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REGULATING RESEARCH ON THE TERMINALLY ILL: A PROPOSAL FOR HEIGHTENED SAFEGUARDS

*D. Christian Addicott**

Within a year, if all goes well, the first cancer patient will be injected with two new drugs that can eradicate any type of cancer, with no obvious side effects and no drug resistance. . .

These are heady times for researchers searching for cures, therapies, or vaccines for terminal illnesses ranging from cancer to AIDS to Alzheimer's. Gene therapy and other advances in biotechnology have opened up new areas of research and spawned a major industry devoted to the development, and eventual marketing, of new treatments.² The potential payoff, in both human and financial terms, is huge. Investors are betting billions of dollars on start-up biotechnology companies,³ and patients desperate for a cure are vigorously competing to be included as research subjects.⁴

Yet lurking beneath this optimism is risk. Investors must contend with a highly volatile market in which most companies they pick will be losers.⁵ For those suffering from terminal illnesses, the risk is more profound. They must contend with the likelihood that their dreams of a cure will prove to be illusory, and with the chance that the experimental

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1. Gina Kolata, *A Cautious Awe Greets Drugs That Eradicate Tumors in Mice*, N.Y. TIMES, May 3, 1998, at A1.

2. See *Special Report: Curing Cancer — How to Tell the Hype from the Hope*, TIME, May 18, 1998, at 38-51 [hereinafter *TIME Special Report*].

3. See Andrew Pollack, *For Biotechnology Investors, A Week of Lessons on Volatility*, N.Y. TIMES, May 10, 1998, at B6.

4. See Kolata, *supra* note 1, at A1 (stating that even before receiving any publicity a developer of potential new cancer drugs received "hundreds of calls a day from cancer patients, pleading for the drugs").

5. See Pollack, *supra* note 3, at B6.

treatments they receive may injure or kill them.⁶ First-hand experience with this risk has led me to question the sufficiency of the informed consent paradigm as applied to research involving the terminally ill as subjects.

In 1993, my mother, who was suffering from metastatic breast cancer, died of "regimen-related toxicities" while participating in research designed to determine the maximum tolerable dose of busulfan and cytoxin that could be administered safely in conjunction with an autologous peripheral stem cell transplant.⁷ Deciding whether to participate in the study was difficult for her. Despite familiarity with the medical jargon, a graduate degree in health administration, and twenty years of experience working in hospitals, she had great difficulty analyzing the risks and benefits rationally. Because of the fear, anxiety, and sadness she felt knowing that her death was an imminent possibility, logic seemed to fail her. Ultimately, her decision was based more on emotion, intuition, and the advice of her doctors.

6. Both the benefits and risks of human research are often exaggerated. For example, in Phase I cancer trials, response rates as low as four to six percent are sometimes seen, and complete responses are extremely rare. However, the chance of having a fatal reaction to the drugs tested in these studies is between one-half and one percent. See Christopher K. Daugherty et al., *Learning from Our Patients: One Participant's Impact on Clinical Trial Research and Informed Consent*, 126 ANNALS INTERNAL MED. 892, 896 (1997) (citing G. Decoster et al., *Responses and Toxic Deaths in Phase I Clinical Trials*, 1 ANNALS ONCOL. 175 (1990); D.D. Van Hoff & J. Turner, *Response Rates, Duration of Response, and Dose Response Effects in Phase I Studies of Antineoplastics*, 9 INVEST. NEW DRUGS 115 (1991)).

7. Busulfan and cytoxin are common cancer chemotherapy drugs. Stem cells are produced by bone marrow and mature into the blood cells, such as T-cells, that comprise the front lines of the immune system. Chemotherapy kills cells that, like cancer cells, multiply quickly. Because stem cells also multiply quickly, high-dose chemotherapy cripples the immune system. An autologous stem cell transplant seeks to avoid this side effect by collecting healthy stem cells from the patient prior to chemotherapy, and then reintroducing the cells into the body after the chemotherapy drugs have been flushed from the patient's system. The term "regimen-related toxicities" refers to side effects of the research protocol as opposed to effects of illness.

Research has yet to establish "whether high-dose chemotherapy (HDC) followed by bone marrow or peripheral blood stem-cell transplant offers breast cancer patients better survival odds than conventional treatment." Joan Stephenson, *Researchers Struggle with Trial of Stem-cell Transplants for Breast Cancer*, 277 JAMA 1827, 1827 (1997).

If someone experienced and educated in the medical field had such difficulty understanding and weighing the risks, what does it really mean for terminally ill patients to give their "informed consent" to participate in research that has the potential to save or extinguish their lives? Is the current regulatory system adequate to ensure that the terminally ill are not taken advantage of when they participate in such research? Does it ensure that they receive the information necessary to make these difficult decisions? And does it prevent inattentive or unethical researchers from coercing the terminally ill into participating in experiments that may not be in their best interest? These are the central questions to which this Article responds.

Part I of this Article describes the modern federal regulatory system in the United States. Part II argues that the terminally ill are vulnerable to research abuse for a variety of reasons. Part III proposes and analyzes potential regulatory reforms designed to better protect the unique interests of terminally ill research subjects. This Article concludes that the following regulatory reforms should be adopted:

- (1) The terminally ill should be classified under the regulations as a vulnerable population;
- (2) Institutional Review Boards (IRBs) that approve research involving the terminally ill should be required to include or consult with at least one member who would represent the interests of the terminally ill;
- (3) Researchers who involve the terminally ill as subjects should be trained to recognize the psychological difficulties that the terminally ill face;
- (4) With a few exceptions, research on the terminally ill should be prohibited unless it is intended to provide a therapeutic benefit to the subjects;
- (5) Terminally ill patients should receive psychological evaluations before participating in research studies; and
- (6) Subject advocates should be available to assist the terminally ill during the informed consent process.

I. FEDERAL REGULATION OF RESEARCH INVOLVING HUMAN SUBJECTS

Research with human subjects in the United States is peer-reviewed by local Institutional Review Boards. The primary obligations of IRBs are to ensure that research conducted at each institution is ethically and

scientifically sound — based on a determination that the risks posed to the research subjects are justified by the potential benefits of the research — and to ensure that the participants in these studies are selected in an equitable manner and give their informed, voluntary consent prior to participating. Additional protections are provided for children, prisoners, and other “vulnerable” populations, but the terminally ill are not identified as “vulnerable,” and no specific regulations are in place to protect their interests. Indeed, after heavy lobbying by AIDS activists and others, some of the regulatory hurdles for approval of and access to new drugs have been lowered.

A. General Regulatory Framework

The federal regulations⁸ lay out broad guidelines for the conduct of research involving human subjects with which IRBs must comply. There are structural regulations governing the composition and duties of IRBs, substantive regulations governing the types of research that may be con-

8. Regulations governing research sponsored by Department of Health and Human Services (HHS), codified at 45 C.F.R. §§ 46.101-46.124 (1998) served as the model for the development of the “Federal Policy for the Protection of Human Subjects.” PRESIDENT’S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS IN MEDICINE AND BIOMEDICAL AND BEHAVIORAL RESEARCH, IMPLEMENTING HUMAN RESEARCH REGULATIONS 1 (1983). These rules, referred to collectively herein as “the regulations,” or “the federal regulations,” have been adopted by the various federal agencies that conduct or sponsor human subject research: the Department of Agriculture (7 C.F.R. pt. 1c), the Department of Energy (10 C.F.R. pt. 745), the National Aeronautics and Space Administration (14 C.F.R. pt. 1230), the Department of Commerce (14 C.F.R. pt. 1230; 15 C.F.R. pt. 27), the Consumer Product Safety Commission (16 C.F.R. pt. 1028), the International Development Cooperation Agency, Agency for International Development (22 C.F.R. pt. 225), the Department of Housing and Urban Development (24 C.F.R. pt. 60), the Department of Justice (28 C.F.R. pt. 46), the Department of Defense (32 C.F.R. pt. 219), the Department of Veterans Affairs (38 C.F.R. pt. 16), the Environmental Protection Agency (40 C.F.R. pt. 26), the National Science Foundation (45 C.F.R. pt. 690), and the Department of Transportation (49 C.F.R. pt. 11). Similar regulations have been adopted by the Food and Drug Administration (FDA) for the investigation of new drugs. See 21 C.F.R. pts. 312, 314. Except where noted, all references in this Article to the federal regulations are to the HHS regulations; however, the arguments made are equally applicable to research sponsored by other federal agencies. For an excellent summary of these regulations, see JEREMY SUGARMAN ET AL., *ETHICS OF RESEARCH WITH HUMAN SUBJECTS: SELECTED POLICIES AND RESOURCES* (1998).

ducted, and procedural rules to ensure that subjects give their informed consent.

1. Institutional Review Boards

IRBs are the backbone of the federal regulatory system.⁹ For the most part, federal regulatory agencies do not regulate research involving human subjects directly. Instead, IRBs perform the critical functions of reviewing, approving, monitoring, and, where appropriate, terminating research.¹⁰ Before approving research, an IRB must find that subject risk will be minimized; that risks are reasonable relative to benefits; that selection of subjects is equitable; that material facts will be disclosed; that the subjects will give their informed, voluntary consent; that there will be ongoing risk/benefit analysis; that subjects' privacy will be maintained; and that there are additional safeguards for "vulnerable" subjects.¹¹

Originally, IRBs were comprised almost exclusively of physicians and scientists who were peers of the researchers whose projects they reviewed.¹² In response to concerns that this arrangement involved a conflict of interest, the regulations subsequently were revised to require more diversity. Current regulations mandate that each IRB have at least five members, "with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution."¹³ Racial and ethnic diversity must be taken into account.¹⁴ If research involving vulnerable populations is regularly reviewed, someone with knowledge about those populations should be included on the IRB.¹⁵ There must be at least one person whose "primary area of con-

9. For a comprehensive description and analysis of the evolution and current role of IRBs, see ROBERT J. LEVINE, *ETHICS AND REGULATION OF CLINICAL RESEARCH* 321-63 (2d ed. 1986).

10. See 45 C.F.R. §§ 46.101-46.124; LEVINE, *supra* note 9, at 321-63.

11. See 45 C.F.R. § 46.111 (1998). One leading commentator identifies six ethical norms that underlie most codes and regulations governing research on human subjects: "There should be 1) good research design, 2) competent investigators, 3) a favorable balance of harm and benefit, 4) informed consent . . . 5) equitable selection of subjects . . . [and] 6) there should be compensation for research-related injury." LEVINE, *supra* note 9, at 19.

12. LEVINE, *supra* note 9, at 323-25.

13. 45 C.F.R. § 46.107(a) (1998).

14. See *id.* §§ 46.107(a), 46.107(b).

15. See *id.* § 46.107(a); see *infra* Part I.B.1.

cern" is scientific, and at least one whose is not.¹⁶ Finally, there must be at least one person who is unaffiliated with the institution.¹⁷ Given the flexibility of these guidelines, the composition and internal workings of IRBs vary immensely from institution to institution.¹⁸

2. *Substantive Limitations on the Types of Research that Will Be Approved*

Before approving any research the IRB must conclude that the risks to human subjects are acceptable. The research must employ procedures to minimize any risk that does exist.¹⁹ Moreover, the research must not be approved unless the risks are reasonable when weighed against the anticipated benefits to the subjects and the importance of the knowledge that could be gained from the research.²⁰ More specific, and more strict, rules limit the types of research that may be conducted on "vulnerable" populations such as pregnant women, fetuses, children, and prisoners.²¹

3. *Ensuring the Informed Consent of Research Subjects*

Historical abuses have exposed the potential for human experimentation to exploit the vulnerable and defenseless.²² At the same time, human experimentation is critical to the development of new treatments

16. See 45 C.F.R. § 46.107(c).

17. See *id.* § 46.107(d).

18. See THE PRESIDENT'S ADVISORY COMMITTEE, THE HUMAN RADIATION EXPERIMENTS: FINAL REPORT OF THE PRESIDENT'S ADVISORY COMMITTEE 543-48 (statement by Jay Katz) (1996); see also generally BRADFORD H. GRAY, HUMAN SUBJECTS IN MEDICAL EXPERIMENTATION: A SOCIOLOGICAL STUDY OF THE CONDUCT AND REGULATION OF CLINICAL RESEARCH (1975).

19. See 45 C.F.R. § 46.111(a)(1) (1998).

20. See *id.* § 46.111(a)(2).

21. See *infra* Part I.B.2. A revision of this policy is currently under consideration; if adopted, pregnant women would no longer be considered "vulnerable" under the regulations. See Protection of Human Research Subjects, 63 Fed. Reg. 27,793-95 (May 20, 1998); SUGARMAN ET AL., *supra* note 8, at 153.

22. See Patricia A. King, *Race, Justice, and Research*, in BEYOND CONSENT: SEEKING JUSTICE IN RESEARCH 96-99 (Jeffrey Kahn et al. Eds., 1998) (discussing the Tuskegee Syphilis Study); PRESIDENT'S ADVISORY COMMITTEE, *supra* note 18, at 273-75 (discussing abuses involving prisoners); Henry K. Beecher, *Ethics and Clinical Research*, 274 NEW ENG. J. MED. 1354, 1354 (1966) (providing one of the first documentations of post-World War II abuses in the United States); see generally JAY KATZ, EXPERIMENTATION WITH HUMAN BEINGS (1972) (providing throughout numerous examples of unethical experimentation on humans).

and therapies for human ailments. These competing concerns ultimately were balanced — and human experimentation legitimated — through the doctrine of informed consent. The doctrine holds that experiments should be conducted on human beings only if they freely consent after being provided with all of the information relevant to the decision.²³ In this way, human experimentation, with its concomitant benefits, could proceed with little risk that historical abuses would be repeated.

Accordingly, before an IRB approves research, it must find that the researchers will seek the legally effective informed consent of subjects.²⁴ Researchers must give subjects “sufficient opportunity to consider whether or not to participate [and] minimize the possibility of coercion or undue influence.”²⁵ Relevant information must be communicated to the subject in plain language, and researchers may not seek waivers of liability for negligence.²⁶ To satisfy the basic elements of informed consent, researchers must disclose that the study involves research;²⁷ describe the procedures to be followed, the expected risks and discomforts to the subject, and any anticipated benefits; and explain any alternative courses of treatment that might be beneficial.²⁸

To understand the protections that the regulations provide to vulnerable populations,²⁹ two elements of informed consent must be considered separately: voluntariness and information. These concerns play different roles in different contexts. Both prisoners and children, for

23. See LEVINE, *supra* note 9, at 96-153. The Nuremberg Code explains informed consent as follows:

The *voluntary* consent of the human subject is absolutely essential. This means that the person involved should have *legal capacity* to give consent; should be so situated as to be able to exercise *free power of choice*, without the intervention of any element of force, fraud, deceit, duress, over-reaching or other ulterior form of constraint or coercion; and should have sufficient *knowledge* and *comprehension* of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision.

Id. at 98.

24. See 45 C.F.R. § 46.111(a)(3) (1998).

25. *Id.* § 46.116.

26. See *id.*

27. This requirement recognizes that patient-subjects often will presume that they are being treated, not studied. See *infra* Part II.A.6.

28. See 45 C.F.R. § 46.116(a) (1998) (“Basic elements of informed consent”). In addition, the regulations provide a number of other requirements of informed consent, some of which apply only in special situations. See 45 C.F.R. §§ 46.116(a)(5)-(8), 46.116(b)-(f), 46.117 (“Documentation of informed consent”).

29. See *infra* Part I.B.

example, are considered "vulnerable" populations that are entitled to extra procedural safeguards before any research can go forward.³⁰ But different concerns underlie these protections. With prisoners, the concern is that their consent cannot be given voluntarily due to the inherently coercive nature of the prison environment. With children, the concern is whether they can sufficiently understand information in order to make a rational decision about whether to participate in research. With the terminally ill, both concerns may be present.³¹

B. Additional Protections for "Vulnerable" Populations

The regulations contain a number of general provisions designed to protect any human subject who may be vulnerable to coercion or undue influence. In addition, there are specific provisions regulating research involving pregnant women, fetuses, *in vitro* fertilization, children, and prisoners. Essentially, the regulations provide three types of protections: (1) structural provisions governing how IRBs will be comprised and who will make decisions, (2) substantive provisions governing what types of research will be allowed, and (3) procedural provisions to ensure that no research is done without the voluntary and informed consent of the human subjects.

*1. General Provisions Applicable to All Research*³²

The regulations use but do not define the term "vulnerable."³³ Instead, the regulations give examples of the types of subjects who are vulnerable, and implicitly empower IRBs to assess the vulnerability of types of subjects not listed.³⁴ Even when the current regulations were first proposed after an exhaustive analysis of the then-existing regulatory scheme, neither the Department of Health and Human Services (HHS)

30. See *infra* Part I.B.2.

31. See *infra* Part II.

32. The term "all research" refers to all research to which the regulations apply. Although the reach of the regulations is extremely broad, there is some research in the United States involving human subjects that continues to escape the net of federal regulation. See 45 C.F.R. § 46.101 (1998) ("To what does this policy apply?").

33. See 45 C.F.R. § 46.102 (failing to define the terms "vulnerable" or "vulnerable category of subjects"); see also 45 C.F.R. §§ 46.107 (governing the composition of IRBs), 46.111(a)(3) (listing criteria for research approval), and 46.111(b) (requiring additional safeguards when coercion is likely).

34. See, e.g., 45 C.F.R. § 46.107.

nor the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research provided any specific criteria with which to define vulnerable populations.³⁵

Structurally, vulnerable subjects are protected by encouraging representation of their interests on the IRBs. Section 107 of the model federal policy states that

if an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.³⁶

The presence of vulnerable populations as research subjects also may affect the types of research that are approved. Before an IRB may ap-

35. See PRESIDENT'S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS IN MEDICINE AND BIOMEDICAL AND BEHAVIORAL RESEARCH, IMPLEMENTING HUMAN RESEARCH REGULATIONS 23 (1983) [hereinafter COMMISSION REPORT]. The report does not define the term "vulnerable," but perhaps implies that the ability to give legal informed consent is the appropriate criterion to assess vulnerability. The report states:

Ethical concerns about [children and the mentally disabled] revolve around the issue of informed consent. Children, because of their age, are generally unable to provide legally effective informed consent. Those institutionalized as mentally disabled may or may not be able to give informed consent or their capacity may fluctuate over time.

Id.; see also Federal Policy for the Protection of Human Subjects, 53 Fed. Reg. 45,660, 45,666-67 (1988) (proposed Nov. 10, 1988) (discussing the effects of a proposed change with regard to representation of vulnerable persons on IRBs, but failing to define vulnerability).

36. 45 C.F.R. § 46.107(a) (1998). The previous version of this rule was more strict. It required IRB *representation* whereas the current rule requires only *consideration* of representation. See 45 C.F.R. § 46.107(a) (1985). HHS received a number of comments arguing that this relaxation of the regulations would put vulnerable populations at risk. See Federal Policy for the Protection of Human Subjects, 53 Fed. Reg. 45,660, 45,665 (1988) (proposed Nov. 10, 1988). The agency's response underscores the critical role that IRBs play in the federal regulatory scheme:

The Interagency Committee expects that institutions will use good judgment and diligence in selecting persons as IRB members who can fulfill the requirements of [section 107] In approving assurances the Federal Departments and Agencies that conduct, support, or regulate the research will review IRB composition to ensure that the membership is appropriate.

Federal Policy for the Protection of Human Subjects, 53 Fed. Reg. 45,660, 45,665-66.

prove research, it must determine that the selection of subjects is equitable.³⁷ In making this determination, the IRB "should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons."³⁸

Finally, research involving vulnerable populations receives heightened scrutiny to ensure the informed consent of the subjects. Before approving a protocol involving subjects "likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons," the IRB must ensure that "additional safeguards have been included in the study to protect the rights and welfare of these subjects."³⁹

2. Additional Protections for Particular Vulnerable Classes

The regulations create additional structural protections for certain vulnerable classes. First, for research involving pregnant women, fetuses, and human *in vitro* fertilization,⁴⁰ one or more "ethical advisory boards" is authorized to render advice as to whether certain types of research are ethical.⁴¹ The ethical advisory boards do not have any independent power to limit the types of research that can be done; rather, they are authorized to provide advice to HHS before certain types of research are approved.⁴² Second, for research involving prisoners, a majority of the IRB members must have no association with the prison from which the human subjects are selected, and at least one member of the IRB (or IRBs, if more than one reviews the research) must be a prisoner or "prisoner representative with appropriate background and expe-

37. See 45 C.F.R. § 46.111(a)(3) (1998).

38. *Id.*

39. *Id.*

40. See 45 C.F.R. pt. 46, subpt. B ("Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization"). These rules predate the model rule and apply only to HHS-sponsored activities. See 45 C.F.R. § 46.201.

41. See 45 C.F.R. § 46.204 (1998). No ethical advisory boards are currently constituted. Interview with Anna C. Mastroianni, Assistant Professor, University of Washington School of Law and the Public Health Genetics Program, Seattle, WA (Oct. 9, 1998).

42. See 45 C.F.R. § 46.204(c).

rience.”⁴³

Substantively, there are also significant limitations on the types of research that may be conducted. For research involving pregnant women or fetuses, unless the research is designed to meet the health needs of the mother or the fetus, the IRB should not approve it if it involves more than minimal risk to the fetus.⁴⁴ The IRB also should not approve such research if appropriate studies have not already been completed on animals and non-pregnant persons.⁴⁵

Restrictions on research involving prisoners are even more strict.⁴⁶ Researchers may examine the causes, effects, and consequences of incarceration or criminal behavior;⁴⁷ prisons as institutions;⁴⁸ conditions such as drug addiction that affect prisoners as a class;⁴⁹ and methods of

43. *Id.* § 46.304.

44. *Id.* §§ 46.206-46.208.

45. *See* 45 C.F.R. § 46.206(a)(1).

46. *See* 45 C.F.R. § 46.306 (1998). The regulations governing the use of prisoners as research subjects, 45 C.F.R. pt. 46, subpt. C, are very restrictive and reflect a basic presumption that any “consent” they give to participate in research is inherently suspect due to their incarceration. *See* 45 C.F.R. § 46.302 (1998) (“Inasmuch as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and informed decision whether or not to participate as subjects in research, it is the purpose of this subpart to provide additional safeguards for the protection of prisoners.”). This suspicion is, of course, warranted and a natural response to the notorious experiments conducted by Nazi doctors during World War II. These so-called experiments have been exhaustively documented and discussed elsewhere, beginning with the Nuremberg trials. *See generally* ROBERT J. LIFTON, *THE NAZI DOCTORS: MEDICAL KILLING AND THE PSYCHOLOGY OF GENOCIDE* (1986); CLAUDE J. LETULLE, *NIGHTMARE MEMOIRE: FOUR YEARS AS A PRISONER OF THE NAZIS* (1987) (recounting the personal experiences of a prisoner who was forced to assist in Nazi experiments on humans); GERALD L. POSNER & JOHN WARE, *MENGELE: THE COMPLETE STORY* (1986) (recounting in detail experiments conducted by Josef Mengele at the Auschwitz concentration camp between 1943 and 1945). Experimental abuses involving prisoners are by no means confined to the Nazis. *See* KATZ, *supra* note 22, at 1013-52 (discussing case studies of a variety of experiments on prisoners, many of which were conducted in the United States after World War II). Interestingly, however, the regulations primarily respond to this concern not by imposing procedural safeguards, but rather by tacitly creating an irrebuttable presumption that prisoners cannot give their informed consent to participate in most types of research.

47. *See* 45 C.F.R. § 46.306(a)(2)(i).

48. *See id.* § 46.306(a)(2)(ii).

49. *See id.* § 46.306(a)(2)(iii).

improving the health or well-being of the prisoners.⁵⁰ No other research may use prisoners as human subjects.⁵¹

There are also substantive restrictions on the types of research that may be conducted on children.⁵² If the risk to the child subjects is minimal, research may be approved if the requirements of informed consent are met for both parents and child.⁵³ Research likely to yield generalizable knowledge that is "vital to the understanding or amelioration of the subjects' disorder or condition" may be conducted if the risk "represents a minor increase over minimal risk."⁵⁴ If greater risk is involved,⁵⁵ the research must be intended to benefit the subject, the risk must be "justified" by the benefit, and the risk/benefit ratio of the experimental therapy must be at least as favorable as that provided by available alternative approaches.⁵⁶ IRBs may not approve research that fails to meet these requirements unless the Secretary of HHS makes an exception after finding that: (1) the research presents an opportunity to understand a serious health problem facing children; and (2) the research will be conducted ethically.⁵⁷

The regulations also impose further procedural safeguards to ensure that certain vulnerable research subjects do not participate without providing their fully informed consent. For research involving pregnant

50. See *id.* § 46.306(a)(2)(iv).

51. See 45 C.F.R. § 46.306(b).

52. See 45 C.F.R. §§ 46.404-46.406. Like prisoners, children historically have fallen victim to a wide variety of experimental abuse. See Ross G. Mitchell, *The Child and Experimental Medicine*, 1 BRIT. MED. J. 722, 725-26 (1964), reprinted in KATZ, *supra* note 22, at 963-64. Orphans, or "foundlings," were frequently used as research subjects with little or no thought to whether they had given their consent, and even the children of the researchers were sometimes used. See *id.* (discussing an 1894 experiment in which the researcher injected his son with a "crude extract of endocrine glands").

53. See 45 C.F.R. § 46.404 (1998).

54. *Id.* § 46.406 (1998). Minimal risk "means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." *Id.* § 46.102(i).

55. That is, any risk greater than "a minor increase over minimal risk." *Id.* § 46.406(a).

56. See *id.* § 46.405.

57. See 45 C.F.R. § 46.407. Additional requirements are imposed when the potential research subjects are wards of the state. See 45 C.F.R. § 46.409.

women⁵⁸ and fetuses,⁵⁹ the regulations suggest that the informed consent requirement is met if members of the IRB or "subject advocates" (1) participate in or at least carefully monitor the informed consent procedures, and (2) monitor or evaluate the research itself to determine whether any unanticipated risks to the subjects arise.⁶⁰ Also, to prevent undue influence, researchers cannot influence abortion decisions,⁶¹ determine the viability of a fetus at the termination of a pregnancy,⁶² or offer monetary or other incentives to terminate pregnancies for purposes of the research.⁶³ For research involving prisoners as subjects, IRBs may approve research only if: (1) the researchers do not provide inappropriate incentives to participate, such as better living conditions, food, or amenities; (2) the risks of participation would be acceptable to a non-prisoner volunteer; (3) the subjects are selected fairly; (4) relevant information is presented in comprehensible language; and (5) the prisoners' participation does not affect parole decisions.⁶⁴ Finally, when children are used as research subjects, their parents must provide their informed consent,⁶⁵ and the children themselves generally must "assent" to participation.⁶⁶

58. See 45 C.F.R. § 46.207 (1998).

59. See *id.* § 46.208.

60. See *id.* § 46.205(a)(2). This Article argues that similar safeguards should be employed to protect the terminally ill from coercion and undue influence. See *infra* Part III.

61. See *id.* § 46.206(a)(3)(i).

62. See 45 C.F.R. § 46.206(a)(ii).

63. See *id.* § 46.206(b).

64. See *id.* § 46.305(a).

65. See *id.* §§ 46.116 (general requirement of legally effective informed consent), 46.408(b), 46.408(c). There are, however, a number of caveats and qualifications to this rule. See *id.* §§ 46.408(b), 46.408(c).

66. See 45 C.F.R. § 46.408(a). Exceptions to this rule apply when the IRB determines that because of age, maturity, or psychology, the child-subject is incapable of assenting, or if the IRB determines that the research "holds out a prospect of direct benefit that is important to the health or well-being of the [child] and is available only in the context of research." *Id.* Thus, in at least some circumstances — so long as legally effective parental consent is obtained — the regulations tacitly authorize research involving child subjects against their will.

3. *The Terminally Ill as a "Vulnerable" Population?*

Commentators have long recognized that the terminally ill share some of the characteristics of "vulnerable" populations such as children and prisoners. "[L]ike children, their ability to make informed decisions is often either impaired or disregarded, and, like soldiers and prisoners, they are . . . 'captives' of their disease, their physicians and hospital, and their enforced isolation."⁶⁷ Yet current federal regulations provide no explicit protections for the terminally ill beyond those required whenever a human subject is employed in an experiment.⁶⁸

The terminally ill, unlike prisoners, children, pregnant women, and fetuses, have no dedicated regulations to ensure that they are not victimized in unethical research. Thus, if they are entitled to any regulatory protection, it must be found in the general regulations applicable to all "vulnerable" populations.⁶⁹ It is unclear whether and to what extent these rules apply.⁷⁰ On the one hand, the relevant regulatory provisions and the official government publications neither list nor discuss the ter-

67. KATZ, *supra* note 22, at 1053; *see also* LEVINE, *supra* note 9, at 77-79; JONI N. GRAY ET AL., *ETHICAL AND LEGAL ISSUES IN AIDS RESEARCH* 52 (1995) ("To be sure, research participants with fatal illnesses are vulnerable in many ways").

68. *See* 45 C.F.R. pt. 46 (1998). However, the terminally ill were mentioned as a potentially *incompetent* group in the Belmont Report, which served as the basis for the current federal regulations. THE NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, THE BELMONT REPORT 13 (1978) [hereinafter THE BELMONT REPORT] ("Each class of subjects that one might consider incompetent (e.g., infants and young children, mentally disabled patients, the terminally ill and the comatose) should be considered on their own terms").

69. These provisions encourage IRBs to include members of vulnerable populations if the IRB works with those populations, requires "equitable" selection of subjects considered in light of their "vulnerability," and requires additional safeguards to prevent coercion and undue influence. *See supra* Part I.B.1.

70. This discussion is relevant only to the terminally ill who are legally competent adults. Whether a terminally ill person who has been judged legally incompetent can participate in research is determined by whether his or her legally authorized representative consents. *See* 45 C.F.R. § 46.116. Similarly, children are already entitled to substantial protection under separate regulations. *See* 45 C.F.R. §§ 46.407-46.409; *see also supra* Part I.B.2.

minally ill as a vulnerable population.⁷¹ Moreover, labeling the terminally ill as vulnerable would further stigmatize people already suffering greatly from loss of personal autonomy and dignity.⁷² Accordingly, an IRB could, consistent with federal regulations, conclude that the terminally ill were not vulnerable.

On the other hand, the regulations leave the term "vulnerable" undefined and open-ended.⁷³ When examples of vulnerable populations are provided, the lists vary from provision to provision, strongly suggesting that the types of populations listed were meant to be illustrative, rather than denominative. If, as this Article argues,⁷⁴ the terminally ill share a number of relevant characteristics with the vulnerable populations listed in the regulations, an IRB would be well within its authority to treat the terminally ill as vulnerable. Indeed, a number of commentators seem to assume that the terminally ill are considered a vulnerable population under the regulations.⁷⁵

The most that can be said with any certainty, however, is that the regulations leave the assessment of vulnerability of the terminally ill to the IRBs. Thus, in some cases the regulatory protections may apply, and in other cases they may not.

C. *The Call for Fewer Regulatory Restrictions on Research Involving the Terminally Ill*

The terminally ill have long been the subject of both formal and informal research that has yielded many important medical advances. In recent years, however, the terminally ill have not sought regulatory protection. On the contrary, generally they are not only willing to par-

71. See, e.g., 45 C.F.R. §§ 46.101-46.409; see generally, e.g., PRESIDENT'S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS IN MEDICINE AND BIOMEDICAL RESEARCH, IMPLEMENTING HUMAN RESEARCH REGULATIONS: THE ADEQUACY AND UNIFORMITY OF FEDERAL RULES AND OF THEIR IMPLEMENTATION (1983); FOOD AND DRUG ADMINISTRATION, CURRENT ISSUES IN HUMAN SUBJECT PROTECTION (1996). But see THE BELMONT REPORT, *supra* note 68, at 13 (stating that the terminally ill may be considered "incompetent").

72. See *infra* Part II.A.

73. See 45 C.F.R. §§ 46.107(a), 46.111(a)(3), 46.111(b)(1998).

74. See *infra* Part II.

75. See, e.g., GRAY ET AL., *supra* note 67, at 31-32 (assuming that IRBs are required under 45 C.F.R. § 46.111(b) to ensure that additional safeguards are in place for AIDS patients, and that at least for IV drug users with AIDS, the IRBs would be required to include an advocate for those individuals on the IRB).

ticipate in research, but they often compete vigorously for the opportunity to do so, believing that experimental therapies offer their only hope of survival.⁷⁶ With the emergence of AIDS in the 1980s, political activists successfully channeled these concerns and eliminated some of the regulatory safeguards impeding the availability of new treatments.⁷⁷

Unlike the general HHS regulations, which have no exceptions to facilitate research involving the terminally ill,⁷⁸ the Food and Drug Administration (FDA) has adopted a number of specific regulations to allow for faster approval and distribution of experimental drugs.⁷⁹ Generally, before a new drug can be prescribed, it must gain FDA approval, which requires the completion of three successive phases of human testing.⁸⁰ In Phase I, a small number of healthy subjects receive the drug and are monitored for side effects to determine whether the drug is safe.⁸¹ In Phase II, the drug is tested on a slightly larger population of infected or symptomatic individuals.⁸² If the results of Phase II are promising, Phase III testing is done on a larger sample to further examine the efficacy of the drug.⁸³ Following Phase III, the researchers may submit an application to the FDA to have the drug approved for widespread use.⁸⁴

Patients with "life-threatening or seriously debilitating illnesses" may

76. See TIME *Special Report*, *supra* note 2, at 38-51.

77. See Lisa Terrizzi, *The Need for Improved Access to Experimental Drug Therapy: Aids Activists and Their Call for a Parallel Track Policy*, 4 ADMIN. L.J. 589, 589 (1991); Daugherty et al., *supra* note 6, at 894 (noting that AIDS activists argued that the goal of regulation "should be to maximize patient opportunity and choice to participate in clinical research rather than to maximize patient safety").

78. See 45 C.F.R. §§ 46.101-46.409 (1998).

79. See 21 C.F.R. pt. 312 (1998) (Investigational New Drug Application), subpart E (Drugs Intended to Treat Life-threatening and Severely Debilitating Illnesses), §§ 312.80-312.88 (1998); 21 C.F.R. pt. 314 (Applications for FDA Approval to Market a New Drug or an Antibiotic Drug), subpt. H (Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses), §§ 314.500-314.560; 21 C.F.R. pt. 601 (Licensing), subpt. E (Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses), §§ 601.40-601.46.

80. See *id.* at pt. 312. Subsequent to FDA approval, Phase IV studies are sometimes done to monitor the safety and efficacy of the drug. 21 C.F.R. § 312.22(c) (1998).

81. See *id.* § 312.21(a).

82. See *id.* § 312.21(b).

83. See *id.* § 312.22(c).

84. See 21 U.S.C. § 355(b) (Supp. 1998).

gain more rapid access to new drugs in two ways.⁸⁵ First, physicians can now prescribe drugs that are being tested in Phase II to the terminally ill if no adequate alternative therapy is available and the drug sponsor is making a diligent effort to have the FDA approve the drug.⁸⁶ Second, for drugs intended to treat life-threatening or seriously debilitating illnesses, the drug sponsor can seek "fast-track" approval, whereby the FDA may approve the drug without Phase III testing.⁸⁷

As regulatory hurdles have been lowered and potentially life-saving new therapies made more widely available, some physicians and researchers have begun "to reconsider the 50-year-old Nuremberg paradigm that participants in human research are ignorant and vulnerable and must be protected."⁸⁸ A recent article calls for abandonment of paternalistic attitudes toward research on the terminally ill, noting that the modern environment is radically changed:

Before the emergence of AIDS and its effect on clinical trials and drug development, clinical research was perceived as a process of human experimentation that sometimes involved cruel, even inhumane, treatment. Today, clinical trials and access to the drug development process are viewed as valuable societal goods and rights that should be guaranteed.⁸⁹

This paradigm shift, however, may be problematic. The terminally ill have lobbied successfully for the right to decide which drugs to take to treat their illnesses, arguing that paternalistic regulation is unnecessary because they are not vulnerable. The goal of deregulating access to drugs is laudable, but based on a false premise. That is, terminally ill patients should have the right to make intimate, personal decisions about their course of treatment, but they are also vulnerable to abuse when they participate in human research.⁹⁰

85. For an excellent summary of the historical development of these regulatory reforms to speed up access to investigation drugs for the terminally ill, see Steven R. Salbu, *Regulation of Drug Treatments for HIV and AIDS: a Contractarian Model of Access*, 11 YALE J. ON REG. 401, 410-17 (1994).

86. See 21 C.F.R. § 312.34(b)(1)(i)-(iv) (1998).

87. See *id.* § 312.80.

88. Daugherty et al., *supra* note 6, at 892 (citing THE BELMONT REPORT, *supra* note 68).

89. *Id.*

90. See *id.* (arguing that "[a] more informed and meaningful dialogue between investigators and patients who have terminal illnesses would recognize patients' vulnerability but also their autonomous decision-making ability").

II. THE VULNERABILITY OF THE TERMINALLY ILL

Many factors contribute to the vulnerability of the terminally ill. Individuals' psychological responses to terminal illness vary widely. Some employ healthy coping mechanisms, but many suffer from a variety of psychological problems — such as acute anxiety, depression, anger, and dependency — that can make it difficult, if not impossible, to rationally evaluate the pros and cons of participating in potentially life-threatening research. In addition, tremendous financial and professional rewards for discovering new treatments and publishing the results provide a strong incentive for researchers to bend or break the rules. As a result, the terminally ill patient considering whether to participate as a research subject is highly vulnerable to coercion and undue influence.

A. Psychological Manifestations of Terminal Illnesses and the Effect on Decision-making Capacity

Being diagnosed with a terminal illness often initiates a profound psychological response in patients and sometimes causes a variety of psychopathologies. Psychological symptoms may be exacerbated by the physiological symptoms of the disease. Further, patients may be reluctant to question the authority of their physicians. Working together, these factors may limit the terminally ill patient's ability to engage in autonomous, rational decision-making.

1. "Normal" Psychological Responses to Terminal Illness

Psychologists have not reached consensus regarding the emotional and psychological processes that normally occur upon being diagnosed with a terminal illness. Freud hypothesized that the general human fear of death was rooted in a fear of the unknown.⁹¹ Others have argued that "death anxiety does not pertain to physical death, but to the primordial feelings of helplessness and abandonment. The fear of the unknown of death is the fear of the unknown of annihilation of self, of being, of identity."⁹²

Regardless of the source of humans' fear of death, most experts seem to agree that people live most of their lives in a state of denial about

91. See generally Sigmund Freud, *Thoughts for the Times on War and Death*, in SIGMUND FREUD, 4 COLLECTED PAPERS (1915).

92. E. Mansell Pattison, *The Living-Dying Process*, in PSYCHOSOCIAL CARE OF THE DYING PATIENT 133-34 (Charles A. Garfield ed., 1978).

their own mortality, largely ignoring the reality of death except when forced to confront it.⁹³ Denial is generally viewed as a healthy coping mechanism.⁹⁴ Diagnosis with terminal illness, however, makes death imminent and often forces patients to come to terms with their formerly suppressed anxieties and fears.⁹⁵

While recognizing that individuals employ a wide variety of coping mechanisms and thus handle terminal illnesses in different ways, psychologists have identified three phases through which the terminally ill typically pass: acute, chronic, and terminal.⁹⁶ In the acute phase, brought on by the diagnosis of terminal illness, the patient may experience profound emotional turmoil and severe anxiety.⁹⁷ The diagnosis presents a problem that cannot be solved, and the patient is forced to try to assimilate the new information and fundamentally restructure his or her views of life and death.⁹⁸

The crisis of diagnosis also may trigger latent psychological problems of "dependency, passivity, narcissism, identity . . . [o]ne is faced not only with the immediate dying process but also with the unresolved feelings from one's own lifetime and its inevitable conflicts."⁹⁹ Some may respond initially with "immobilization," unable to react to the crisis

93. See generally ERNEST BECKER, *THE DENIAL OF DEATH* (1973).

94. See *id.*

95. See Pattison, *supra* note 92, at 134 (discussing a number of earlier studies).

96. See Kenneth J. Doka, *When Illness is Prolonged: Implications for Grief*, in LIVING WITH GRIEF WHEN ILLNESS IS PROLONGED 6-7 (Kenneth J. Doka & Joyce Davidson eds., 1998) [hereinafter LIVING WITH GRIEF]; ELISABETH KÜBLER-ROSS, *ON DEATH AND DYING* (1969).

Elisabeth Kübler-Ross argued in her seminal work, *ON DEATH AND DYING*, that patients progress through a series of six set stages: first shock, then denial, anger, bargaining, depression, and finally acceptance. See KÜBLER-ROSS, *supra*. Modern theory acknowledges that these psychological responses to terminal illness are common, but rejects the thesis that patients progress in a linear manner through each of the stages. See Charles A. Garfield, *Elements of Psychosocial Oncology: Doctor-Patient Relationships in Terminal Illness*, in PSYCHOSOCIAL CARE OF THE DYING PATIENT, *supra* note 92, at 103; Pattison, *supra* note 92, at 133-34 (noting, however, that there are phases where certain psychological responses are seen most frequently: the acute diagnosis phase, the chronic living-dying phase, and finally the terminal phase immediately preceding death).

97. See Doka, *supra* note 96, at 7.

98. See Pattison, *supra* note 92, at 145-46.

99. *Id.*

because they feel as though it is not happening to them.¹⁰⁰ Many experience "an overwhelming, insuperable feeling of inadequacy—a potential dissolution of the self. There is bewilderment, confusion, indefinable anxiety, and unspecified fear."¹⁰¹

In the chronic phase, the initial crisis of diagnosis has subsided, but the patient nevertheless must contend with the physical deterioration that accompanies a terminal illness. Additionally, the patient must continue to cope with the knowledge of impending death. In some patients, there may be a recovery phase, if, for example, there is a remission of the illness. Finally, the terminal phase constitutes the physical process of dying.¹⁰²

Depending on the patient, the psychological trauma of terminal illness manifests in many different ways. Some patients persistently deny to themselves and others that they have an illness at all.¹⁰³ Others respond primarily with anger, blaming themselves, others, and even their genetic ancestors for their illness.¹⁰⁴ The anger response can tend to alienate medical personnel and make communication more difficult.¹⁰⁵ Often, terminally ill patients become depressed, withdrawing from their support network and losing the will to live.¹⁰⁶ Another common response is la-

100. *See id.*

101. *Id.* (citing R. Noyes Jr. & R. Kletti, *Depersonalization in the Face of Life-Threatening Danger: A Description*, 39 PSYCHIATRY 19, 19 (1976)).

102. *See* Doka, *supra* note 96, at 6-7.

103. *See* PSYCHIATRIC CARE OF THE MEDICAL PATIENT 5 (Alan Stoudemire & Barry S. Fogel eds., 1993)[hereinafter PSYCHIATRIC CARE]; SHARON L. ROBERTS, BEHAVIORAL CONCEPTS AND THE CRITICALLY ILL PATIENT 197-222 (2d ed. 1986) (noting that denial manifested itself on a continuum ranging from rationalization to "magical thinking" to complete withdrawal from reality, and discussing a number of case studies where patients persistently refused to acknowledge their serious illnesses or alter their behavior accordingly); *see also* Orville Eugene Kelly, *Living with a Life-Threatening Illness*, in PSYCHOSOCIAL CARE OF THE DYING PATIENT, *supra* note 92, at 51-68 (discussing author's personal response to cancer diagnosis, and noting that he wondered "whether a mistake had been made; maybe [he] didn't have cancer at all").

104. *See* PSYCHIATRIC CARE, *supra* note 103, at 6; ROBERTS, *supra* note 103, at 197-222; *see also* Garfield, *supra* note 96, at 103.

105. *See* ROBERTS, *supra* note 103, at 197-222. *See also* Garfield, *supra* note 96, at 111.

106. *See* PSYCHIATRIC CARE, *supra* note 103, at 6; ROBERTS, *supra* note 103, at 197-222. Feelings of loneliness and isolation may exacerbate this problem. *See id.* at 223-51; *see also* Kelly, *supra* note 103, at 59-68 (after being diagnosed with

beled "dependency." Because the illness limits the patient's autonomy and control over his life, he may become child-like, regressing back to "passive behaviors characteristic of early developmental phases" of life.¹⁰⁷ Perhaps the most pervasive response is anxiety. "The onset of illness is always accompanied by heightened anxiety, as the patient questions the extent and degree of the particular ailment."¹⁰⁸

In cancer patients, even among mentally healthy patients, hopelessness, anxiety, and fear are normal responses. The universal fears of cancer patients have been dubbed the six Ds: death, dependency, disfigurement, disability interfering with normal life functions, disruption of relationships, and discomfort or pain resulting from the disease itself.¹⁰⁹ How well the patient copes with these fears is a function of a variety of factors: (1) the nature and progression of the disease itself; (2) the patient's level of psychological adjustment prior to onset of the disease; (3) the extent to which the disease threatens to impair the normal activities of the patient; (4) the culture and religion of the patient; (5) the patient's support network; (6) the patient's potential for rehabilitation; and (7) the patient's personal style for coping.¹¹⁰ In critically ill patients, similar psychological reactions are seen.¹¹¹

2. Psychological Disorders Among the Terminally Ill

The terminally ill often suffer from a variety of psychological ailments that frequently are never diagnosed or treated.¹¹² For example, in a significant percentage of cancer patients the illness induces diagnosable psychiatric disorders. In one study, where 215 cancer patients at

cancer, author notes as follows: "I was very depressed. I began to isolate myself from everyone. Much of the time I spent in bed. . . . My family was falling apart. Communications had nearly stopped."); Garfield, *supra* note 96, at 104 (noting that preparatory depression, i.e., depression caused by anticipated loss of one's body, and relationships with others, often manifests itself in "frightening dreams, irritability, extreme sadness, anorexia, and apathy").

107. See PSYCHIATRIC CARE, *supra* note 103, at 7.

108. *Id.*

109. See Lynna M. Lesko et al., *Oncology*, in PSYCHIATRIC CARE, *supra* note 103, at 565.

110. *See id.*

111. See ROBERTS, *supra* note 103, at 197-222 (noting that critically ill patients frequently suffer from sleep deprivation, hopelessness, anger or hostility, avoidance or denial, feelings of powerlessness, loneliness, and depression).

112. See generally PSYCHIATRIC ASPECTS OF TERMINAL ILLNESS (Samuel C. Klagsbrun et al., eds., 1988)[hereinafter PSYCHIATRIC ASPECTS].

three major cancer centers were selected at random, forty-seven percent of the patients suffered from psychiatric disorders.¹¹³ Of the patients with disorders, sixty-eight percent had "adjustment disorder with depressed, anxious, or mixed mood; 13% had major depression; 8% had an organic mental disorder; 7% had a personality disorder; and 4% had anxiety disorder."¹¹⁴ Only eleven percent of these disorders existed prior to disease or treatment.¹¹⁵ Other studies have indicated a similar prevalence of psychiatric disorders in cancer patients.¹¹⁶

3. *Physiological Symptoms of Illness and Treatment That May Impair Cognitive Function*

Depending on the illness, the physiological symptoms of disease or its treatments may directly impair cognitive function. With cancer, for example, as one physician notes, "[f]atigue, recovery from surgery and radiation, [and] toxicity from drugs (including antibiotics and pain medicine) may all alter thinking ability, dampening the sharpness, rapidity, and productivity of the [patient's] thought processes."¹¹⁷ The loss of mental functioning is more direct and obvious with Alzheimer's disease, where "physical death" often occurs well after what some have referred to as psychological death.¹¹⁸ Similarly, in AIDS patients, "because AIDS often involves degradation of mental processes, the ability to give competent consent may be compromised."¹¹⁹

In cardiac patients, a combination of physical and mental processes often produces acute anxiety. With the onset of physical symptoms of cardiac disease, such as angina and arrhythmias, patients experience acute "anxiety related to fears of heart attacks, disability, and sudden

113. See Lesko et al., *supra* note 109, at 566.

114. *Id.*

115. See *id.*

116. See *id.* (citing J.B. Bukberg et al., *Depression in Hospitalized Cancer Patients*, 46 PSYCHOSOM. MED. 199 (1984) (finding that fifty-six percent of cancer patients suffered from depression)).

117. Stephen P. Hersh, *Death From The Cancers*, in LIVING WITH GRIEF, *supra* note 96, at 100.

118. See Carol Williams & Brenda Moretta, *Systemic Understandings of Loss and Grief Related to Alzheimer's Disease*, in LIVING WITH GRIEF, *supra* note 96, at 120 (citing D. COHEN & C. EISDORFER, THE LOSS OF SELF: A FAMILY RESOURCE FOR THE CARE OF ALZHEIMER'S DISEASE AND RELATED DISORDERS (1986)).

119. GRAY ET AL., *supra* note 67, at 53.

death.”¹²⁰ Patients “may fear annihilation or object loss, or may struggle with feelings of passivity, impotence, or guilt . . . [which are] magnified by the acute autonomic and physiologic concomitants of acute cardiac disease (cold sweats, nausea, light-headedness, shortness of breath, chest tightness, etc.).”¹²¹

The terminally ill patient who is hospitalized for a long period of time also may experience physical and psychological responses to her environment which further hamper her ability to make informed decisions. Due to the unfamiliar environment and the increased sensory input of the hospital, many patients suffer from sleep deprivation.¹²² Sleep deprivation exacerbates the physical and emotional trauma of terminal illness, and may lead to lassitude, lethargy, hallucinations, disorientation, confusion, restlessness, irritability, apathy, poor judgment, memory disturbance, delusions, paranoid ideation, and hostility.¹²³ Patients also commonly experience extreme anxiety over seemingly routine matters such as the prospect of being transferred from one room to another.¹²⁴

4. *The Coercive Effect of Hospitalization*

The terminally ill are frequently hospitalized. Thus, like prisoners, who are dependent on their guards and other prison employees for their daily needs as well as for their well-being, the terminally ill are often completely dependent on the hospital's researchers and staff. As a result, patients actively seek to avoid upsetting the researchers and to curry favor with them. Patients who respond with anger to their disease, and who subjectively displace and direct such anger toward their doctors, are nevertheless reluctant to express these feelings for fear of retaliation.¹²⁵ Also like prisoners, the terminally ill often have little control

120. James L. Levenson, *Cardiovascular Disease*, in *PSYCHIATRIC CARE*, *supra* note 103, at 540.

121. *Id.*

122. See Roberts, *supra* note 103, at 63-94.

123. See *id.* at 68 (citing Jean Hayter, *The Rhythm of Sleep*, *AM. J. NURSING* 457, 457 (1980)); Gina Zelechowski, *Sleep and the Critically Ill Patient*, *CRITICAL CARE UPDATE*, Feb. 1979, at 5; Luva Fabijan & Marie Gosselin, *How to Recognize Sleep Deprivation in Your ICU Patient and What to Do About It*, *CANADIAN NURSE*, Apr. 1982, at 21.

124. See Roberts, *supra* note 103, at 298-330.

125. See PRESIDENT'S ADVISORY COMMITTEE, *supra* note 18, at 472 (quoting a research subject's feelings when deciding whether to undergo a bone marrow transplant: "They were really pushing this procedure. . . . It was very obvious to me

over their environment, which may further heighten anxiety.¹²⁶

5. Effect on Decision-making Capacity

The psychological manifestations of terminal illness may affect patients' ability to give informed consent in a variety of ways.¹²⁷ First, they may impair cognitive function.¹²⁸ Research suggests that persons suffering from depression have difficulty processing information and reasoning.¹²⁹ It seems likely that patients who react to their terminal illnesses with extreme anxiety, anger, or denial would encounter similar difficulties. In addition, even if cognitive abilities remain intact, depression may undermine the risk/benefit analysis on which the validity of informed consent rests. Many researchers have suggested that depressed persons would be less likely to consent to participate in research because of pessimism, or a tendency to overestimate risk and underestimate benefit.¹³⁰ In fact, the opposite may be true. Depressed persons may be

that they wanted people to sign up for this bad, and I did not want to upset my doctor. . . . Y'know I'm totally helpless. I'm in his hands and, so part of it was, I wanted to keep him happy and, uh, there was some pressure."); *see also* Roberts, *supra* note 103, at 298-330 ("The individual may feel justified in his anger or hostility, but he may not be able to demonstrate his anger overtly toward the staff. He may fear that if he expresses outward anger toward his nurse or doctor, they may retaliate by not providing him with care.").

126. *See* Roberts, *supra* note 103, at 298-330 (noting that patients feel powerless because of loss of control over "admission procedures, the choice of doctor, decision-making ability, schedules, and routines." Even a dropped call light may result in extreme anxiety. "The critically ill patient who is already in an anxiety crisis may depend heavily upon the security of visual and verbal contact with his nurse. Without such contact, he may feel overwhelming powerlessness and alienation.").

127. *See generally* NATIONAL BIOETHICS ADVISORY COMMISSION, RESEARCH INVOLVING PERSONS WITH MENTAL DISORDERS THAT MAY AFFECT DECISIONMAKING CAPACITY (December 1998) [hereinafter NBAC REPORT].

128. *See id.* at 7-8 (noting that the following conditions, which are often found among the terminally ill, may affect cognitive function and decisionmaking capacity: dementia associated with Alzheimer's disease, HIV infection, and neurological conditions such as Parkinson's disease and Huntington's disease; delirium caused by "systemic medical conditions, side effects of medications, or intoxication with or withdrawal from psychoactive agents or toxins;" and depression).

129. *See id.* at 8 (citing Shirley Hartlarge et al., *Automatic and Effortful Processing in Depression*, 113 PSYCHOL. BULL. 247-48 (1993); Jane E. Baker & Shelly Channon, *Reasoning in Depression: Impairment on a Concept Discrimination Learning Task*, 9 COGNITION & EMOTION 579-97 (1995)).

130. *See, e.g.,* Jan Marta, *The PSDA and Geriatric Psychiatry: A Cautionary*

more likely to consent because the notion of risk is meaningless to them.¹³¹ In essence, they become malleable and vulnerable to coercion precisely because they do not care whether they live or die.

Feeling desperate, terminally ill patients may fail to try to evaluate risks and benefits at all, having already made up their minds to try any available treatment. A May 1998 front page article in the New York Times discussed the potential for angiostatin and endostatin as a cancer treatment that works by cutting off the blood supply to the tumors.¹³² Dr. Judah Folkman, who discovered the drugs, stated that "he gets hundreds of calls a day from cancer patients, pleading for the drugs."¹³³ This occurs despite the fact that the drugs have never been tested on human beings, and neither the risks nor the benefits of the drugs are known. This phenomenon thus inverts the roles of doctor and patient in informed consent negotiations. Instead of the doctor seeking the consent of the patient, the patient seeks the consent of the doctor to allow him to participate.¹³⁴ Orville Kelly, a cancer patient who started a support group to help other cancer patients deal with the emotional trauma of their illnesses, notes that once patients become desperate, "many seem willing to try anything in the event that it might work. For them, false hope is better than no hope at all."¹³⁵

6. Therapeutic Misconception

Partly as a result of their desperation, terminally ill research subjects often will completely fail to understand that they are participating in

Tale, 4 J. CLINICAL ETHICS 80, 80 (1993); Linda Ganzini et al., *Do-not-resuscitate Orders for Depressed Psychiatric Inpatients*, 43 HOSP. COMMUNITY PSYCHIATRY 915, 915 (1992); Mark D. Sullivan & Stuart J. Youngner, *Depression, Competence, and the Right to Refuse Life-saving Treatment*, 151 AM. J. PSYCHIATRY 971, 971 (1994).

131. See generally Carl Elliott, *Caring About Risks: Are Severely Depressed Patients Competent to Consent to Research?*, 54 ARCH. GEN. PSYCHIATRY 113 (1997) (arguing that the severely depressed persons may be incompetent to give their informed consent because they do not care about risks and because they are not authentically acting as themselves).

132. See Kolata, *supra* note 1, at A1.

133. *Id.*

134. Desperate terminally ill patients are also prone to try to convince their physicians to try so-called "alternative medicine" along with their normal course of treatment. See Edmund D. Pellegrino, *Emerging Ethical Issues in Palliative Care*, 279 JAMA 1521, 1521 (1998).

135. Kelly, *supra* note 103, at 65.

research that may not be intended primarily for their benefit. This phenomenon has become known as "therapeutic misconception."¹³⁶ The patient-subject tends to pay little attention to written forms,¹³⁷ and more careful informed consent procedures may be equally impotent. One study examined the motivation and understanding of patients participating as subjects in Phase I cancer research.¹³⁸ The study found that patients were motivated to participate almost exclusively because of the hope of curing their illnesses. Subjectively, the patients thought they understood the potential risks and benefits of the research, but they were in fact unaware that the purpose of the research was to study dose schedules and toxicity levels of drugs, not to cure them.¹³⁹

Another study examined subjects' understanding after participating in a double-blind research study in which the major risk was receiving a placebo.¹⁴⁰ Despite a comprehensive informed consent process that involved a written form, verbal explanations, and even an interview by a psychiatrist, only ten out of nineteen patients understood that the purpose of the study was research. The other nine subjects thought that the purpose of the study was "to make them better." Moreover, eighteen of the nineteen patients reported that they decided to participate, in part, because they expected to receive better treatment in the research ward.¹⁴¹

Thus, an examination of the decision-making of terminally ill patients

136. PRESIDENT'S ADVISORY COMMITTEE, *supra* note 18, at 484 (noting that "patient-subjects view research participation as a way of obtaining the best medical care, even when participating in research holds out very little prospect of direct benefit") (citing Paul S. Appelbaum et al., *The Therapeutic Misconception: Informed Consent In Psychiatric Research*, INT'L J. OF L. & PSYCHIATRY 5 (1982)). See GRAY ET AL., *supra* note 67, at 52 (arguing that "people with HIV infection are often desperate for a cure or an effective means of ameliorating symptoms" and that "this desperation may lead to an increased likelihood of confusion of research with treatment").

137. See generally C.W. LIDZ ET AL., INFORMED CONSENT: A STUDY OF DECISION-MAKING IN PSYCHIATRY (1984).

138. See generally Christopher K. Daugherty et al., *Perceptions of Cancer Patients and Their Physicians Involved in Phase I Trials*, 13 J. CLIN. ONCOL. 1062-72 (1995).

139. See *id.*

140. See C.W. Lidz & L.H. Roth, *The Signed Form: Informed Consent?*, in SOLUTIONS TO ETHICAL AND LEGAL PROBLEMS IN SOCIAL RESEARCH 145-157 (R.F. Boruch and J.S. Cecil eds., 1983) (cited in GRAY ET AL., *supra* note 67, at 39).

141. See *id.*

undercuts the ability of the doctrine of informed consent to legitimate research. To the extent that patient-subjects tend not to analyze the risks of research and to presume that the doctor-researchers are always acting in their best interests, informed consent is a fiction. For the patients who attempt to undertake such an analysis, they may find their decision-making capacity hamstrung by the psychological and physiological ravages of their illnesses.

B. Financial and Professional Incentives

Biomedical research is no longer a pure scientific endeavor. It is an enormous industry with billions of dollars of assets and tens or hundreds of thousands of participants.¹⁴² As of 1988, there were over 50,000 full-time faculty members at American medical schools.¹⁴³ With their careers dependent on obtaining research grants and publishing the results of their work, researchers have "recruited experts in management, financial administration, production, science writing, and marketing, along with a host of supporting personnel, research assistants, and graduate students."¹⁴⁴ Researchers thus face potential conflicts of interest whenever the ethical requirements of research threaten to impede their personal aspirations or cut into profits of the research industry.¹⁴⁵

An excellent example of how much is at stake can be found in AIDS research and the battle over the discovery of HIV. With a potential Nobel prize at stake, and certainly the prospect of lucrative proceeds to be derived from HIV tests and, perhaps, vaccines, French and American researchers have been battling in court over the bragging rights for a decade.¹⁴⁶ In short, there is a conflict of interest, and the greater the potential payoff in terms of prestige and cash, the greater the potential for research abuse.¹⁴⁷

Financial conflicts of interest are compounded by the existence of for-

142. See TIME *Special Report*, *supra* note 2, at 51.

143. See Robert U. Massey, *Cultural Contents in the History of the Use of Human Subjects in Research*, in THE USE OF HUMAN BEINGS IN RESEARCH 19, 22 (Stuart F. Spicker et al., eds., 1988).

144. *Id.*

145. See *id.* at 23; see also Stephenson, *supra* note 7, at 1827 (suggesting that financial incentives exist to continue to conduct stem-cell transplants on breast cancer patients — despite equivocal results — because "[a]utologous peripheral stem-cell transplant units reportedly are moneymakers for medical centers").

146. See GRAY ET AL., *supra* note 67, at 1-3.

147. See *id.* at 3.

profit IRBs. Currently, only two to three percent of IRBs are commercial, but the percentage is rising.¹⁴⁸ Furthermore, some researchers whose experiments are rejected as scientifically unsound or unethical by an IRB will hire a commercial IRB to review and approve the research.¹⁴⁹

Professor Jay Katz, who helped develop the federal regulations, summarized a number of these concerns in his 1994 testimony to Congress.¹⁵⁰ First, "[t]he majority of IRB members are on the faculty of the institutions to which the investigators belong."¹⁵¹ Accordingly, IRB members are reluctant to disapprove of their colleagues' research for fear that their own research subsequently will be subjected to similarly harsh scrutiny.¹⁵² Second, IRBs are under pressure from their institutions to approve research protocols because those institutions rely on the revenues from the research for their existence, and thus researchers are penalized to the extent that research is slowed by efforts to comply with ethical and regulatory obligations.¹⁵³ Third, research is increasingly sup-

148. See Vicki Brower, *Vulnerable Groups at Risk from "Commercial" Ethical Review Boards*, 3 NATURE MED. 70, 70 (1997).

149. See *id.* (discussing recent testimony before the Committee on Government Reform and Oversight's subcommittee on human resources). The author recounts two examples of this trend. In one, a research protocol for a new drug to treat schizophrenia was rejected by an IRB because the research would require subjects to go untreated prior to beginning the study. The researcher, however, found a more sympathetic IRB elsewhere to approve the study and is now defending a lawsuit after the suicide of a subject who went untreated. In the other, a physician's protocol was rejected by one IRB because it called for asthmatic children to be taken off their medication, but subsequently was approved by a commercial IRB hired by the researcher to review the protocol. See *id.*

150. See Jay Katz, *Problems in Securing Informed Consent of Subjects in Experimental Trials of Unapproved Drugs and Devices*, Testimony before the U.S. House Subcommittee on Regulation, Business Opportunities, and Technology of the Committee on Small Business, 125-35 (May 23, 1994).

151. See *id.* at 131.

152. See *id.*

153. See *id.* at 133. Professor Katz argues as follows:

Academic institutions rely on the revenues which accrue from the assessment of indirect costs to the providers of grants. Research proposals have to be generated and completed at a rapid rate to assure future grant support. Thus investigators are under considerable pressure to recruit subjects as quickly as possible to support the institutions' buildings, laboratories, staff and salaries. With respect to the needs of their institutions, and career advancement and future grant support as well, physician-investigators are thus the victims of an institutional system (their own institutions and the National In-

ported by pharmaceutical and biotechnology companies that use their own private IRBs to approve the very work their investigators propose. It should thus come as little surprise that research is rarely rejected for ethical reasons.¹⁵⁴

C. Attitudes of Physician Researchers

As recently as the 1960s, physicians routinely avoided telling patients that they had terminal illnesses, and sometimes actively misled them to believe they did not.¹⁵⁵ Although most doctors no longer misinform their patients, some evidence indicates that, for some patients at least, the diagnosis of death may hasten or even cause death.¹⁵⁶ Thus, when doctors decide not to inform their patients out of concern for their health, doctors may be shielded from liability under the "therapeutic exception" to the requirement of informed consent.¹⁵⁷

Doctors are trained to heal, not to facilitate death and ease pain. Often

stitutes of Health) which [penalizes] them if in fulfillment of their ethical disclosure obligations toward patient-subjects, the pace of research would be slowed. These pressures impact significantly on the speed with which the process is conducted so that patient-subjects will not refuse to participate.

Id.

154. *See id.* at 134-35.

155. *See* Norman B. Levy, *Fatal Illness: What Should the Patient be Told?*, in PSYCHIATRIC ASPECTS, *supra* note 112, at 42.

In this country, the practice of informing patients about fatal illnesses has changed radically since the early 1970s; before then, there was a tendency not to tell patients their diagnoses. Fitts and Radvin (1953) questioned 444 Philadelphia physicians concerning their attitudes toward being forthright with their patients regarding their fatal illness and found that only 37% of them usually informed patients of their diagnoses. In a classic study of 219 physicians at Michael Reese hospital in Chicago (Oken (1961), only 12% stated that their usual policy was to tell patients that they had cancer. Feifel (1965) reported that between 10% of 31% of physicians favored letting patients know that they were dying.

Id.

156. *See* G.W. Milton, *Self-willed Death or the Bone-pointing Syndrome*, in PSYCHOSOCIAL CARE OF THE DYING PATIENT, *supra* note 92, at 125-27 (arguing that upon diagnosis of a terminal illness, some patients cause their own deaths in a matter essentially homologous to the phenomenon where a person who has been cursed, or "bone-pointed" by an Aboriginal witch-doctor, will often die soon afterward).

157. *See, e.g.,* *Arato v. Avedon*, 858 P.2d 598, 600 (Cal. 1993) (holding that the jury reasonably could have found under the therapeutic exception that physician did not have a duty to disclose life expectancy of patient with pancreatic cancer).

it is difficult for them to assume the latter role. The wife of a terminally ill cancer patient notes that "it is understandably difficult for doctors who treat terminally ill patients to reconcile the need to heal . . . with the desire of some patients to let the disease take its natural course."¹⁵⁸ One doctor who worked with the terminally ill stated, "I've realized that for the past 25 years when a patient of mine has been terminally ill, I'd walk into the room talking constantly, approach the bed, and back out of the room talking. I do this because I have nothing to offer medically and I'm not willing to deal with the patient's emotional stress."¹⁵⁹

Doctors and staff of research facilities who work with the terminally ill are not immune from the suffering and death that surrounds them. Physicians fear death like anyone else, and many may be reluctant to communicate openly with dying patients.¹⁶⁰ Some studies indicate that physicians may deny death more than the general population.¹⁶¹ Thus, physicians' traditional reluctance to communicate openly with their patients may simply be a manifestation of their desire to avoid confronting their own fears of death.¹⁶²

Regardless of the source, to the extent that old attitudes persist, physicians may hesitate to communicate the details of possible courses of treatment. As a result, the terminally ill may not receive adequate information upon which to base informed consent decisions.

III. PROPOSED REGULATORY REFORMS

Any effective regulatory regime must balance the goal of preventing

158. Sandra L. Barger, *Personal Professional Support: From a Patient's Point of View*, in *PSYCHOSOCIAL CARE OF THE DYING PATIENT*, *supra* note 92, at 67 (1978).

159. Garfield, *supra* note 96, at 105. Dr. Garfield notes that physicians' psychological reactions mirror those of their patients; they often exhibit anger, denial, and depression when confronted with the fact that their patients are going to soon die. *See id.*

160. *See* Pattison, *supra* note 92, at 134.

161. *See* H. Feifel, *The Function of Attitudes Towards Death*, in *GROUP FOR THE ADVANCEMENT OF PSYCHIATRY, DEATH AND DYING: ATTITUDES OF PATIENT AND DOCTOR* (1965).

162. *See* Pattison, *supra* note 92, at 134-35 (1978) ("I have found that most dying patients . . . want to share their dying experience with others. It is rare that such discussions upset the dying person. But I have seen many nurses, physicians, and mental health personnel become nervous, anxious, upset, and distraught [at the prospect of such discussions]").

abuse of the terminally ill with the need to streamline the processes for development and approval of new therapies as well as with the right of the terminally ill to preserve their dignity and make these difficult decisions themselves. This is a hard balance to strike. Regulating research to prevent abuse slows down the process for approval of new drugs and therapies, and may indirectly insult the dignity of patients or the integrity of researchers. While accounting for these competing concerns, certain regulatory reforms would improve the process for approving and conducting research on the terminally ill. The proposals follow the typology of the regulations themselves. Subpart A offers structural and institutional reforms; subpart B argues for restrictions on the types of research in which the terminally ill may be involved; and subpart C proposes and analyzes alternative ways to better ensure that the terminally ill do not participate in research without giving their fully informed, voluntary consent.

A. Structural and Institutional Reforms

1. Regulatory Recognition of the Vulnerability of the Terminally Ill

At a minimum, all human research regulations that discuss "vulnerable" populations and give examples thereof should be amended to include the terminally ill.¹⁶³ Certainly some researchers, commentators, and IRBs consider the terminally ill to be vulnerable and treat them as such when applying the relevant regulatory provisions.¹⁶⁴ Yet absent explicit recognition, the possibility remains that many researchers and IRBs will overlook the vulnerability of their terminally ill subjects. Even among those researchers who recognize their vulnerability, without further impetus they may fail to take the time to understand and respond to the unique psychological trauma induced by the diagnosis of terminal illness. Granted, merely listing the terminally ill as a type of vulnerable class may have little direct regulatory impact, but it will allow the regulations to assume a vital hortatory role,¹⁶⁵ calling on researchers and

163. General regulations applicable to all vulnerable classes are discussed in Part I.B.1, *supra*.

164. Articles by a number of authors who are either researchers or members of IRBs, or both, provide at least indirect evidence that some decision-makers treat the terminally ill as a vulnerable class. See, e.g., KATZ, *supra* note 22, at 1053; LEVINE, *supra* note 9, at 77-79.

165. See JOHN H. MERRYMAN ET AL., THE CIVIL LAW TRADITION: EUROPE,

IRBs to familiarize themselves with the unique difficulties their subjects face.

Alternatively, the regulations could explicitly define the vulnerable populations and include the terminally ill among them. Such a step would make the job of IRBs simpler and more mechanical: if research involved subjects on the vulnerable list, the "vulnerability" regulations would apply; if research did not involve such subjects, the vulnerability regulations would not apply. The drawback of this approach, of course, is that it would make it more difficult for the set of vulnerable populations to expand or contract according to society's notions of vulnerability. It also would seem to strip IRBs of the discretion and responsibility to make independent inquiries into whether subjects had an impaired ability to make rational decisions. For subjects who were not on the "vulnerable" list, but who nevertheless suffered some form of impairment in their decision-making capacity, this could have serious consequences. Moreover, from a practical standpoint, regulators have shown persistent reluctance to attempt to define the term. Thus, the more prudent approach seems to be to continue to leave the definition of "vulnerability" open-ended, but clarify that the term encompasses the terminally ill.

Recognizing the vulnerability of the terminally ill would have only minimal impact on the speed with which research is conducted, and thus would not substantially reduce the societal benefits of such research. The general regulations applicable to vulnerable classes are fairly unobtrusive for researchers and IRBs alike.¹⁶⁶ Compliance with these provisions, which vest broad discretion in the IRBs and researchers and allow for substantial flexibility, should not affect scientific progress.

Categorizing the terminally ill as vulnerable would, however, threaten their dignity and autonomy. Advocates for the terminally ill have been lobbying for thirty years — culminating in the political and regulatory success of gaining swifter access to potentially life-saving drugs¹⁶⁷ — for recognition that they are not passive, vulnerable, and incapable of understanding or coping with their diagnoses. They have demanded and won the right to be informed. They have played an increasingly active

LATIN AMERICA, AND EAST ASIA 48-50 (1994) (discussing how within the civil law tradition — but not the common law tradition — the law has played both hortatory and pedagogical roles even absent coercive effect).

166. *See supra* Part I.B.1.

167. *See supra* Part I.C.

role in steering the direction of their treatments. Considered in this light, stigmatizing the terminally ill as "vulnerable" could be a dangerous step backward.¹⁶⁸

This concern is legitimate, but rests on the false presumption that recognizing the vulnerability of the terminally ill necessarily undermines the project of making them more active participants in their treatment. Vulnerability and personal autonomy are not disjunctive concepts. Indeed, because the terminally ill are uniquely vulnerable, they deserve greater recognition of their right to determine the course of treatment. The psychological trauma accompanying terminal diagnosis is a crisis of loss of self. The terminally ill patient must cognitively and emotionally come to grips with the prospect of permanent personal annihilation. At the same time, the patient's body may be failing, and most aspects of her everyday life are profoundly altered. Recognition of the right of such a patient to make both important and seemingly trivial decisions is not just a normative proposition; it is a form of psychotherapeutic treatment. By exercising personal autonomy, the patient regains a measure of dignity and reaffirms the continued existence and vitality of the self.¹⁶⁹ Active participation in the informed consent process also may enhance patients' ability to understand the risks and benefits of research.¹⁷⁰

Researchers and regulators alike have already demonstrated the ability to understand the subtlety of this dynamic. For example, the regulations governing research involving children recognize the possibility of the coexistence of vulnerability and autonomy. Children are explicitly listed as vulnerable and entitled to substantial regulatory protection.¹⁷¹ Yet, at the same time, children are recognized as autonomous decision-makers who generally must give their "assent" to treatment.¹⁷² Recognition of

168. See GRAY ET AL., *supra* note 67, at 37 (arguing that rigorous compliance with informed consent provisions denies "vulnerable populations" — including people with AIDS — the right to make important personal choices . . . [and] [s]uch protection is particularly questionable when its effect is to deny access to experimental treatments when no effective, FDA-approved treatment is available").

169. See *supra* Part II.

170. See, e.g., Vijay L. Melnick et al., *Clinical Research in Senile Dementia of the Alzheimer Type*, 32 J. AM. GERIATRICS SOC. 531, 536 (1984) (suggesting that the informed consent process would be improved if potential subjects critiqued drafts of information materials prior to their use in research), *cited in* NBAC REPORT, *supra* note 127, at 52-53.

171. See 45 C.F.R. §§ 46.401-46.409 (1998).

172. See *id.* § 46.408(a). Only when the research is likely to provide a direct

the vulnerability of the terminally ill patient will not reverse the momentum of the patients' rights movement. On the contrary, it will advance the movement by demanding researchers treat terminally ill patients not as either vulnerable or autonomous, but rather as complete people who are grappling with the psychological impact of their illnesses, but who nevertheless are entitled to make their own decisions.

2. *Constitution of Institutional Review Boards*

Recognition of the terminally ill as a vulnerable class would require IRBs who work with the terminally ill to consider including an expert on the terminally ill as a member of the IRB.¹⁷³ Prior to 1988, this requirement was mandatory. IRBs that worked with vulnerable subjects had to "include one or more individuals primarily concerned with the welfare of those subjects."¹⁷⁴ The Interagency Committee, which proposed the new rules, received a number of comments stating that the new, optional rule would weaken the position of vulnerable human subjects.¹⁷⁵ The Committee responded, however, by stating that it "expects that institutions will use good judgment and diligence in selecting persons as IRB members who can fulfill the requirements."¹⁷⁶

Assuming regulators do not adopt vulnerable population representation on IRBs as a general requirement, they nevertheless should consider doing so for IRBs that work with the terminally ill. Such an exception has been made for research involving prisoners, where the IRB must include a prisoner representative.¹⁷⁷ Moreover, the National Bioethics Advisory Commission (NBAC) recently recommended that "[a]ll IRBs that regularly consider proposals involving persons with mental disorders should include at least two members who are familiar with the nature of these disorders and with the concerns of the population being

benefit to children that cannot be obtained except through the research may children be included in research without their "assent." *See id.* "'Assent' means a child's affirmative agreement to participate in research." *Id.* § 46.402(b); *see also supra* Part I.B.2.

173. *See* 45 C.F.R. § 46.107(a).

174. 45 C.F.R. § 46.107(a) (1985); *see also* 51 Fed. Reg. 20,204, 20,207 (1986) (proposed June 3, 1986); 53 Fed. Reg. 45,660, 45,665 (1988) (proposed Nov. 10, 1988).

175. *See* 53 Fed. Reg. 45,660, 45,665 (1988).

176. *See id.* at 45,660, 45,665.

177. *See* 45 C.F.R. § 46.304; *see also supra* Part I.B.2.

studied.”¹⁷⁸ A similar recommendation is warranted for the terminally ill. Unlike children, for example, where issues of vulnerability are straightforward, the vulnerability of the terminally ill is complex, highly individuated, and subtle. Even more importantly, this vulnerability must be balanced against the fact that the terminally ill are also competent, autonomous adults entitled to do their own decision-making.¹⁷⁹ IRBs should include at least one member who understands these complexities and can adequately represent the interests of terminally ill subjects. At a minimum, IRBs should be required to consult with an expert on the terminally ill when reviewing research protocols that involve the terminally ill as subjects.

This proposal has essentially no drawbacks. It would not directly affect scientific progress. Indirectly, the proposal could tend to slow research only to the extent that the IRBs might be inclined to scrutinize more carefully the ethics of research involving the terminally ill. But this is a desirable trade-off. Some might object that it is illogical to require IRB representation for the terminally ill but not for other vulnerable classes such as the mentally ill. This may be true, but argues more for the inclusion of IRB representatives for other vulnerable classes than for the exclusion of representatives for the terminally ill.¹⁸⁰ Requiring representation of the terminally ill on IRBs could greatly enhance the responsiveness of researchers to their needs, and would do so at minimal cost to society.

3. *Psychological Training for Investigators*

Researchers who use the terminally ill as subjects should receive training to ensure they understand the psychological difficulties confronting their subjects. The generalized training that researchers may have received in medical school is inadequate. Researchers, by virtue of their frequent contact with their dying subjects, will often have a sophisticated intuitive understanding of the psychological difficulties their subjects face and how they cope with them. Periodic formal training, when coupled with this experience, should make researchers highly responsive to the psychological needs of their patients. It should also better enable them to distinguish normal psychological responses from

178. NBAC REPORT, *supra* note 127, at 52-53.

179. *See supra* Part III.A.1.

180. *See* NBAC REPORT, *supra* note 127, at 52-53 (recommending representation of mentally ill on IRBs).

pathological ones, and to recognize when their subjects should be referred for psychological consultation. Ideally, psychological training for researchers should be accompanied by formal involvement of psychologists in the research protocol.¹⁸¹

B. Restrictions on Types of Research that May Be Conducted Using Terminally Ill Subjects

Categorical bans on certain types of research constitute the most controversial means of regulating in this arena. Whenever research is banned, any benefit that might have been derived therefrom is lost. Hence, regulators should not impose such restrictions lightly. Nevertheless, as with children and prisoners, certain types of research involving the terminally ill warrant a presumption of coercion or undue influence and should be outlawed even if researchers purport to obtain the informed consent of their subjects.

1. Research Not Intended to Provide Direct Therapeutic Benefit to Subjects

Generally, research should not be conducted on the terminally ill if it is not intended to benefit them. This is true regardless of the level of risk involved. Even if the risk of the research is seemingly minimal, IRBs should not approve the study if it is not expected to benefit the subjects. For example, it is inappropriate to use the terminally ill to develop methods of arteriography.¹⁸²

This approach is intentionally modeled after the regulations governing research with prisoners,¹⁸³ which impose an outright ban on any research that is not related in some way to prisons or prisoners.¹⁸⁴ Like prisoners, the terminally ill are often captive and physically vulnerable. Just as prisoners might "consent" to participate in research to try to garner favor or to avoid retaliation, so too might the terminally ill consent to research

181. See *infra* Part III.C.2.

182. See generally James A. Helmsworth et al., *Arteriography of the Aorta and Its Branches by Means of the Polyethylene Catheter*, 64 AM. J. ROENTGENOLOGY 196 (1950), excerpted in KATZ, *supra* note 22, at 1054-56. A number of patients died as a result of the experimental methods, but the researchers argued that "it is imperative to weigh the dangers of the procedure against the value of the information obtained." *Id.* at 1056.

183. See 45 C.F.R. §§ 46.301-46.306 (1996).

184. See *supra* Part I.B.2.

in which they would prefer not to be involved because they want to please the researchers who also may be in charge of their medical care.¹⁸⁵ The regulations should not allow researchers to put the terminally ill in the perceived conundrum of choosing between being a "good patient" and following their true desires.

The more lenient approach applied to research involving children, and now recommended for research involving the mentally ill,¹⁸⁶ is not appropriate for the terminally ill. When the risk is minimal, current regulations allow children and parents to consent to research that will not benefit the children.¹⁸⁷ In addition to children not being physically captive, like prisoners and sometimes the terminally ill, such research is often justified because there are no other appropriate subjects available. It is often impossible to study developmental psychology and physiology except by employing children as research subjects.¹⁸⁸ This is not true with the terminally ill. Generally, if the research is not intended to benefit the subject of the study, other non-vulnerable subjects could be employed.

Three narrow exceptions should be made to this ban. First, as with research involving children,¹⁸⁹ when the risk involved is only slightly over minimal risk, the terminally ill should be allowed to consent to participate as subjects provided the research is intended to yield important, generalized knowledge about their condition, even if it is unlikely to benefit them personally. Second, an exception should be allowed if HHS consults with appropriate legal, medical, and ethical experts and concludes that the research is ethical; presents an important opportunity to learn about the subjects' condition; and ensures that subjects will participate only after giving their informed consent.¹⁹⁰ Third, sociological, psychological and epidemiological research that presents no medical risk to subjects should not be banned. Particularly with AIDS and other infectious disease research, these types of studies are of vital impor-

185. *See supra* Part II.A.4.

186. *See* NBAC REPORT, *supra* note 127, at 60-61.

187. *See* 45 C.F.R. § 46.404; *see supra* Part I.B.2.

188. *See* NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, RESEARCH INVOLVING CHILDREN 21-23 (1977).

189. *See* 45 C.F.R. § 46.406 (1998).

190. This proposal is again modeled after an analogous rule currently applied to research involving children as subjects. *See id.* § 46.407.

tance.¹⁹¹

These proposed restrictions on research strike a balance between protecting the terminally ill and ensuring that scientific progress with regard to terminal illnesses is not slowed. There is, however, a downside. First, this proposal would reduce the pool of potential research subjects for unrelated research. The terminally ill, who are often hospitalized, are ideal research subjects: their vital signs are constantly monitored, their diet can be easily tracked, and they are unlikely to move away.¹⁹² Prohibiting certain types of research also reduces patient autonomy and choice. In many cases, this proposal would prevent the terminally ill patient from volunteering to be a research subject out of genuine altruism. For some, this concern is undoubtedly real, but the vast majority of terminally ill patients participate in research because they hope to cure or ameliorate their own conditions.¹⁹³

Recognizing these potential drawbacks, this proposal is nevertheless justified. Informed consent requirements are insufficient to protect the interests of the terminally ill. Without such a ban on unrestricted use of the terminally ill as research subjects, they remain highly vulnerable to abuse.

2. *Research Intended to Provide a Direct Therapeutic Benefit to Subjects*

There should be few additional restrictions¹⁹⁴ on the types of research that will be approved when the research is intended to benefit terminally ill subjects. There are, however, two requirements imposed in the regu-

191. See GRAY ET AL., *supra* note 67, at 35 (noting, however, that ensuring the informed consent of subjects is of heightened importance in AIDS studies that do not provide a direct benefit to patients because subjects may be unaware that the studies are not intended for their benefit).

192. See JOHN AIKIN, THOUGHTS ON HOSPITALS 79 (1971) cited in William Bynum, *Reflections on the History of Human Experimentation*, in THE USE OF HUMAN BEINGS IN RESEARCH, *supra* note 143, at 36 (1988). Note that similar arguments have been made for using prisoners as research subjects. These arguments are resurfacing now as prisoners who suffer from illnesses such as AIDS lobby for the *right* to be included in drug studies. See generally PETER B. MEYER, DRUG EXPERIMENTS ON PRISONERS (1976); see also *supra* Part I.C.

193. See Daugherty et al., *supra* note 6, at 896.

194. There are a number of general restrictions on the types of research that may be done designed to ensure that the research is good science. See 45 C.F.R. § 46.111 (1998); see also *supra* Part I.A.2.

lations governing research on children that should also be applied to research involving the terminally ill.

First, the general regulations applicable to all research require IRBs to determine that the "risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result."¹⁹⁵ When research uses and intends to benefit child subjects, however, the IRB must find that "the risk is justified by the anticipated benefit to the subjects."¹⁹⁶ General knowledge is not weighed in the risk/benefit calculus. The same limitation should be imposed when experimentation involves the terminally ill. If the risks to the terminally ill subjects outweigh the potential benefits to them, the subjects should not be allowed to "consent" in the name of science.

Second, the research should not be approved if a treatment with a more favorable risk/benefit ratio is available to treat the patients' conditions. Again, this mirrors the requirement applicable to research involving children.¹⁹⁷ Researchers' primary obligation when working with the terminally ill should be to treat them as patients, and if better therapies are available, they should be employed.

The primary objection to these restrictions is that they could potentially stifle important medical developments. An IRB could conceivably not approve the research that otherwise would lead to the general cure for cancer on the grounds that the study is so risky, and the possibility of benefit so remote, that there are better, alternative treatments available. For this reason, an exception should be created to allow research to go forward if HHS determines after consultation that the research presents an opportunity for an important advance in the understanding of the terminal condition.

195. 45 C.F.R. § 46.111(a)(2).

196. *Id.* § 46.405(a).

197. *See id.* § 46.405(b) ("[T]he relation of the anticipated benefit to the risk [must be] at least as favorable to the subjects as that presented by available alternative approaches.").

*C. Further Safeguards to Ensure the Informed
Consent of Subjects*

1. Subject Advocates

Used in conjunction with other regulatory reforms suggested above,¹⁹⁸ subject advocates could greatly enhance the informed consent process in human research.¹⁹⁹ Current regulations suggest that when research involves pregnant women, fetuses, or human *in vitro* fertilization, it may be appropriate to employ subject advocates to ensure the adequacy of the informed consent process.²⁰⁰ Nowhere else in the regulations, however, are subject advocates mentioned.²⁰¹ Thus, regulators could have considered and rejected the notion of requiring the use of subject advocates. Indeed, a number of participants in the regulatory debate in 1982 lobbied for the use of subject advocates, but many modern commentators have rejected the idea as overly intrusive.²⁰² Nevertheless, requiring the use of subject advocates for research involving the terminally ill is justified.

As argued in Part II, a number of factors taken together make the terminally ill uniquely vulnerable to coercion and undue influence in the informed consent process. Many of these factors could be neutralized, or at least mitigated, through the use of a subject advocate.²⁰³ A subject advocate trained to recognize the psychological symptoms that accompany terminal diagnoses could help patients cope with depression and

198. See *supra* Parts III.A & III.B.

199. NBAC has suggested the use of "independent advisors" for research involving the mentally ill that entails more than minimal risk. See NBAC REPORT, *supra* note 127, at 37.

200. See 45 C.F.R. § 46.205(a)(2) (1998); see also *supra* Part I.B.2.

201. See 45 C.F.R. §§ 46.101-46.409.

202. Richard J. Bonnie, *Research With Cognitively Impaired Subjects*, 54 ARCH. GEN. PSYCHIATRY 105, 111 (1997) (citing R. Dresser, *Mentally Disabled Research Subjects: The Enduring Policy Issues*, 276 JAMA 67 (1996); J.W. Berg, *Legal and Ethical Complexities of Consent with Cognitively Impaired Research Subjects: Proposed Guidelines*, 24 J. LAW. MED. ETHICS 18 (1996)).

203. See generally M.D. Dowdy et al., *A Study of Proactive Ethics Consultation for Critically and Terminally Ill Patients with Extended Lengths of Stay*, 26 CRIT. CARE MED. 252 (1998) (finding that proactive ethics consultation for the terminally ill increased the quality and quantity of doctor-patient communication, led to more decisions to forgo life-sustaining treatment, and reduced the average length of stay in the intensive care unit).

anxiety that they may feel,²⁰⁴ making them better able to analyze the information they receive. Subject advocates also could ask the difficult questions of researchers which the subjects themselves may be reluctant to ask due to their dependence on and desire to please the researchers,²⁰⁵ thus ensuring that the information subjects receive is more complete. Finally, researchers who for personal, professional, or financial reasons otherwise might be reluctant to disclose all of the relevant information,²⁰⁶ would be more inclined to make full disclosure knowing that the informed consent process will be carefully scrutinized on the subjects' behalf. Subject advocates should have adequate education and training in the psychology of terminal illness,²⁰⁷ as well as sufficient medical knowledge to fully understand the risks and benefits of the research. In addition, to preserve their independence, subject advocates should not be employees of the institution conducting the research.

There are, of course, potential drawbacks. The use of subject advocates could drive a wedge between the subject and researcher, alienating the subject and angering the researcher. It could, incrementally, slow the progress of science. And most importantly, it could be viewed by subjects as personally invasive. Accordingly, the role of the subject advocate should be carefully circumscribed by a number of limitations.

First, subject advocates should not be required unless the experiment presents more than minimal risk to subjects. For low-risk experiments, where the stakes are not as high, IRBs should be left with discretion to decide whether to employ subject advocates. Second, research subjects should be able to decline to use a subject advocate. Whether to participate in research is an extremely intimate and personal decision, often made more on an emotional than on a cognitive level. Especially with subjects already experiencing a crisis of identity resulting from their illnesses,²⁰⁸ their preferences should be respected. Third, to minimize costs²⁰⁹ and delay, subject advocates should be used only to the extent

204. *See supra* Parts II.A.1 & II.A.2.

205. *See supra* Part II.A.4.

206. *See supra* Parts II.B & II.C.

207. In appropriate cases, the roles of psychologist, *see infra* Part III.C.2, and subject advocate could be combined, thus allowing a trusting relationship to form between the subject and the psychologist/advocate.

208. *See supra* Part II.A.

209. The costs of subject advocates presumably would be borne, like other costs of the research, by the research sponsor, the subjects themselves, or by a third party payer, depending on the research. It is important to minimize costs because, at the

necessary to ensure the adequacy of informed consent, or as otherwise requested by the subject. Thus for many subjects, an initial meeting with the subject advocate and the inclusion of the subject advocate in the informed consent negotiations with the researcher may be sufficient.

With these caveats taken into account, requiring subject advocates for any research involving more than minimal risk should have little impact on scientific progress, the dignity of the subjects, or the sanctity of the relationship between subject and researcher.

2. Psychological Evaluation and Care

Given the normal psychological response to terminal illness as well as the prevalence of psychological disorders among the terminally ill,²¹⁰ psychologists should examine subjects to determine if they: (1) are experiencing normal psychological response to the terminal illness; (2) are suffering from a psychological disorder but are legally competent; or (3) are legally incompetent.²¹¹ Like subject advocates,²¹² the psychologist should be independently employed to preserve neutrality. This initial screening would then affect how informed consent is obtained.

On either end of the psychological spectrum, there is little, if any, controversy. Legally incompetent persons cannot consent to be research subjects without the use of a surrogate decision-maker.²¹³ The precise procedures for obtaining proxy consent by a surrogate are complex, evolving, and vary from state to state.²¹⁴ Generally, however, a family member or court-appointed guardian will be able to consent on behalf of

margin, cost escalation could squeeze out some deserving subjects or prevent important research from being conducted.

210. *See supra* Part II.A.2.

211. For a similar argument, see Bonnie, *supra* note 202, at 111 (arguing that whenever there is a possibility of decision-making incapacity, "IRBs should require investigators to use a structured protocol for assessing decision-making capacity and identifying subjects with a possible impairment"). *But see* Pellegrino, *supra* note 134, at 1521 (noting that palliative care patients must give their informed consent to the psychosocial aspects of their care as well as to medical treatments).

212. *See supra* Part III.C.1.

213. *See* 45 C.F.R. § 116 (1997); *see also* GRAY ET AL., *supra* note 67, at 36 (arguing that "[p]eople with debilitating illnesses, such as AIDS (especially when patients are demented or hospitalized), would never profit from research if independent competent consent was always required").

214. *See* Bonnie, *supra* note 202, at 110.

an incompetent person to participate in research intended for her benefit.²¹⁵

Conversely, persons who are merely suffering from the normal psychological effects of terminal illness diagnosis should be allowed to consent on their own behalf. To require more would be overly paternalistic and an insult to autonomy. Steps should nevertheless be taken to ensure the integrity of the informed consent process. Unless medically necessary, the informed consent process should not take place during the acute anxiety phase that accompanies diagnosis with terminal illness,²¹⁶ and subject advocates should be made available to assist them.²¹⁷

Persons who have a psychological disorder of some sort, but who are legally competent, present the most difficulty. On the one hand, the presence of a psychological disorder inherently compromises the legitimacy of informed consent. Thus, some might argue that terminally ill persons suffering from such disorders should simply be excluded from research. On the other hand, if a patient insists on participating in the research and is legally competent to consent, should researchers or regulators have the right to tell him otherwise? This question is difficult precisely because it pits the norm of informed consent against the norm of personal autonomy. Closer scrutiny, however, suggests that personal autonomy should prevail, and that terminally ill persons suffering from psychological disorders should be allowed to consent to participate in research.

The doctrine of informed consent has taken on direct normative connotations in the modern regulatory state. Researchers must obtain informed consent, in part, because they ought to obtain informed consent. In reality, however, the normative content of the informed consent doctrine is derivative, grounded in a more basic ethical vision of the autonomous individual. The Nuremberg Code states that "[the research subject] should be so situated as to be able to exercise free power or choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion."²¹⁸ In short, the doctrine of informed consent is designed to promote the

215. *See id.*

216. *See supra* Part II.A.1.

217. *See supra* Part III.C.1.

218. TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10 181-82 (1949).

ethic of respect for persons.²¹⁹ It would be ironic indeed if in the name of respect for the terminally ill person suffering from a psychological disorder regulators were to refuse to allow her to participate in an experiment that has already been found by an IRB to represent a reasonable risk.²²⁰ However serious the concerns about informed consent may be, these concerns cannot justify the affront to personal autonomy such a refusal would entail.

This conclusion also reflects practical concern over the application of a rule that would exclude the terminally ill with psychological disorders from research. In essence, whether a person was allowed to participate in research — some of which would be potentially life-saving — would turn on the subtle distinctions that psychologists would have to draw to distinguish “normal” psychological responses to terminal illness from psychopathological ones. This would vest enormous power in the hands of psychologists and put inordinate faith in their ability to draw the sometimes extremely fine lines between normal and abnormal.

One commentator has argued for an intermediate approach that in theory represents a good compromise, but in practice presents difficulties. Richard Bonnie suggests that when persons have impaired decision-making capacity but are legally competent, the regulations should require only their *assent*,²²¹ which perhaps could be accompanied by the use of a surrogate decision-maker.²²² This procedure, however, could have unintended consequences.

If different informed consent procedures were used for classes of persons with partially impaired decision-making capacity, the sponsors of the research might assume that there was something psychologically “wrong” with those subjects. As a result, such people could end up being excluded from research altogether. With profits hanging entirely on the success of research, sponsors seek out subjects who have the affliction that their drug or therapy is designed to treat, but who otherwise are

219. See LEVINE, *supra* note 9, at 96 (citing K. Lebacqz & R.J. Levine, *Respect for Persons and Informed Consent to Participate in Research*, 25 CLIN. RES. 101 (1977); K. Lebacqz & R.J. Levine, *Informed Consent in Human Research: Ethical and Legal Aspects*, in W.T. REICH, *ENCYCLOPEDIA OF BIOETHICS* 754 (1978)).

220. 45 C.F.R. § 46.111. This Article suggests that only benefits to the terminally ill research subject, not benefits to scientific advancement, should be considered in the risk/benefit calculus. See *supra* Part III.B.2.

221. This term and its technical definition are borrowed from the regulations governing research on children. See 45 C.F.R. §§ 46.402(b), 46.408.

222. See Bonnie, *supra* note 202, at 110.

as healthy as possible.²²³ Given the increased prevalence of suicide and the decreased general resiliency of persons with some psychological disorders,²²⁴ research sponsors will seek to eliminate these persons from their studies so as to avoid contamination of research results.²²⁵ Thus, even if the regulations allowed for their participation through assent and proxy consent, such subjects could be effectively excluded for fear of research "contamination."

In sum, all potential research subjects suffering from terminal illnesses should receive psychological evaluations. Those who are legally incompetent may participate through proxy consent. Those who are legally competent should be able to consent on their own, regardless of whether they suffer from a psychological disorder or are experiencing a normal response to their illnesses. In addition, ongoing psychological care and monitoring should be available to subjects during the research, but patients should be able to decline psychological care at their discretion. Finally, all psychological evaluations and consultations should be strictly confidential so as to prevent research sponsors from excluding potential subjects to ensure favorable research results.

CONCLUSION

Federal regulations governing human research provide special protections to "vulnerable" populations such as children and prisoners who may be incapable of giving their voluntary informed consent to participate as research subjects. No such protections are extended to the terminally ill. Indeed, over the past fifteen years AIDS activists have fought for deregulation, and the terminally ill now have earlier access to experimental drugs when there are no adequate therapies available, and promising new drugs for the terminally ill are put on a fast track for regulatory approval. The terminally ill have come to be seen by researchers and regulators alike not as passive and weak, but as autonomous agents with the right to evaluate information and make their own

223. Interview with David Nettleton, Software Validation Specialist, Cell Therapeutics, Inc., Seattle, Wash. (Apr. 4, 1998) [hereinafter Nettleton Interview].

224. See generally Pola Grzybowska & Ilora Finlay, *The Incidence of Suicide in Palliative Care Patients*, 11 PALLIATIVE MED. 313 (1997).

225. Nettleton Interview, *supra* note 223. Cell Therapeutics is a small Seattle biotechnology company whose stock dropped from \$15 to \$3 per share after poor results were obtained during a Phase I drug study that may have been contaminated. See *id.*

decisions. These important gains, however, have tended to obfuscate the fact that the terminally ill are highly vulnerable to coercion and undue influence by inattentive or unethical researchers.

A confluence of factors works together to make the terminally ill vulnerable to research abuse. The terminally ill are desperate for a cure and often suffer from depression, anxiety, or other psychological disorders that may be exacerbated by the physiological symptoms of their illnesses. These psychological symptoms make rational decision-making extremely difficult. Also, the terminally ill are often hospitalized, feel dependent on the researchers in whose hands they have placed their lives, and as a result may be reluctant to ask difficult questions — wanting instead to play the good patient to curry favor and to avoid reprisals. Often, patients simply presume that whatever their doctor recommends is in their best interest, and fail to understand the dual roles of the physician/researcher. Moreover, researchers are under tremendous financial and professional pressures to complete their studies quickly and publish the results, and thus may be reluctant to say or do things that will decrease the likelihood of enrolling eligible subjects.

Accordingly, regulatory reforms need to be made to better protect the terminally ill and ensure that they participate as subjects in research only after giving their truly informed consent. The regulations should recognize the terminally ill as vulnerable, require a representative of the terminally ill to be a member on IRBs that work with the terminally ill, and require psychological training for researchers who work with the terminally ill. Also, research generally should be conducted on the terminally ill only if it is intended to benefit them. Finally, psychological evaluations and subject advocates should be employed to protect the integrity of the informed consent process.

Inevitably, regulation of human research involves tradeoffs between the personal autonomy and rights of research subjects, potential benefits to society, and the need to prevent research abuse. Reasonable people will differ as to how this balance should be struck. Nevertheless, it is critical that researchers, regulators, and the terminally ill engage with these issues. This Article is intended to provide a framework and starting point for that debate.