S. 261, 316 (1990) (Brennan, J., dissenting) (arguing that requiring clear and convincing evidence of the patient's prior decision to refuse life-sustaining treatment imposes a "markedly asymmetrical evidentiary burden" that undermines the goal of promoting the patient's autonomy).



considerations do not apply to most decisions about medical research. Rather, research is generally an optional activity that is primarily designed to benefit future patients, not the subjects in the study. It is true that, in some situations, participating in certain types of direct-benefit studies may be in the best interests of someone without viable medical alternatives, and in those cases, deference to surrogate decision makers can be justified by the same principles that justify deference to surrogate decisions about medical treatment. However, the rationale for deferring to surrogates would not apply to most other types of research, including all studies not involving a prospect of direct benefit to the subjects. For those studies, if the principles governing treatment decisions are accurately applied, surrogate consent would have to be based on very clear evidence of the incapacitated person's prior decision to participate in research of that nature.<sup>163</sup> For the reasons explained above,<sup>164</sup> this type of evidence will rarely be available.

### *B. Other Proposed Justifications*

A few justifications for research with decisionally impaired subjects that do not rely on the standards applicable to decisions about medical treatment have been discussed in academic literature. These justifications can be divided into two groups. The first, grounded in an individual rights perspective, seeks to show that allowing surrogate consent to research is consistent with the principle of individual autonomy. The second rejects individual autonomy as the governing paradigm and instead relies on communitarian theories about family relationships or individuals' obligations to society.

For those seeking to reconcile surrogate consent to research with individual autonomy, the challenge is to show that enrolling an incapacitated person in research without clear evidence of her wishes respects her right to make her own decisions about the use of her body. One way to do this is to draw on an argument sometimes made to support the use of incapacitated persons as organ donors—the theory of “presumed altruism.” This approach presumes that in the absence of evidence to the

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163. The commission reports discussed in Part II did not recognize this distinction. The NBAC report said nothing about the level of evidence of the incapacitated person's wishes that would be required in any type of study. The NYSAWG would have required heightened evidence of the incapacitated person's wishes only in no-direct-benefit studies involving more than a minor increase over minimal risk. For all other studies, surrogates could rely on “any relevant information” suggesting that “the research is in accordance with the individual's wishes.” NYSAWG REPORT, *supra* note 111, at 26–27. The report's list of “relevant information” is quite broad, including, for example, “statements by the individual about the effect of research participation on the individual's family or on others who have the same condition.” *Id.* at 27. Nothing in the report suggests that surrogates would have to produce specific evidence to support their claims about the incapacitated person's wishes. In contrast to the NYSAWG, the Maryland group would have applied a heightened evidentiary standard to all more-than-minimal-risk no-direct-benefit studies. *See Hoffmann & Schwartz, supra* note 113, at 144 (noting that the group's proposal would have required health care agents to have “direct and explicit evidence of the individual's wish to participate, as documented in accordance with standards and procedures set by the IRB”). However, the heightened evidentiary standard would not have applied to any studies involving a prospective of direct benefits, regardless of the risk level.

164. *See supra* text accompanying notes 125–29.

contrary, all people would altruistically consent to accepting moderate risks for the benefit of others.<sup>165</sup> If this presumption is correct, enrolling an incapacitated person in research—even in a no-direct-benefit study—would be fully consistent with respect for autonomy, as it would simply be promoting the incapacitated person’s probable preferences. In fact, some commentators argue that it is disrespectful of incapacitated persons to deny them the opportunity to act altruistically because doing so treats them “as less than fully human.”<sup>166</sup>

The problem with this approach is that one of the main reasons that altruism is considered commendable is that it is not something we normally expect of people. Instead, altruism is generally regarded as a supererogatory activity—that is, commendable behavior that goes above and beyond what is normally expected in our society.<sup>167</sup> In the absence of evidence of an incapacitated person’s wishes, we should not presume that she would engage in activities that are generally considered extraordinary. Instead, the default assumption should be that she would comply with social expectations but not necessarily exceed them—in other words, that she would act like the law’s hypothetical “reasonable person.” Otherwise, we would be subjecting incapacitated people to higher expectations than those to which the rest of us are held.

Moreover, it is far from clear that most people would, in fact, altruistically assume the risks of research for the benefit of other people. Most competent people have never volunteered to be research subjects; in fact, interest in participating in clinical trials among United States residents has been declining for the past decade, forcing — researchers to look overseas to attract a sufficient number of subjects.<sup>168</sup> Therefore, the presumption that incapacitated people would probably consent to be research subjects rests on a weak empirical foundation.

Rather than attempting to reconcile surrogate consent to research with respect for individual autonomy, other approaches rely on theories that de-emphasize autonomy in favor of communitarian values. In general, communitarians reject liberalism’s focus on “the individual as a bounded, integrated whole that is separate from other individuals,”<sup>169</sup> and instead emphasize that individuals “are partly defined by the communities [they] inhabit.”<sup>170</sup> As a result, they argue, laws and policies should seek to strengthen communities and their internal values, rather than treating individual autonomy as inherently superior to all other goods.<sup>171</sup>

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165. *But cf.* CANTOR, *supra* note 133, at 175 (pointing out that lifelong incapacitated persons are unable to develop personal values concerning altruism). *See generally* Michael T. Morley, Note, *Proxy Consent to Organ Donation by Incompetents*, 111 YALE L.J. 1215 (2002).

166. Morley, *supra* note 165, at 1242; *see also In re Pescinski*, 226 N.W.2d 180, 184 (Wis. 1975) (Day, J., dissenting) (arguing that preventing incapacitated persons from donating their kidneys “condemn[s] the incompetent to be always a receiver, a taker, but never a giver”).

167. *See, e.g.*, David Orentlicher, *Making Research a Requirement of Treatment: Why We Should Sometimes Let Doctors Pressure Patients to Participate in Research*, HASTINGS CTR. REP., Sept.–Oct. 2005, at 24.

168. *See Research Notes—Clinical Trials: Efforts to Increase Participation Examined*, AM. HEALTH LINE, June 22, 2006.

169. Gaia Bernstein, *Accommodating Technological Innovation: Identity, Genetic Testing, and the Internet*, 57 VAND. L. REV. 965, 977 (2004).

170. Michael J. Sandel, *Introduction to LIBERALISM AND ITS CRITICS* 1, 6 (Michael J. Sandel ed., 1984).

171. *See* WILL KYMLICKA, *MULTICULTURAL CITIZENSHIP: A LIBERAL THEORY OF MINORITY*

Drawing on this communitarian framework, some commentators argue that the reason society should defer to surrogates' decisions about medical research is that surrogates are typically close relatives of the incapacitated person, and society has an interest in promoting the value of "family autonomy." Those who take this position emphasize the trust society places in families, the privacy inherent in family life, and the self-imposed social obligations that certain families assume.<sup>172</sup> Under this approach, deference to surrogates is appropriate not because surrogates will necessarily know the incapacitated person's wishes, but because it respects families' rights to establish and enforce their own values, including the value of self-sacrifice.

However, even accepting that intra-familial decisions are entitled to some level of deference, it is not clear why that deference should extend to decisions to enroll an incapacitated family member in medical research. Communitarian theory does not demand deference to any decisions that are made within close-knit communities. Rather, the goal of deferring to communities' decisions is to strengthen "the purposes and ends characteristic of those communities."<sup>173</sup> While it may sometimes be the case that a surrogate's decision to enroll an incapacitated family member in research stems from the family's "characteristic" willingness to expose themselves to risks for the benefit of others, there is no reason to assume that this will necessarily be true. Under a system that authorizes surrogate consent to research, families would be free to expose their incapacitated relatives to risks that no one else in the family would ever voluntarily accept. As a practical matter, there would be no way to determine whether a decision to enroll an incapacitated relative in a no-direct-benefit study reflects a family's shared commitment to the value of self-sacrifice, or whether the family's belief in self-sacrifice extends only to those family members who cannot make decisions for themselves.

Moreover, appeals to family autonomy as a justification for surrogate decision making rest on the questionable assumption that all families are necessarily cohesive "communities." Some incapacitated persons, if able to state their preferences, would probably say that they reject many of the values that are important to their relatives. In a liberal society, it is inappropriate to force someone to adhere to a community's self-proclaimed values unless the individual has voluntarily agreed that those values should bind her.<sup>174</sup> This is why we do not allow Jehovah's Witness families to refuse blood transfusions on behalf of incapacitated relatives without clear evidence that the person in need of the transfusion embraced the religious convictions held by the rest of the

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RIGHTS 91 (1995) (explaining that some communitarian theories call for the state to "reinforce people's allegiances" to ends that are "constitutive of people's identity").

172. See generally Kathleen Cranley Glass & Marc Speyer-Ofenberg, *Incompetent Persons as Research Subjects and the Ethics of Minimal Risk*, 5 CAMBRIDGE Q. HEALTHCARE ETHICS 362, 368-69 (1996).

173. Sandel, *supra* note 170 (emphasis added); see also Michael J. Sandel, *Justice and the Good*, in LIBERALISM AND ITS CRITICS 159, 167 (Michael J. Sandel ed., 1984) ("For a society to be a community in this strong sense, community must be constitutive of the shared self-understandings of the participants and embodied in their institutional arrangements, not simply an attribute of certain of the participants' plans of life.").

174. See KYMLICKA, *supra* note 171, at 152 ("Liberals are committed to supporting the right of individuals to decide for themselves which aspects of their cultural heritage are worth passing on.").

family.<sup>175</sup> The fact that an individual is related to people who hold particular values does not mean that the individual necessarily embraces those values herself.

Admittedly, there is one context in which the law lets families impose their values on persons incapable of consenting—the area of parental decision making for minor children. For example, in *Wisconsin v. Yoder*,<sup>176</sup> the Supreme Court held that Amish parents had the right to take their children out of school after the eighth grade, despite a state law requiring children to attend school until age sixteen, in order to promote Amish beliefs in the importance of remaining “aloof from the world.”<sup>177</sup> The Court emphasized the importance of protecting the parents’ ability to enforce their community’s values without demanding proof that the children themselves embraced those values.<sup>178</sup> *Yoder* is not an isolated decision. As noted above, the law generally gives parents broad leeway in making decisions for their minor children—even decisions that deviate from widely-held social values—as long as the parents’ decisions do not rise to the level of abuse or neglect.<sup>179</sup>

However, there are important differences between parental decisions for minor children and surrogate decisions on behalf of incapacitated adults. First, cases protecting the parents’ right to make decisions without undue state interference are grounded in large part on the unique role that parents play in *raising* their children. For example, in *Yoder*, the Court emphasized the “values of parental direction of the religious upbringing and education of their children in their early and formative years.”<sup>180</sup> Similarly, in *Pierce v. Society of Sisters*, the Court emphasized the parents’ role in “nurtur[ing]” a child and “direct[ing] his destiny.”<sup>181</sup> Raising a child involves unique rights and responsibilities not applicable to other types of intra-familial relationships. Most importantly, a parent of a minor child is expected to instill values and behavior that will help the child develop into a responsible person. The principle of parental autonomy protects parents’ right to shape their children’s character consistent with the parents’ own values and preferences, which arguably includes the right to teach the value of altruism by enrolling their children in research.<sup>182</sup> This justification does not apply to decisions by family members on behalf of incapacitated adults. For example, an adult child caring for a parent with Alzheimer’s has neither the right nor the ability to control the parent’s moral development. When family members are acting as caretakers rather than child-raisers, the argument for deference is considerably weaker.<sup>183</sup>

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175. *E.g.*, *In re Hughes*, 611 A.2d 1148 (N.J. Super. Ct. App. Div. 1992); *In re Dorone*, 534 A.2d 452 (Pa. 1987).

176. 406 U.S. 205, 234 (1972).

177. *Id.* at 210.

178. *See id.* at 242 (Douglas, J., dissenting in part) (criticizing the majority for “assum[ing] an identity of interest between parent and child”).

179. *See supra* note 173 and accompanying text.

180. *Yoder*, 406 U.S. at 213–14.

181. 268 U.S. 510, 535 (1925).

182. Randall Baldwin Clark, *Speed, Safety, and Dignity: Pediatric Pharmaceutical Development in an Age of Optimism*, 9 U. CHI. L. SCH. ROUNDTABLE 1, 28 (2002) (arguing that enrolling children in no-direct-benefit research could be “yet another context in which children might develop the charitable instincts that parents want them to possess”).

183. This distinction raises a difficult question: what standard should apply to parents making decisions about research for minor children with mental impairments who will never

Moreover, the general assumptions we have about the attitudes of parents toward their minor children are not necessarily applicable to other types of family relationships. Parents are presumed to be motivated by the child's best interests,<sup>184</sup> a presumption that is justified not just because they love their children but also because protecting one's offspring is a basic biological imperative.<sup>185</sup> In general, parents see their children as their legacy and contribution to the future. The same cannot be said for an adult child caring for an aging parent, a parent caring for a never-competent adult child, or one spouse caring for another. Moreover, family caregivers often "endure negative psychological and emotional costs because of compromised relationships, sacrifices of one's own family and career, and social isolation."<sup>186</sup> In some instances, these burdens can lead to "the development of negative feelings toward the care recipient,"<sup>187</sup> which should make us wary about presuming that family surrogates will always be motivated by incapacitated persons' well-being.<sup>188</sup>

Rather than attempting to justify surrogate decision making by relying on an open-ended principle of family autonomy, another group of communitarian-inspired commentators shifts the focus to claims about incapacitated persons' social responsibilities. Norman Cantor, the most articulate proponent of this position, argues that research with incapacitated subjects can be justified by "a concept of justice or fairness that is associated with mutual interdependence within communities."<sup>189</sup> He argues that principles of social justice permit surrogates to "impose some measure of sacrifice" on incapacitated persons "in return for the social or family child-rearing benefits being conferred on that person,"<sup>190</sup> including benefits such as "decent food, shelter, and care."<sup>191</sup> In response to the concern that "[t]he use of a social-justice rationale raises a specter of the past abusive exploitation of disabled populations,"<sup>192</sup> Cantor emphasizes the difference between government-imposed sacrifices and

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develop the capacity to make their own decisions? Such parents cannot justify exposing the child to risk by appealing to the educational aspects of research participation. In these cases it may be appropriate to require the parents' decisions to conform to whatever limitations apply to surrogate decision making for adult incapacitated subjects.

184. See, e.g., *Troxel v. Granville*, 530 U.S. 57, 66 (2000).

185. E.g., Elizabeth S. Scott & Robert E. Scott, *Parents as Fiduciaries*, 81 VA. L. REV. 2401, 2433-34 (1995).

186. Stefan Staicovici, *Respite Care for All Family Caregivers: The Lifespan Respite Care Act*, 20 J. CONTEMP. HEALTH L. & POL'Y 243, 251 (2003).

187. *Id.*

188. As Rebecca Dresser points out:

Proxies and surrogates may see a dementia patient's research participation as a vehicle to secure services or other benefits that ease caregiving responsibilities. Biological relatives may seek to enroll a family member in studies that offer the promise of reducing their own risks of future disease affliction. In empirical studies, some representatives said they would be willing to enroll a decisionally incapable relative in research even if they thought the relative would refuse participation if capable. Some representatives also said they would enroll a relative in a study that the representatives would refuse for themselves.

Rebecca Dresser, *Dementia Research: Ethics and Policy for the Twenty-First Century*, 35 GA. L. REV. 661, 675-76 (2001).

189. CANTOR, *supra* note 133, at 186.

190. *Id.* at 187.

191. *Id.*

192. *Id.*

sacrifices accepted by the incapacitated person's close relatives.<sup>193</sup> He also argues that the notion of "intrinsic human dignity"<sup>194</sup> places objective limits on the extent to which surrogates can "extract sacrifices" from incapacitated persons.<sup>195</sup> For example, he would limit surrogate consent to studies involving only minimal risk or, perhaps, studies involving a "minor increase"<sup>196</sup> over minimal risk; he would require that researchers demonstrate the "absolute necessity of using" incapacitated persons;<sup>197</sup> and he maintains that incapacitated persons' objections to research should always be honored.<sup>198</sup>

Yet, even with Cantor's proposed limitations, there are dangers in relying on claims about incapacitated persons' obligations to society as a justification for authorizing surrogate consent to research. The argument that incapacitated persons have an obligation to "pay back" for the receipt of social benefits implies that the care they receive is contingent—that is, a transfer of resources that must be reimbursed rather than the expression of an unconditional social obligation. Moreover, while Cantor is careful to emphasize that he is not advocating government compulsion, a focus on duties sends the message that surrogates who withhold consent are acting inappropriately. Surrogates may therefore feel greater pressure to consent to studies even if they are not formally compelled.

Ultimately, neither individualistic nor communitarian theories can adequately explain why surrogates should be permitted to enroll incapacitated persons in research. Individualistic arguments depend on fictions about incapacitated persons' presumed preferences that are neither credible nor consistent with the expectations we have for the rest of society. Communitarian theories about family autonomy rest on the questionable assumption that surrogate consent will be motivated by a shared familial commitment to the value of self-sacrifice, as well as the assumption that incapacitated persons necessarily share the values of their families. Finally, arguments that appeal to incapacitated persons' social obligations convey a message that threatens to undermine society's commitment to protecting the most vulnerable.

#### IV. AN ALTERNATIVE APPROACH

One response to the difficulty of justifying surrogate consent to research is to conclude that research with incapacitated persons should simply be prohibited. This conclusion cannot be dismissed out of hand. Past abuses of human subjects in research should certainly give us pause about permitting vulnerable individuals to be enrolled in studies without their own authorization, especially studies that involve risks without the prospect of direct benefits. The increasing commercialization of research, coupled with the corresponding rise in financial conflicts of interest, heightens the concern that researchers will insufficiently look out for the best interests of subjects.<sup>199</sup> Moreover,

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193. *Id.* at 188.

194. *Id.* at 191.

195. *Id.* at 192–93.

196. *Id.* at 194.

197. *Id.* at 198.

198. *See id.* at 199.

199. Jesse A. Goldner, *Dealing with Conflicts of Interest in Biomedical Research: IRB Oversight as the Next Best Solution to the Abolitionist Approach*, 28 J.L. MED. & ETHICS 379,

the oversight system for research has insufficient resources to carry out its responsibilities effectively,<sup>200</sup> thus creating the risk that researchers who push their ethical boundaries will not be identified or controlled.

Nonetheless, prohibiting research with incapacitated subjects, or limiting such research to the small number of persons who have left clear and convincing evidence of their desire to participate, is not the solution. The flaw with restrictive policies is that by focusing entirely on the risks associated with being a research subject, they ignore incapacitated persons' interest in receiving the benefits of improved medical treatments. From a public policy perspective, it makes no sense to assume that any burdens on the interests of research subjects are inherently improper, regardless of the level of those burdens, without taking into account the harm of excluding an entire population from the potential benefits of scientific advances.

This Part therefore proposes an analytical framework that recognizes incapacitated persons' dual interests in research—their interest in being protected from the risks of being involuntary research subjects, as well as their interest in reaping the benefits of studies that depend on the permissibility of surrogate consent. It begins by explaining the theory behind the framework and the implications of that theory for the types of studies for which surrogate consent should be permitted. It then considers how the proposed justification affects the way we conceptualize the surrogate's role.

*A. Two Levels of Best Interests: Broadening the Risk-Benefit Assessment Beyond the Level of the Individual Study*

As discussed in the previous Parts, a common theme to all approaches to surrogate consent is that to the extent they are concerned with the best interests of incapacitated persons, their focus is on the risks and benefits those persons face from being subjects in particular studies. This narrow focus ignores the fact that incapacitated people are affected not only by the studies in which *they* are the subjects, but also by studies in which *other* incapacitated people are subjects, given that they may benefit from treatments resulting from studies in which they do not personally participate. In light of this fact, incapacitated people face risks and benefits no matter how society's overall surrogate consent policy is structured. The more restrictive the policy, the more it protects individuals from being enrolled in studies with unfavorable risk-benefit profiles, but the less opportunity those persons have to benefit from studies in which they do not personally participate. The more permissive the policy, the more likely individuals will reap the benefits of research conducted with other incapacitated people, but the greater risk they face of being enrolled in studies that do not further their immediate medical interests and expose them to potential harm.

As a result, determining the best interests of incapacitated persons requires two different levels of risk-benefit analysis. First, we must identify the risks and benefits associated with enrolling in particular studies to determine whether enrolling in those studies will promote the best interests of the individual subjects. Second, we must step back from the particular study and evaluate the risks and benefits to incapacitated people from a broader, systemic perspective. Here, the relevant question is whether it is better or worse for incapacitated people *to be governed by a policy* that permits

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380 (2000).

200. Carl H. Coleman, *Rationalizing Risk Assessment in Human Subject Research*, 46 ARIZ. L. REV. 1, 3 (2004).

surrogates to consent to studies like the one under consideration. Although the two questions are related, they need not yield identical answers. In some cases, even if it is not in an individual's best interests to be enrolled in a particular study, given the balance between the study's risks and the expected direct benefits (or lack thereof), it may be in that person's best interests to be governed by a policy that puts her at risk of being enrolled in studies of that nature.<sup>201</sup> Whether that is in fact the case would depend on whether the risks to which she will be exposed as a result of the policy are outweighed by the benefits she is likely to receive from other studies that could not have been conducted unless the policy existed. Ultimately, the goal for public policy should be to create a rule that provides a net benefit to the persons who will be directly affected—that is, to those individuals who would bear the risk of being enrolled in studies that the policy authorizes, but who also would have to forego the benefits of any studies that the policy does not allow.

The claim that it may be in the best interests of incapacitated persons to be governed by a public policy that authorizes surrogate consent to no-direct-benefit research does not depend on proving that such a policy would necessarily provide greater benefits to each and every individual. In fact, it is possible that some people would end up worse off in such a system, as they might be enrolled in no-direct-benefit studies without receiving any benefits from research performed with other incapacitated people. For example, this might be true for persons who have conditions that were inadequately studied in the past. While such persons might benefit from concurrent or future research conducted with other incapacitated people, they would not be able to reap the benefits of any prior research. However, when we say that a particular course of action is in individuals' best interests, we are making a statement about the *ex ante* probability of benefit and harm, not a guarantee that every single person will necessarily benefit *ex post*. By way of analogy, if treatment A has a seventy-five percent success rate and treatment B has a twenty-five percent success rate, and there is no way to determine *ex ante* which treatment would work better for any particular person, it would be in every individual's best interests to receive treatment A—even though some people might actually end up worse off than if they had been given treatment B.<sup>202</sup>

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201. The possibility that individuals may be better off being governed by a policy that leads to negative outcomes in specific situations, while seemingly paradoxical, is in fact widely recognized. For example, this is the premise underlying the widely accepted theory of "rule utilitarianism." See John Lawrence Hill, *A Utilitarian Theory of Duress*, 84 IOWA L. REV. 275, 317 (1999) (explaining that rule utilitarianism "holds that one should follow the rule that tends to maximize happiness in similar cases *even if doing so does not maximize happiness in this particular case*") (emphasis added).

202. A well-known example of this *ex ante* approach to risk-benefit assessment is John Rawls's social contract approach to political justification. See JOHN RAWLS, *A THEORY OF JUSTICE* 15–19 (rev. ed. 1999). Rawls states that a system of rules is legitimate if it would be accepted by individuals deliberating behind a "veil of ignorance"—that is, without knowing what particular social advantages or status they would have once the rules are implemented. *Id.* Rawls argues that behind this veil, persons would rationally choose a system that granted everyone as much liberty as possible, as long as everyone else had the same amount of liberty, and they would apportion benefits and burdens equally, unless an unequal distribution would make everyone, especially the less fortunate, better off. *Id.* The approach proposed in this Article is consistent with this Rawlsian analysis. From behind a veil of ignorance, it is likely



A systemic approach to assessing the best interests of incapacitated persons reflects aspects of both the communitarian and individual rights approaches discussed in Part III. Like communitarian theories, the approach presented here does not treat individuals as atomistic units unconnected to the rest of society. Instead, the proposed approach looks at individuals as affected not only by what happens to them when they are enrolled in studies, but also by what happens to other people like them (i.e., by research conducted with other incapacitated people). At the same time, it rejects those aspects of communitarianism that focus on group interests at the expense of the individual. Thus, under the proposed approach, a surrogate consent policy would be justifiable only to the extent that it provides a net benefit to the *same* individuals who will bear the burdens of the policy. In other words, the justification for nonconsensual research is not that incapacitated people should accept risks for the benefit of others, but that they should accept risks if doing so is necessary to increase the likely benefits to *them*.

The argument presented here is different from the claim that incapacitated persons can legitimately be exposed to risky research in exchange for their receipt of “decent food, shelter, and care.”<sup>203</sup> The risk-in-exchange-for-care argument claims that it is appropriate to impose burdens on incapacitated persons in exchange for unrelated benefits—that is, benefits that could also be provided without requiring the recipients to accept the risk of being enrolled in research without their personal authorization. By contrast, under the approach proposed here, incapacitated persons could be exposed to the risks of research only to the extent that doing so is necessary to provide them with benefits that would otherwise be unattainable. Thus, incapacitated people are not being asked to make sacrifices in order to pay back a debt to society. Rather, the theory is that allowing surrogate consent, even to some types of no-direct-benefit research, is ultimately better for incapacitated people than a system in which surrogate consent is not allowed.<sup>204</sup>

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that people would accept some risk of being enrolled in studies without their personal authorization, but only if there were no other way that they could reap the benefits of improved medical treatments, and only if those benefits would have greater value to them than the risk of being made an involuntary research subject. While such an approach would create a certain degree of inequality, insofar as the risk of being enrolled in research involuntarily would fall entirely on persons without decision-making capacity, the inequality is necessary to promote better medical treatments for those who would be disproportionately burdened.

203. CANTOR, *supra* note 133, at 187.

204. Although the argument presented here represents a departure from the way that risk-benefit assessment is usually carried out in health care, the idea of evaluating individuals' best interests from a systemic perspective has been advanced in other legal areas. For example, David Rosenberg relies on a similar analysis to explain why it is in everyone's best interest to adopt a rule requiring mass tort cases to be adjudicated by class actions, as opposed to individual litigation. See David Rosenberg, *Mandatory-Litigation Class Action: The Only Option for Mass Tort Cases*, 115 HARV. L. REV. 831 (2002). While such a rule would impose burdens on some people, by preventing them from bringing individual lawsuits that might offer them greater financial rewards than participating in a class action, those burdens would be outweighed by the fact that a mandatory system is more likely to “maximize individual welfare by securing optimal deterrence and insurance.” *Id.* at 832. The structure of Rosenberg's argument is similar to the argument presented here. In both situations, the claim is that everyone is better off by accepting limits on individual autonomy, even if those limits impose burdens on certain people, if those limits are necessary to create a system that ultimately maximizes

This approach also explains why it is ethically acceptable to enroll incapacitated people in research they have not personally authorized despite the fact that the law does not require similar sacrifices from persons who have decision-making capacity. For conditions that affect decisionally capable persons, there is no need to deviate from our usual commitment to individual autonomy, because whatever research needs to be conducted can take place with subjects who have voluntarily agreed to participate.<sup>205</sup> By contrast, important research on capacity-impairing conditions could not be conducted if we limited such research to individuals whose desire to participate could clearly be established.<sup>206</sup> Thus, the justification for policies that impose greater burdens on incapacitated people than on people with capacity is that incapacitated people would be even worse off without such policies because they would lose the potential long-term benefits of medical progress.

In order for a policy authorizing surrogate consent to research to provide a long-term net benefit to incapacitated people, it would have to satisfy several conditions. First, to be able to say that members of the target population would be better off in a system that allows them to be enrolled in research even if their wishes are uncertain, research with incapacitated subjects should offer the affected population potential benefits that would otherwise be unattainable. Thus, incapacitated persons should be used as subjects only in studies that cannot be conducted with competent persons, and such research should be limited to conditions of unique concern to persons with impaired decision-making capacity. It would be inappropriate to enroll incapacitated persons in studies directed at conditions that affect the general population (e.g., cancer research) unless participating in the study is genuinely in the best interests of the individual subjects.

These conditions are consistent with recommendations proposed by other commentators.<sup>207</sup> However, the framework proposed here also suggests another condition that has not been part of the existing policy discussion. This condition stems directly from the trade-off on which the entire framework is grounded—that is, the assumption that incapacitated persons will benefit from research performed with other persons like them, in exchange for accepting comparable risks for the benefit of similarly situated persons. Reasonable people would be unlikely to accept this trade-off unless they had some assurance of *actually receiving* the treatments resulting from research conducted with other incapacitated subjects. Thus, an acceptable policy on research with incapacitated subjects should include mechanisms to provide such persons access to the fruits of medical research.

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individual well-being.

205. Of course, this statement must be tempered by the fact that the ideals of informed consent are often not realized in practice. See, e.g., Nancy Neveloff Dubler, *Remaining Faithful to the Promises Given: Maintaining Standards in Changing Times*, 32 SETON HALL L. REV. 563, 567 (2002). Many research subjects agree to participate because of a “therapeutic misconception”—the mistaken belief that everything that happens to them in research is motivated by the researchers’ commitment to their personal medical needs, rather than the researchers’ pursuit of general knowledge. Rebecca Dresser, *The Ubiquity and Utility of the Therapeutic Misconception*, 19 SOC. PHIL. & POL’Y 271, 271 (2002). These problems demonstrate the importance of continued efforts to improve the process of informed consent to research.

206. See *supra* text accompanying notes 125–29.

207. NBAC REPORT, *supra* note 57, at 55–56; NYSAWG REPORT, *supra* note 111, at 28.

A variety of mechanisms could be created to ensure that incapacitated persons have access to treatments resulting from research with other persons. For example, as a condition of conducting research with decisionally impaired subjects, research sponsors could be required to undertake measures to ensure better access to medications to members of the population being studied. Such an obligation would be similar to policies applicable to research conducted in developing countries. The guidelines of the Council for International Organizations of Medical Sciences state that sponsors of research in developing countries should ensure that “any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.”<sup>208</sup> Some commentators have urged sponsors to take an even broader view of their obligations to research participants. One policy group recommended that, in addition to providing the products of research to the host country, sponsors should consider measures such as “enhancing health care or research facilities, providing critical equipment, other physical infrastructure such as roads or vehicles, training of health care and research staff, and training of individuals in research ethics.”<sup>209</sup>

In addition to expected benefits, the risks of a study are also important considerations. On the one hand, a rule permitting incapacitated people to be enrolled in minimally or moderately risky research can be justified by the benefits those persons are likely to receive from similar research conducted with other incapacitated people. In such a system, it is unlikely that anyone would be subjected to burdens that are disproportionate to the benefits they can expect to receive. On the other hand, there is less justification for a system that would permit incapacitated people to be enrolled in

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208. COUNCIL FOR INT’L ORG. OF MED. SCI. & WORLD HEALTH ORG., INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS Guidelines 51–53 (2002).

209. Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries, *Fair Benefits for Research in Developing Countries*, in ETHICAL AND REGULATORY ASPECTS OF CLINICAL RESEARCH 354, 354 (Ezekiel J. Emanuel, Robert A. Crouch, John D. Arras, Jonathan D. Moreno & Christine Grady eds., 2003). It might be argued that offering incapacitated persons greater access to health care in exchange for enrolling in research would constitute an “undue inducement.” A possible response to this argument is that concerns about undue inducement are unwarranted as long as the risks of a study are not excessive. As Ezekiel Emanuel argues, “[u]ndue inducement is when we offer people goods to assume *clearly excessive and unreasonable risks*.” Ezekiel J. Emanuel, *Undue Inducement: Nonsense on Stilts?* AM. J. BIOETHICS, Sept./Oct. 2005, at 9, 11 (emphasis in original). In addition, to the extent that the concern with undue inducement is that it compromises the voluntariness of an individual’s decision to enroll in research, *see, e.g.*, Harold Y. Vanderpool, *A Quartet of Criticisms*, AM. J. BIOETHICS, Sept./Oct. 2005, at 16, 17, this concern is attenuated in studies in which consent is provided by a surrogate. In research with competent persons, establishing the voluntariness of the subject’s decision is critical because the main justification for exposing competent persons to risks is that they have voluntarily agreed to assume them. *See supra* text accompanying notes 74–76. By contrast, under the proposed framework, the acceptability of research with incapacitated persons depends less on the surrogate’s motivations for consenting and more on characteristics of the study itself—specifically, whether it fits within a policy that provides a net benefit to incapacitated people. Because the surrogate’s reasons for consenting do not determine the ethical acceptability of the research, there is less reason to be concerned about the “purity” of the surrogate’s choice.

studies involving high risks<sup>210</sup> without a corresponding direct benefit—for example, a symptom-provoking study involving a significant risk of serious injury. If high-risk studies were permitted, individuals would be subjected to significant burdens that could very well outweigh the benefits they could expect to receive from research conducted with other incapacitated people.

Thus, the approach proposed here suggests that surrogate consent should not be a sufficient basis for enrolling incapacitated persons in high-risk, no-direct-benefit studies. Instead, such research should be limited to persons whose wishes to participate can be established through clear and convincing evidence. NYSAWG reached a similar conclusion; it would have limited no-direct-benefit studies involving “more than a minor increase over minimal risk” to persons who had executed a “research advance directive” that specifically stated their willingness to be enrolled in that kind of research.<sup>211</sup> Theoretically, it might be possible to clearly establish an individual’s desire to participate in such research even in the absence of a written advance directive,<sup>212</sup> but a bright line rule requiring advance written instructions seems appropriate here, given the potential for abuse.

### *B. The Role of Surrogate Decision Makers*

The proposed approach requires decisions to be made at three different levels: administrative agencies, IRBs, and individual surrogates. First, administrative agencies (primarily DHHS) would promulgate regulations identifying the type of studies for which surrogate consent is appropriate, taking into account the considerations discussed in the previous section. Such regulations could be modeled on the existing regulations governing research with children, which among other things, place limits on the level of permissible risk.<sup>213</sup> Once the criteria for approving studies have been adopted at the regulatory level, the determination of whether a particular study satisfies those criteria would either be left to local IRBs or, for particularly sensitive studies, a national board.<sup>214</sup>

The more difficult question under the proposed framework is determining the role that surrogates would play. As explained above, the premise of the framework is that it is appropriate to enroll incapacitated people in research without their authorization if

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210. “High risk” should be defined as “more than a minor increase over minimal risk,” the standard used in the existing federal regulations on research with children. *See* 45 C.F.R. § 46.406 (2008). A “minor increase” is by definition “minor,” and preventing this minor increase could exclude many important types of research, such as studies involving brain imaging. *See supra* text accompanying notes 58–59.

211. NYSAWG REPORT, *supra* note 111, at 32–33. By contrast, NBAC would allow surrogate consent to more-than-minimal-risk, no-direct-benefit research without the subject’s advance authorization, provided that the study was approved by a special national panel and the subject’s surrogate consents. NBAC, *supra* note 57, at 61.

212. *See, e.g., In re Westchester County Med. Ctr.*, 531 N.E.2d 607, 613–14 (N.Y. 1988) (holding that clear and convincing evidence of an incapacitated person’s decision to refuse life-sustaining treatment need not be in writing).

213. Ideally, the regulations would also address other issues that arise in research with incapacitated subjects, such as the process of determining incapacity.

214. *See, e.g.,* 45 C.F.R. § 46.407 (2008) (requiring the approval of a national board for pediatric research that would otherwise not be approved under the regulatory standards).

the risks to which they will be exposed are commensurate with the benefits they can expect to receive from research conducted with other incapacitated people. Assuming that standard is met, one might ask why surrogate consent should also be necessary. If surrogates have the option of refusing to consent to any type of research for particular individuals, those people would get all the benefits of the system without assuming any of the risks—in other words, there could be a substantial free-rider problem.<sup>215</sup> This danger arguably suggests that participating in research should be mandatory for incapacitated people, assuming an IRB has determined that a study meets the criteria outlined in the previous section.

However, a system in which incapacitated persons could be enrolled in research without first obtaining consent from a surrogate would have several significant drawbacks. First, one of the benefits of requiring surrogate consent is that it provides a mechanism for overseeing what happens to incapacitated subjects in research.<sup>216</sup> If it were permissible to enroll incapacitated people in research without a surrogate's authorization, both researchers and IRBs might be less vigilant about limiting the risks to which incapacitated people are exposed.

In addition, requiring surrogate consent can help identify those individuals for whom enrolling in research presents an unusually significant imposition. Even in studies classified as "minimal risk," what is minimal risk for most people can constitute a significant burden on others. For example, as NBAC observed, "a diversion in routine can, for some dementia patients, 'constitute real threats to needed order and stability, contribute to already high levels of frustration and confusion, or result in a variety of health complications.'"<sup>217</sup> Participating in research may also pose a special burden on individuals with religious or moral objections to particular medical interventions.

Requiring surrogate consent also shows respect for the family as the primary locus of decision making for incapacitated persons. In Part III, it was argued that the notion of family autonomy provides an insufficient basis for exposing incapacitated people to the risks of no-direct-benefit research.<sup>218</sup> However, that does not mean that a family's objections to enrolling their relatives in research are not entitled to respect. One need not accept an open-ended principle of "family autonomy" to recognize that cutting families out of the process entirely would be disrespectful of an important social institution.

Finally, it is simply unrealistic to think that a mandatory system would ever be adopted in our society. Despite the free-rider problem, conscripting incapacitated persons into research without even asking their families just seems offensive. Any proposal to adopt a mandatory system would therefore generate substantial public opposition.

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215. Cf. Rosamond Rhodes, *Rethinking Research Ethics*, AM. J. BIOETHICS, Jan./Feb. 2005, at 7, 15 (arguing that all people should be required to perform "periodic service as research subjects," and suggesting that "[t]o 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").

216. See Dresser, *supra* note 60, at 27.

217. NBAC REPORT, *supra* note 57, at 44.

218. See *supra* text accompanying notes 173–79.

What then are the implications of this Article's shift in perspective for the process of surrogate decision making? First, the approach proposed here underscores the importance of ensuring that surrogates understand the differences between participating in research and receiving ordinary medical treatment. If a study offers no potential direct benefits to subjects, that fact should be made clear to surrogates in unambiguous language.<sup>219</sup> In studies involving a prospect of direct benefit, the researchers should explain how receiving an investigational intervention as part of a research study differs from receiving that same intervention in the context of an individualized physician-patient relationship.<sup>220</sup> They should also tell surrogates whether participating in the study is the only way to receive the investigational intervention, or whether that intervention could also be obtained without participating in research.<sup>221</sup>

Second, the proposed approach requires modifying the substantive standards surrogates are asked to apply in deciding whether to enroll incapacitated persons in research. This does not mean that the wishes/best interests standards should be completely abandoned. In some cases, the surrogate may have knowledge of an incapacitated person's wishes about being a research subject. In other cases, participating in research might be a reasonable choice from the perspective of a best interests analysis. However, researchers should not mislead surrogates into thinking that they will usually be able to justify decisions to enroll incapacitated people in research under the wishes/best interests framework that governs ordinary treatment decisions. Instead, as part of the informed consent process, surrogates should be told that they are being asked to deviate from the incapacitated person's immediate interests in order to provide potential benefits to other incapacitated people—just as the prospective subject may have benefited from comparable risks assumed by other incapacitated people in similar situations. Because the surrogate's authority to consent is grounded in a policy designed to promote the best interests of incapacitated persons, the surrogate need not feel that consenting would be disrespectful or exploitative of the prospective subject. However, surrogates will ultimately have to rely on their own moral framework in deciding whether this rationale provides an acceptable justification for them.

Finally, the framework developed in this Article suggests that surrogates should see their roles as extending beyond the incapacitated person's experience in the specific study to which the surrogate is consenting. Because the justification for exposing incapacitated people to the risks of research is that they may benefit from similar research performed with other incapacitated people, a surrogate who consents to research should assume an obligation to advocate for the subject's access to the benefits derived from other medical research. One way to carry out this responsibility would be to ensure that the IRB has imposed sufficient conditions on the research sponsors to promote incapacitated persons' access to the fruits of medical research,<sup>222</sup> and to take action against the sponsors if those conditions are not satisfied.

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219. See Nancy M.P. King, *Defining and Describing Benefit Appropriately in Clinical Trials*, 28 J.L. MED. & ETHICS 332, 334 (2000) ("When benefit cannot reasonably be expected, the consent form should say, '[Y]ou will not benefit.'").

220. See *supra* text accompanying notes 33–40.

221. See *supra* text accompanying notes 46–50.

222. See *supra* text accompanying notes 205–06.

In addition to providing a more coherent justification for authorizing surrogate consent to medical research, the approach proposed in this Article should help surrogates better understand the nature of the decisions they are being asked to make. Instead of telling surrogates that consenting to research itself provides a benefit to incapacitated persons by carrying out their wishes or promoting their best interests, the proposed approach emphasizes that participating in research is often more of a burden than a benefit. The justification for imposing these burdens is that the subjects are likely to be better off in the long run because they will have access to the fruits of research conducted with other incapacitated people. Surrogates would therefore be encouraged to ensure that this promise of broader access is actually carried out.

#### CONCLUSION

As the amount of research with incapacitated human subjects continues to increase, the lack of clear legal authority for this research is becoming increasingly untenable. Previous attempts to authorize and regulate this research have been unsuccessful in part because of their lack of a coherent and persuasive ethical framework. This Article seeks to move the policy debate forward by providing a new way of thinking about the ethics of research with incapacitated persons. Because the framework developed here is grounded in a commitment to the long-term best interests of incapacitated persons, it responds to the criticism that authorizing research with incapacitated persons constitutes a form of exploitation. At the same time, because it clearly differentiates the justification for surrogate consent to research from the principles underlying surrogate consent to medical treatment, it shows why laws that simply authorize surrogate consent without any significant limitations do not provide an appropriate model. Finally, by shifting the focus away from the often irrelevant wishes/best interests inquiry, it provides the foundation for a more honest and useful message to surrogates about what is at stake in their decisions.