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Promoting Medical Research Without Sacrificing Patient Autonomy: Legal and Ethical Issues Raised by the Waiver of Informed Consent for Emergency Research

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PROMOTING MEDICAL RESEARCH WITHOUT
SACRIFICING PATIENT AUTONOMY: LEGAL
AND ETHICAL ISSUES RAISED BY THE WAIVER
OF INFORMED CONSENT FOR EMERGENCY
RESEARCH

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*[W]e have been all too willing, in our longing to conquer disease and death, "to possess the end and yet not be responsible for the means, to grasp the fruit while disavowing the tree, to escape being told the cost, until someone else has paid it irrevocably."*¹

I. Introduction

The first principle of the Nuremberg Code is that "[t]he voluntary consent of the human subject is absolutely essential."² The reader should be aware, however, that if she is rushed to the hospital emergency room after a car crash with severe brain trauma, a heart attack, or similar medical emergency, and if she is unconscious or otherwise incapacitated, she may be entered into an experimental research project, including a randomized, placebo-controlled clinical trial, without her consent. This opportunity is brought to her compliments of the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS). These agencies have issued regulations that provide a waiver of informed consent requirements for emergency research under certain conditions.³ The regulations allow a waiver when the potential subject is in a life-threatening situation, where consent of the subject or a surrogate cannot be obtained, and available treatments are unproven or unsatisfactory. Recognizing the vulnerability of the unconscious patient in the emergency setting, the regulations attempt to provide additional protections, such as public disclosure of the proposed research and consultation with the community from which subjects may be drawn. But should the waiver be allowed at all? And if so, are the present protections sufficient to safeguard patient interests in light of early reports that suggest such protections, particularly the community and public disclosure requirements, may be ineffective?

The current waiver of informed consent for experimentation on human subjects in the emergency setting is fraught with ambiguities and, at least in part, may be unethical. Advancement of medical research in the critical-care environment is a worthy goal, and for the most part, the waiver represents a justifiable exception to the requirement of informed consent. In its present form, however, it is not drawn sufficiently narrowly to assure respect for individual autonomy. Moreover, it fails to provide clear guidelines to aid the researcher in complying with the waiver's requirements.

1. Jay Katz, *Human Experimentation and Human Rights*, 38 ST. LOUIS U. L.J. 7, 39 (1993) [hereinafter Katz, *Human Experimentation*] (quoting Edmond Cahn, *Drug Experiments and the Public Conscience*, in DRUGS IN OUR SOCIETY 225, 260 (Paul Taladay ed., 1988)).

2. *Permissible Medical Experiments*, in 2 TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10 (1949), reprinted in THE ETHICS OF RESEARCH INVOLVING HUMAN SUBJECTS; FACING THE 21ST CENTURY 431 (Harold Y. Vanderpool ed., 1996) [hereinafter ETHICS OF RESEARCH].

3. See 21 C.F.R. § 50.24 (1999) (FDA regulation); 61 Fed. Reg. 51,531 (1996) (DHHS waiver, to be codified at 45 C.F.R. pt. 46). The DHHS regulation adopts and is virtually identical to the FDA regulation.

This article analyzes the need for the waiver, the waiver's benefits, and the criticisms and concerns it has generated. This article advocates greater protections for potential subjects, including amending state laws governing durable powers of attorney for health care to allow an agent to decide whether the principal should participate in medical research, and amending the current federal waiver provision to provide greater disclosure. It also calls for heightened protections for potential research subjects. Finally, the article explores the need for a National Human Research Board equipped to resolve the difficult ethical questions arising from waivers of informed consent, as well as experimentation on human subjects generally.

II. Overview of the Waiver of Informed Consent for Emergency Research

A. The Regulations⁴

The Secretary of Health and Human Services and the Commissioner of Food and Drugs proposed to amend the FDA's informed consent rules on September 21, 1995. After a comment period, the proposed rule became effective November 1, 1996.⁵ The rules provide that before conducting research under a waiver of informed consent, the Internal Review Board (IRB) responsible for approving the investigation, along with the concurrence of a physician unconnected to the IRB or the research, must find and document that the research is necessary to determine the safety and effectiveness of a particular intervention, that the human subjects are in a life-threatening situation, that available treatments are unproven or unsatisfactory,⁶ and that without the waiver, conducting the research would not be feasible.⁷ The waiver applies only where consent of the subject cannot be obtained owing to the subject's medical condition, and the research intervention must take place before consent can be obtained from a legally authorized representative or family member.⁸ The researchers must have no reasonable way of prospectively identifying likely subjects.⁹ The regulations require that the research intervention offer the prospect of direct benefit to the subject, and proof of appropriate animal and other preclinical studies must be presented to the IRB to support this potential benefit. Further, the risks must be reasonable in light of "what is known about the medical condition of the potential class of subjects."¹⁰ The research may include "randomized, placebo-controlled investigations."¹¹

4. See *infra* Appendix for reprint of FDA regulations.

5. The FDA allowed a 45-day comment period on the proposed rule. Comments were received from clinical investigators, Internal Review Boards, patient advocacy groups, trade associations, professional societies, drug and medical device companies, and private citizens. These comments are summarized at 61 Fed. Reg. 51,498-51,526 (1996).

6. See 21 C.F.R. §§ 50.24(a), (a)(1) (1999).

7. See *id.* § 50.24(a)(4).

8. See *id.* §§ 50.24(a)(2)(i)-(ii).

9. See *id.* § 50.24(a)(2)(iii).

10. *Id.* §§ 50.24(a)(3)(i)-(iii).

11. *Id.* § 50.24(a)(1).

The investigator must commit to attempt to obtain consent from a legally authorized representative or family member¹² during a specifically designated therapeutic window.¹³ The regulations require additional protections for the potential subjects, including consultation with representatives of the community from where the research is to be carried out¹⁴ and public disclosure of the clinical investigation both prior to the trial and after completion of the research, which must include the demographic characteristics of the research population.¹⁵ The IRB must insure that the protocol includes procedures to inform the subject, legal representative, or family member at the earliest opportunity that the subject has been involved in the research, and the representative must be provided with sufficiently detailed information and given the opportunity to discontinue the subject's participation in the research.¹⁶ This notice is required even if the subject dies before a representative can be contacted.¹⁷ The regulations also require an independent data monitoring committee to oversee the investigation.¹⁸ Finally, if the research qualifies for the waiver of informed consent, the protocol must be submitted to the FDA through an investigational new drug application (IND) or an investigational device exemption, even if the drug or device has already been approved for other indications.¹⁹

B. Why Do We Need The Waiver

The FDA proposed the waiver in response to growing concern that the existing rules "were making high quality acute care research activities difficult or impossible to carry out at a time when the need for such research is increasingly recognized."²⁰ One purpose of the new rules was to harmonize a conflict between the FDA and the DHHS rules.²¹ The DHHS guidelines approved waivers of informed consent only when the proposed research posed minimal risk to patients.²² The effect of this "minimal risk" restriction was to exclude much emergency resuscitation research, where the situation was often life-threatening and the medical condition itself presented significant risk.²³ On the other hand, the FDA rule allowed an exception from the general requirement of informed consent if, in the investigator's opinion, "immediate use of the test article is . . .

12. *See id.* § 50.3(m) (defining a family member to include "any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship").

13. *See id.* § 50.24(a)(5).

14. *See id.* § 50.24(a)(7)(i).

15. *See id.* § 50.24(a)(7)(iii).

16. *See id.* § 50.24(b).

17. *See id.*

18. *See id.* § 50.24(a)(7)(iv).

19. *See id.* § 50.24(c).

20. 61 Fed. Reg. 51,498 (1996) (to be codified at 21 C.F.R. § 50.24).

21. *See id.*

22. *See* 45 C.F.R. § 116(d)(1) (1999).

23. *See* James G. Adams & Joel Wegener, *Acting Without Asking: An Ethical Analysis of the Food and Drug Administration Waiver of Informed Consent for Emergency Research*, 33 ANNALS EMERGENCY MED. 218, 219-20 (1999).

required to preserve the life of the subject."²⁴ This apparently precluded giving either the standard treatment or a placebo in an emergency research protocol. If the test article is *required* to preserve life, it would be unethical to withhold the test article from an appropriate patient, thus eliminating the potential for a control group.²⁵ The new waiver rule harmonized the FDA and DHHS rules in the emergency context and clarified when a waiver of informed consent could be issued for emergency research.²⁶

During the comment period on the proposed rule, a number of presenters touted the waiver as facilitating research in the emergency patient population, which would "ultimately speed the wide availability" of tested and proven drugs and devices to those in life-threatening situations.²⁷ The new rule was applauded as "a much needed step in the advancement of vital emergency research,"²⁸ "a major step towards increasing the available therapies and medical care available for [the] critically ill or injured,"²⁹ and "a significant step forward towards advancing medical care."³⁰ One organization commented that it was "particularly pleased with the balance . . . between the need for conducting high quality clinical research in an effort to develop better treatments for critically ill patients and the protection of human subjects."³¹ Another organization recognized that once the waiver is implemented, it would "help to expedite study enrollments, thus allowing for earlier study completion . . ."³² For the most part, the proposed waiver was lauded by physicians, clinical researchers and investigators, and professional associations.

III. The Principle at Stake: Respect for Individual Autonomy

So why all the fuss? With the waiver of informed consent for emergency research so widely hailed, and with so many critically ill patients now able to receive the "opportunity" to participate in potentially life-saving "treatments," what is the downside? The primary objection to the waiver of informed consent is that it fails to respect individual autonomy; thus, some discussion of the evolution and development of this international human principle is necessary.

At the heart of the physician's Hippocratic Oath is that the physician must "do no harm" to the patient.³³ On its face, then, the Hippocratic Oath prohibits all

24. 21 C.F.R. § 50.23(b) (1999).

25. See Adams & Wegener, *supra* note 23, at 220.

26. See 61 Fed. Reg. 51,498, 51,501 (1996). The existing FDA and DHHS regulations were not superseded by the waiver provision; these rules have been retained and are useful in situations not covered by the new waiver. See *id.* at 51,503.

27. *Id.* at 51,498.

28. *Id.* (comment of the American College of Physicians and the Project on Informed Consent of the University of Pennsylvania Center for Bioethics).

29. *Id.* (comment of the Brain Injury Association).

30. *Id.* (comment of the Coalition of Acute Resuscitation and Critical Care Researchers).

31. *Id.* (comment of the American Heart Association).

32. *Id.* (comment of the National Stroke Association).

33. Traditionally, doctors have taken the Hippocratic Oath as part of their medical school graduation

research with human subjects designed to produce generalized knowledge.³⁴ Clinical research is undertaken for the benefit of society, and its focus is on the production of knowledge that will be socially useful.³⁵ That clinical experimentation is contrary to the basic ethic of the Hippocratic Oath became painfully evident when the world focused on the atrocities committed by the Nazi doctors during World War II, which culminated in the 1946 Nuremberg trials. At Nuremberg, the world had two options: on the one hand, it could have embraced the Hippocratic Oath, which would require strict physician-patient loyalty and would have rendered experimentation for generalized knowledge unethical, or it could embrace a new ethic that would allow patients to become "subjects" in some morally allowable way.³⁶ The world chose to allow human experimentation, and the course chosen is reflected in the second principle of the Nuremberg Code: "[t]he experiment should be such as to yield fruitful results for the good of society"³⁷ Full-blown utilitarianism was prevented, however, by the first principle of the Nuremberg Code: "[t]he voluntary consent of the human subject is absolutely essential."³⁸ Thus, the principle of autonomy, or self-determination, was born.³⁹ The research enterprise could proceed so long as the autonomy of the individual was respected through his or her informed consent to participate in the research.

The Nuremberg Code, however, did not address how autonomy was to be respected when the potential subject was incapacitated or otherwise unable to consent. This concern was addressed in the Declaration of Helsinki, adopted in 1962, which offers recommendations for conducting experiments using human subjects.⁴⁰ The Declaration states that "[w]here physical or mental incapacity makes it impossible to obtain informed consent, permission from the responsible relative replaces that of the subject"⁴¹ Thus, the concept of surrogate consent was born, allowing a departure from the Nuremberg Code proclamation that consent of the subject is essential. Consent of the subject was no longer essential after the adoption of the Declaration of Helsinki.

Despite the lofty aspirations expressed in the Nuremberg Code and the Declaration of Helsinki, the period between 1946 and 1966 in the United States was unregulated by the federal government, and in fact, reflected a virtual ignorance, and sometimes even blatant disregard, for these emerging principles.

ceremony. The tenet, "First, do no harm," is generally attributed to Hippocrates. See HIPPOCRATES, EPIDEMICS, bk. I, § XI, at 625 (W.H.S. Jones trans., Harvard University Press 1948).

34. See Robert M. Veach, *From Nuremberg Through the 1990's: The Priority of Autonomy, in ETHICS OF RESEARCH*, *supra* note 2, at 45.

35. *See id.*

36. *See id.* at 46.

37. *Id.*; see also *ETHICS OF RESEARCH*, *supra* note 2, at 431.

38. Veach, *supra* note 34, at 46.

39. *See id.*

40. See WORLD MEDICAL ASS'N, DECLARATION OF HELSINKI (1964) (rev. 1975, 1983, 1989), reprinted in *ETHICS OF RESEARCH*, *supra* note 2, app. B at 433.

41. *Id.* at 465.

A highly controversial article by Henry K. Beecher, M.D., provided twenty-two examples of unethical research conducted between 1948 and 1965 by well-known investigators at leading medical schools and government institutions who published their results in leading medical journals, yet often risked the health or life of their subjects without their knowledge or consent.⁴² Largely because of the controversy generated by the Beecher article, the FDA and the National Institute of Health (NIH) developed internal guidelines that were codified as federal regulations in 1974.⁴³ Also in that year, the newly formed National Commission for the Protection of Human Subjects of Biomedical Research and Behavioral Research (National Commission) was established and directed to identify basic ethical principles underlying the conduct of biomedical research involving human subjects and to develop federal guidelines.⁴⁴ Of the seventeen reports generated by the National Commission, the best remembered is the Belmont Report, which identifies three fundamental principles to be respected in experimentation on human subjects: respect for persons; beneficence; and justice.⁴⁵ After the Belmont Report, federal regulations were revised to reflect officially sanctioned ethical principles set forth as guides for the resolution of ethical problems.⁴⁶

The first ethical principle of the Belmont Report, "Respect for Persons," requires not only respect for individual autonomy but protections for those with diminished autonomy as well.⁴⁷ Recognizing that some individuals lose the capacity for self-determination due to their illness, the principle of respect for persons requires additional protections for those persons unable to consent.⁴⁸ The second principle of the Belmont Report, "Beneficence," embodies the obligation to maximize benefits and minimize harm to the subject.⁴⁹ The third principle, "Justice," requires fairness in the selection of research subjects and fair distribution of the benefits and burdens of the research.⁵⁰ Thus, when informed consent of the subject cannot be obtained, but the principles of justice and beneficence dictate that the person must have the opportunity to participate in the research, the focus is on the additional protections that are provided and on whether these additional protections are sufficient to protect individual autonomy.

42. See Henry K. Beecher, *Ethics and Clinical Research*, 274 *NEW ENG. J. MED.* 1354 (1966); see also *ETHICS OF RESEARCH*, *supra* note 2, at 9.

43. See *ETHICS OF RESEARCH*, *supra* note 2, at 10.

44. See William J. Winslade & Todd L. Krause, *The Nuremberg Code Turns Fifty*, in *ETHICS CODES IN MEDICINE* 150 (Ulrich Trohler & Stella Reiter-Theil eds., 1996).

45. See *id.* at 151; NATIONAL COMM'N FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL & BEHAVIORAL RESEARCH, *THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH* (DHEW Publication No. (OS) 78-0012, Apr. 18, 1978) [hereinafter *BELMONT REPORT*], reprinted in *ETHICS OF RESEARCH*, *supra* note 2, app. C at 437.

46. See *ETHICS OF RESEARCH*, *supra* note 2, at 10.

47. *BELMONT REPORT*, *supra* note 45, at 439.

48. See *id.* at 440.

49. See *id.*

50. *Id.* at 441-42.

The issue, then, is whether the waiver of informed consent for emergency research provides additional protections sufficient to protect individual autonomy. If not, the waiver is unethical and must not be allowed.

One scholar, Baruch A. Brody, sees the waiver of informed consent for emergency research as a successful balancing of the multiple values surrounding the research effort.⁵¹ These values include the desperate social need for research to test promising treatments for patients in an emergency setting presenting acute crises such as strokes and closed head injuries and the potential for direct benefit to those patients in the treatment group, if the new treatment in fact proves beneficial.⁵² These values must, however, be weighed against the need to protect individuals from the exploitation and harm by researchers in the event the new therapies turn out to be harmful, and respect for individual autonomy, which includes the right of persons not to be used for research without their consent or the consent of those who speak for them.⁵³

While ideally all of these values can be respected in a normal setting, this may not be possible in the emergency setting where the subject is incapacitated and the time within which one can obtain consent is limited.⁵⁴ Even when a patient is conscious and her consent can be obtained, conditions such as time pressure and emotional trauma raise questions as to whether consent truly can be voluntary.⁵⁵

Brody asserts that even when individual autonomy cannot be respected because consent cannot be obtained, the research can still be conducted ethically, as long as the other three values (great social need, potential of direct benefit to subjects, and protection of individuals from exploitation and harm) are sufficiently present.⁵⁶ In Brody's opinion, the FDA rules go far in ensuring that this is the case. The first value of social need is sufficiently present, he explains, because the FDA regulations allow a waiver to be issued only when the situation is life-threatening, available treatments are unproven or unsatisfactory, and the research is necessary to determine the safety and effectiveness of the particular intervention.⁵⁷ Moreover, the second value, potential benefit to the patients in the treatment, is promoted by the FDA requirement that animal and other preclinical studies support the potential for direct benefit to the patient.⁵⁸ The third value, protection of the patient-subject from harm and exploitation, is addressed through the community consultation provision,⁵⁹ supervision of research by the indepen-

51. See Baruch A. Brody, *In Case of Emergency: No Need for Consent*, 27 HASTINGS CENTER REP., Jan-Feb 1997, at 7.

52. See *id.*

53. See *id.*

54. See *id.*

55. See *id.*

56. See *id.*

57. See *id.* at 8; see also 21 C.F.R. § 50.24(a)(1) (1999).

58. See Brody, *supra* note 51, at 8.

59. See *id.*; see also 21 C.F.R. § 50.24(a)(7)(i).

dent data and safety monitoring board,⁶⁰ and the requirement for FDA approval even when the drug being tested is already approved for other uses.⁶¹

IV. Criticisms and Concerns Generated by the Waiver

The principal concern of bioethicists does not seem to be that a waiver could be granted at all; rather, the concern is that the waiver should be accompanied by protections sufficient to compensate for not obtaining the subject's informed consent. Following is an analysis of the primary concerns generated by the waiver.

A. The Waiver Blurs the Distinction Between Therapy and Research

As a practical matter, the doctrine of informed consent imposes similar disclosure and consent obligations for therapy and for research. For research, however, the informed consent process also is subject to review by IRBs.⁶² Jay Katz, a leader in the field of bioethics, notes, however, that in therapeutic encounters, unlike research encounters, the physician's sole concern should be the welfare of the patient.⁶³ This basic expectation is what gives physicians the discretion and authority to make decisions on behalf of their patients.⁶⁴ In clinical research, however, patient-subjects are used for scientific ends. In the research setting, the investigators do not view the participants as patients, but as subjects to be objectified in pursuit of answers to the research question.⁶⁵ Patients must understand that they are being asked to advance the interests of medical science, rather than receiving the most advanced treatment available.⁶⁶ Whenever clear distinctions are not made between research and treatment, the waiver becomes problematic because some people are being recruited to serve the ends of others.⁶⁷ Katz accuses the FDA of misleading the public by blurring the distinction between research and treatment.⁶⁸ The FDA's position is that research under the waiver is appropriate only if "evidence support[s] the potential of providing direct benefit to the individual subjects."⁶⁹ Thus, the FDA's characterization of the type of research conducted under the waiver implies that patients

60. See Brody, *supra* note 51, at 8; see also 21 C.F.R. § 50.24(7)(iv).

61. See Brody, *supra* note 51, at 8.

62. See Katz, *Human Experimentation*, *supra* note 1, at 13-14.

63. See *id.* at 14.

64. Katz notes, however, that even this basic presumption is questionable, given medical advances that offer patients choices that, because they can decisively impact their quality of life, require very subjective patient decisions. Moreover, because today a patient's available options may impact the physician economically, a physician's self-interest could readily influence his recommendations to his patient. See *id.* at 17.

65. See *id.* at 15-16.

66. See Jay Katz, *Blurring the Lines: Research, Therapy and the IRBs*, HASTINGS CENTER REP., Jan-Feb. 1997, at 9 [hereinafter Katz, *Blurring the Lines*]; see also Katz, *Human Experimentation*, *supra* note 1, at 9-54.

67. See *id.*

68. See Katz, *Blurring the Lines*, *supra* note 66, at 9.

69. *Id.* (quoting FDA comments at 61 Fed. Reg. 51,499 (1996)).

could expect to receive beneficial treatment; in fact, argues Katz, this is not the case, and the implication is unethical.⁷⁰ Moreover, seriously ill patients are likely to be confused about the purpose of the research, and may not view the risks and benefits realistically.⁷¹

On the other hand, one could say that within the physician-patient therapeutic relationship, several exceptions to the informed consent principle are already recognized, and recognizing a waiver of informed consent for emergency research is not a significant additional step. One commentator, Norman Fost, explains that informed consent is not an absolute principle, and in fact, it has been altered in several ways generally considered ethical.⁷²

For example, virtually all states allow for surrogate or proxy consent under certain circumstances, based on the principle of substituted judgment, which ideally reflects what a patient would have wanted.⁷³ Furthermore, the principle of implied consent operates when a patient allows her doctor to conduct low risk, routine blood chemistries, x-rays, or urinalyses without being provided with the details of the testing process.⁷⁴ Another principle acknowledges the right of a patient to choose not to be informed of her condition and to allow her physician to act in her best interests.⁷⁵ Even the informed consent of our military personnel may be waived for "military expediency," under certain conditions which, in the government's opinion, affect our national security or war interests.⁷⁶

Virtually all jurisdictions recognize that a patient in an emergency condition who is unconscious or otherwise unable to consent to treatment is presumed to consent to treatment based on a reasonable person standard.⁷⁷ The principle of presumed consent is based on the presumption that a reasonable person would consent to treatment based on the best judgment of the treating physician.⁷⁸ Such

70. *See id.* at 9.

71. *See* Richard S. Saver, *Critical Care Research and Informed Consent*, 75 N.C. L. REV. 205 (1996).

72. *See* Norman Fost, *Waived Consent For Emergency Research*, 24 AM. J. L. & MED. 163, 163-64 (1998). On the other hand, consent alone, even if informed, is not necessarily sufficient. *See id.* at 163. After all, no one would argue that experimentation by the Nazi doctors during World War II would have been permissible had they obtained the consent of their subjects. *See id.*

73. *See id.* at 173.

74. *See id.*

75. *See id.* at 174.

76. *See Doe v. Sullivan*, 938 F.2d 1370, 1371 (D.C. Cir. 1991) (affirming the district court's refusal to enjoin the Department of Defense from using an unapproved drug on Operation Desert Storm troops without their consent); *see also* George J. Annas, *Protecting Soldiers from Friendly Fire: The Consent Requirement for Using Investigational Drugs and Vaccines in Combat*, 24 AM. J. L. & MED. 245, 245 (1998).

77. For example, under Texas law, informed consent is implied as a matter of law if a patient is unconscious or otherwise unable to give consent and immediate surgery or other medical care or procedure is necessary to preserve the patient's life or health. *See Gravis v. Physicians & Surgeons Hosp.*, 427 S.W.2d 310, 311 (Tex. 1968).

78. *See* Fost, *supra* note 72, at 174.

a standard embodies the recognition that some persons would in fact not consent, yet those persons would be treated anyway.⁷⁹

Even when informed consent is obtained from a patient, it often can be described as an "elaborate ritual" since many fully competent patients do not truly understand in any meaningful sense the risks and benefits of alternative treatments.⁸⁰ Often, the informed consent process provides, at best, physician protection against malpractice claims, but one should not mistake this process for truly informed consent.⁸¹ The consent problem is heightened in the emergency research situation where the risks are substantial and serious. Fost's point, then, seems to be that the lines between treatment and research really *are* "blurred," and the basic principles supporting alterations of the informed consent doctrine in the therapeutic relationship are rightfully extended to the research forum.

B. The Standard for Consent Should Be Higher in Research Studies — Not Waived

Of general agreement is the principle that standards for consent should be higher in the research setting. One reason is that, because the risks are not known in advance (as, for example, with approved drugs), only the patient can decide to assume them, and deferral to the physician is not appropriate.⁸² Moreover, the research subject cannot be presumed to consent to research that may not necessarily benefit her.⁸³ In addition, the researcher and the subject have conflicting interests — the subject for her own well-being and the researcher (even the kindly researcher) for the well-being of future patients who may benefit from the research.⁸⁴

Arguably, this heightened standard for research is met by the FDA waiver and its accompanying layers of protection for subjects in clinical trials. One compelling viewpoint is that the waiver provides more protection for the critical care subject than a patient receiving "innovative therapy" in the routine care setting.⁸⁵ While under routine care, in certain circumstances, a physician is at liberty to experiment on her patients.⁸⁶ Under the principle of presumed consent, a patient is presumed to consent to treatment judged appropriate by her physician. This treatment, however, may take the form of an "innovative therapy" — use of a drug that is unreviewed and uncontrolled, whose efficacy is unknown, and that may be harmful to patients.⁸⁷ The difference between innovative therapy and

79. *See id.*

80. *Id.* (quoting F.J. Ingelfinger, *Informed "but Uneducated" Consent*, 287 NEW ENG. J. MED. 465 (1972)).

81. *See Fost, supra* note 72, at 175.

82. *See* Richard Delgado & Helen Leskovic, *Informed Consent in Human Experimentation: Bridging the Gap Between Ethical Thought and Current Practice*, 34 UCLA L. REV. 67, 68-69, 88-90 (1986); *see also* Saver, *supra* note 71, at 271 n.65.

83. *See id.*

84. *See id.* at 91, 97-98.

85. *See Fost, supra* note 72, at 175.

86. *See id.*

87. *See Fost, supra* note 72, at 176 ("Many invasive, dangerous interventions were used for decades

research is that the physician is not constrained by regulatory oversight and there is little likelihood that useful knowledge will be obtained for application to future patients.⁸⁸ One commentator remarked: "[a]s long as you promise not to learn anything from what you're doing, you don't have to go through an IRB."⁸⁹ Moreover, the chance of receiving "innovative therapy" is probably greater in the emergency and critical care setting.⁹⁰ Even when the patient's fully informed consent to receive innovative therapy is obtained, consent alone does not necessarily protect the patient given the conditions of trauma, confusion, and pain a patient often experiences upon arrival at the emergency room. Thus, in this sense, the clinical trial conducted under the FDA waiver, with its requirements for attempting to obtain surrogate consent, along with its community consultation and public disclosure provisions, protects the emergency research subject better than a patient receiving the same treatment under the guise of "innovative therapy."⁹¹

*C. Patients Would Not Want to Enter into a Research Study Without Consent*⁹²

The basis for the emergency waiver is that consent may be implied because, in emergency circumstances, a reasonable person would agree to experimental therapy.⁹³ But when the "therapy" is not necessarily therapy at all, but rather an experimental intervention, patient preferences are not so easily implied.⁹⁴ Attempting to justify critical care research because, in the physician's judgment, the patient may benefit equally from either the standard treatment or the experimental intervention greatly diminishes the principle of patient autonomy.⁹⁵

Nevertheless, some evidence indicates that, in fact, patients in life-threatening emergencies would consent to participation in a research study if they could. In 1990, 558 patients were entered into a randomized, placebo controlled trial of calcium channel-blockers given to comatose survivors of cardiac arrest.⁹⁶ Treatment had to occur within thirty minutes of restoring spontaneous circulation, thus precluding prospective consent in virtually all cases.⁹⁷ Within eight hours, and prior to administering a second dose of medication (or placebo), physicians contacted family members to give full information and to obtain consent to continued participation in the trial.⁹⁸ This deferred consent method was used with 95% of the patients. Detailed reports of these interactions were examined, and

before physicians realized the procedures were unacceptably toxic, ineffective, or both.".)

88. See *id.*

89. Fost, *supra* note 72, at 176 (quoting from a personal conversation with Paul Lietman).

90. See *id.*

91. See *id.* at 177.

92. See *id.* at 175.

93. See Saver, *supra* note 71, at 231.

94. See *id.*

95. See *id.* at 232.

96. See *id.*; see also Norman S. Abramson & Peter Safer, *Deferred Consent: Use in Clinical Resuscitation Research*, 19 ANNALS EMERGENCY MED. 781, 782 (1990).

97. See *id.*

98. See Fost, *supra* note 72, at 178.

results showed that in only twelve instances did families refuse to consent to the patient's continued participation.⁹⁹ In all twelve cases, however, the families believed that it would be better to allow the patient to die because of the severity of the underlying medical condition — not because they did not wish the patient to participate in the experiment.¹⁰⁰ In only six cases did families react negatively because the experiment proceeded initially without consent, but in three of these cases, the concerns were related to the patient's survival with the underlying medical condition — not the patient's participation in the experiment per se.¹⁰¹ Thus, at least in this case, enrolling patients in a randomized clinical trial which gave patients the opportunity to receive a promising experimental treatment, even though some would receive a placebo, was consistent with the families' "understanding of what the patient would have wanted."¹⁰²

D. Use of a Placebo in Research Conducted Under a Waiver Is Unethical

Research conducted under the waiver of informed consent may, under certain circumstances, include a placebo.¹⁰³ Objections to placebo use are based on the principle that giving a placebo without consent is unethical because it offers no conceivable benefit to the patient.¹⁰⁴ Even recognizing the potential for a "placebo effect" — although this is unlikely given the trauma of the patient at the time the placebo is administered — the purpose of a placebo is not to treat the patient. Rather, a placebo is a non-treatment.¹⁰⁵

The FDA, in comment, explains "[i]n *virtually* all cases, when a placebo is used, standard care, if any, would be given to all subjects, with subjects randomized to receive, in addition, the test treatment or a placebo."¹⁰⁶ But why not in all cases? Jay Katz, an outspoken critic of the waiver (placebo) provision, states the answer is simply that the FDA and the research community place a higher value on research which uses the recognized "gold standard" of scientific research, the randomized placebo-controlled trial.¹⁰⁷ Katz bases his opinion on the FDA comment: "[t]he agency believes that it is important to recognize in the regulation that placebo-controlled trials may be conducted under this emergency research provision; thus it is retaining the wording of this section."¹⁰⁸

Katz believes that "if one cuts through the rhetoric, some human beings may be sacrificed for the advancement of science so that future but not *present*

99. *See id.*

100. *See id.*

101. *See id.* at 178.

102. *Id.* at 179.

103. *See* 21 C.F.R. § 50.24 (1999).

104. *See* Fost, *supra* note 72, at 179.

105. *See id.*

106. Katz, *Blurring the Lines*, *supra* note 66, at 10 (discussing 61 Fed. Reg. 51,509 (1996)) (emphasis added).

107. *See id.* at 11.

108. *Id.* at 10-11; *see also* 61 Fed. Reg. 51,509 (stating that the FDA anticipates that a placebo-controlled trial would be used only when needed to determine whether the standard treatment is in fact useful).

patients (as well as medical device companies, pharmaceutical industries, and investigators) will benefit from the research.¹¹⁰⁹ He proposes that when a waiver is issued, researchers should forego the scientific certainty that they would have gained through use of a placebo arm, when there is "any evidence that the [new] therapy may be helpful."¹¹¹⁰ Katz is not alone in this viewpoint. Another commentator, Baruch Brody, while recognizing the scientific value of placebo-controlled emergency research, questions the appropriateness of allowing a placebo arm in research conducted under a waiver.¹¹¹ In the life-threatening conditions under which emergency research takes place, it is difficult to justify a placebo arm, particularly when the regulations require evidence supporting the potential of the new treatment for direct benefit to the patient in order to issue the waiver.¹¹² The FDA waiver allows use of a placebo where there is some evidence that the new treatment is beneficial, but more evidence is needed.¹¹³ Overall, however, Brody welcomes the FDA regulations as "the triumph of pluralistic casuistry over the absolutism of single values."¹¹⁴

On the other hand, just because a placebo is a non-treatment does not mean that a placebo never benefits the patient.¹¹⁵ If the trial is properly designed, the investigator should be indifferent as to whether the active treatment or the placebo will be more helpful or harmful to the patient.¹¹⁶ One could argue that administering a placebo is not inconsistent with the presumed consent recognized by virtually all states when a patient is in an emergency medical condition and unable to consent.¹¹⁷ Given the basic premise that a reasonable person would more than likely consent to receiving a potentially beneficial experimental treatment where the standard treatment is unproven or ineffective, then a reasonable person would presumably consent to the 50% chance of receiving the new treatment.¹¹⁸ This is so because the patient would have no option that would guarantee that she would receive the experimental drug, since the experimental drug would not be available outside of the trial.¹¹⁹ What may be more difficult to presume, however, is whether the patient would choose the standard treatment, which *would* be available outside the trial, over a 50% chance of receiving a placebo. What may appear to be a case of whether the glass is half-full or half-empty may be much more when presumptions are based on the very subjective concerns of a patient in a life-threatening situation.

109. See Katz, *Blurring the Lines*, *supra* note 66, at 11.

110. *Id.*

111. See Brody, *supra* note 51, at 8.

112. See *id.* at 8-9.

113. See *id.* at 9.

114. *Id.*

115. See Fost, *supra* note 72, at 179.

116. See *id.*

117. See *id.* at 180.

118. See *id.*

119. See *id.*

E. The Waiver Will Disparately Impact Minority Communities

The waiver of informed consent for emergency research may disparately impact African Americans, hispanics, and the poor. Many trauma centers where emergency research likely will take place are located in urban inner cities and in public hospitals in areas where minorities and impoverished citizens reside.¹²⁰ Public hospitals are often associated with universities and are sites for teaching and medical research.¹²¹ Studies have shown that minorities are disproportionately represented in hospital emergency rooms for treatment of life-threatening firearms-related injuries and death and brain trauma, which make them likely subjects for emergency research.¹²² In one year, of 52,000 United States residents that died with traumatic brain injury, forty-four percent were caused by firearms, the leading cause of trauma-associated death for black and hispanic males.¹²³ Thus, these minorities will be disproportionately conscripted into medical experiments without their consent.

On the other hand, the principle of justice requires that societies' benefits and burdens must be distributed fairly.¹²⁴ Subjects may not be selected for research on the basis of their economic or ethnic status, and if these classes are disproportionately selected or specifically targeted, it must be for a reason directly related to the type of research conducted.¹²⁵ Justice is the requirement to act fairly and requires that research advances be available to all populations, including the vulnerable.¹²⁶

At the time it was proposed, however, the waiver generated misunderstanding as to how the justice principle would be respected in minority communities. In the preamble notice to its proposed rulemaking, the FDA justified the waiver, suggesting it would likely increase enrollment of minority and low-income patients in critical care studies, noting that surrogate consent was more easily obtained from white, middle, and upper class families than from poor minorities.¹²⁷ At the time, some interpreted this comment to mean that if surrogate consent were sought on behalf of minorities, it would be refused — and the waiver would overcome this barrier.¹²⁸ The FDA later explained its comment had been misinterpreted; it meant that surrogate representatives of minority patients were often harder to locate, and that without the waiver, equitable

120. See Annette Dula, *Bearing the Brunt of the New Regulations: Minority Populations*, HASTINGS CENTER REP., Jan-Feb 1997, at 11 [hereinafter Dula, *Bearing the Brunt*].

121. See *id.*

122. See *id.* at 11-12.; see also Daniel M. Sosin et al., *Trends in Death Associated with Traumatic Brain Injury, 1972 Through 1992*, 273 JAMA 1778 (1995).

123. See Dula, *Bearing the Brunt*, *supra* note 120, at 12.

124. See BELMONT REPORT, *supra* note 45, at 442.

125. See *id.*

126. See Adams & Wegener, *supra* note 23, at 218.

127. See Protection of Human Subjects: Informed Consent, 60 Fed. Reg. 49,086, 49,093 (1995); see also Saver, *supra* note 71, at 253.

128. See Protection of Human Subjects; Informed Consent & Waiver of Informed Consent Requirements, 61 Fed. Reg. 51,498, 51,500 (1996).

numbers of minority patients may not have the opportunity to receive the potential benefits of the emergency research.¹²⁹ Thus, the waiver would allow the hoped-for benefits from the research to be more equitably distributed among minority populations.

Minority populations, however, are suspicious of medical and scientific research, and with significant justification. The most publicized example of the egregious use of minorities without their consent is the Tuskegee Syphilis Study, a non-therapeutic, unconsented-to study of hundreds of black men with syphilis, whose conditions were monitored for over twenty years.¹³⁰ These men were never treated, despite the availability of penicillin.¹³¹ Other documented examples of disregard for the principle of informed consent include research on slave women for finding a cure for urine leakage into the vagina and using black women to perfect the cesarean section.¹³² In the much-publicized Human Radiation Experiments, where humans were used to study the effects of radiation, research subjects were disproportionately members of minority populations.¹³³

Giving minorities the opportunity to participate in emergency research while at the same time respecting that their mistrust of the medical community may inhibit their participation, provides a challenge to the research community. On the one hand, progress may be made through the community consultation and public disclosure requirements, provided the programs are specially tailored to the potential population. On the other hand, in some cases, it may be that the correct determination for the IRB reviewing the research is that some minority communities ought to be excluded.

F. The Community Consultation Provisions Are Inadequate

During the first year in which waivers were available for emergency research, two studies were granted a waiver.¹³⁴ One was a large multicenter trial on the use of an oxygen-carrying drug in hemorrhagic shock, the other was the test of a device for the management of cardiac arrest.¹³⁵ In addition, a waiver under the new rules was granted to a study already in progress at the University of Texas Health Science Center on the use of hypothermia in head trauma.¹³⁶

In February 1999, the first investigational device study performed under the new waiver published its experience with the regulation. This study was a randomized protocol investigating the benefit of circumferential chest compression provided by a pneumatically inflated "vest" compared with standard manual cardio-pulmonary resuscitation (CPR).¹³⁷ Initially, IRB approval of the study

129. *See id.*

130. *See generally* JAMES H. JONES, *BAD BLOOD, THE TUSKEGEE SYPHILIS EXPERIMENT* (1981).

131. *See id.* at 7-9.

132. *See* Annette Dula, *African American Suspicion of the Health Care System Is Justified: What Do We Do About It?*, 3 *CAMBRIDGE Q. HEALTHCARE ETHICS* 347, 347-48 (1994).

133. *See* Dula, *Bearing the Brunt*, *supra* note 120, at 12.

134. *See* Charles Marwick, *Assessment of Exception to Informed Consent*, 278 *JAMA* 1392 (1997).

135. *See id.*

136. *See id.*

137. *See* Mark S. Kremers et al., *Initial Experience Using the Food and Drug Administration*

was deferred due to concern over insufficient community consultation protections in the research protocol.¹³⁸ Moreover, the IRB and the hospital administration and its legal representative expressed considerable reservation about the waiver, specifically about potential malpractice liability.¹³⁹ It was due primarily to concerns over the adequacy of community consultation and the potential for malpractice litigation that the approval process took longer than four months.¹⁴⁰

Ultimately, the study was approved after the investigators added a public forum to present the information and to address community concerns, and notification of the study was posted on large signs in the participating hospital units.¹⁴¹ Notices of the public forum, which included a telephone number and information about the study, were published in the largest major daily newspaper serving the community.¹⁴² Additional means of public disclosure included brochures to current hospital patients, display of posters on the walls of participating hospital units, a video demonstration of Vest CPR played continuously in the doctor's lounge, and other efforts. A total of twelve calls and twenty pre-registrations were received. Of the twenty-five people attending the forum, fifteen (sixty percent) worked in the health care field.¹⁴³ Thus, it may not be surprising that all forum participants approved of the study, and no one expressed ethical concerns. Ultimately, the study was discontinued after four months, due to cumulative costs and slow enrollment.¹⁴⁴ During this four-month period, the protocol was performed on only four patients, and the investigators report that no patient requested exemption from enrollment or expressed concerns about research without consent.¹⁴⁵ The medical staff appeared equally at ease, and no physician expressed major concerns about the ethics of the study.¹⁴⁶ In their article reviewing their experience with the waiver, however, the investigators stressed that the existing community consultation provisions were too broad and led to confusion over what was required.¹⁴⁷

One year after the new regulation took effect, the FDA held a meeting to discuss its progress.¹⁴⁸ One of the principal reasons for holding the meeting was concern over the interpretation of community consultation requirements.¹⁴⁹ At this meeting, a senior legal advisor to the FDA, Mary Pendergast, stated: "[w]e have been disturbed by some of the methods of consultation presented We

Guidelines for Emergency Research Without Consent, 33 ANNALS EMERGENCY MED. 224, 225 (1999).

138. *See id.* The participating hospital was a 593-bed acute care private facility which drew patients from the surrounding five counties.

139. *See id.* at 229.

140. *See id.*

141. *See id.* at 226.

142. *See id.*

143. *See id.*

144. *See id.* at 227.

145. *See id.*

146. *See id.*

147. *See id.*

148. *See Marwick, supra* note 134, at 1393.

149. *See id.*

can't help wondering if the [IRBs], sponsors, and researchers are taking the rule seriously, when the only evidence we see of community consultation is an advertisement in the newspaper."¹⁵⁰

On the other hand, the investigators of the hypothermia study at the University of Texas, in an effort to comply with the community consultation requirement, moved to get Houston's mayor to declare a "Head Injury Day" to increase public awareness of the potential for brain trauma.¹⁵¹ In addition, the investigators used an existing minorities outreach program at the university to spread information about the study to various civic organizations, churches, health and education centers, senior citizens' groups, the chamber of commerce, the local Mothers Against Drunk Driving group, radio programs, and schools.¹⁵²

Another criticism of the community consultation provision is that the regulations provide no guidelines as to who are "representatives of the community" from which the subjects will be drawn, nor any explanation of how "communities" are defined.¹⁵³

While some believe the requirement for community consultation is too ambiguous and that the FDA should have been clearer about what it expected of researchers, others believe the rules allow necessary flexibility.¹⁵⁴ For example, in a proposal involving cocaine addicts at high risk of death from acidosis, potential subjects may be better informed about the study through contacts with former drug addicts and welfare or parole officers than through newspapers or television, and the current rules would allow for this flexible interpretation.¹⁵⁵

At the meeting held one year after the new regulations took effect, the FDA's Associate Commissioner for Health Affairs said the FDA would issue guidance information for those involved in planning and conducting research involving exceptions for consent.¹⁵⁶ To date, however, no such guidelines exist.

G. The Waiver's Surrogate Consent Requirement May Conflict with State Law

The FDA regulations require that, where a waiver is issued, the investigator must commit to attempting to contact (to the extent feasible in the short therapeutic window) a legally authorized representative for the purpose of obtaining consent for the subject's participation in the clinical investigation.¹⁵⁷ Many state statutes that allow a person to designate a durable power of attorney for health care, however, would not extend the agent's authority to decisions about the principal's participation in experimental research. For example, under Texas law, a person may execute a durable power of attorney for health care that designates an agent to "make any health care decision on the principal's behalf

150. *Id.*

151. *See id.* at 1393.

152. *See id.*

153. *See* *Fost, supra* note 72, at 181.

154. *See id.*

155. *See id.*

156. *See id.*

157. *See* 21 C.F.R. § 30.24(a)(5) (1999).

that the principal could make if the principal were competent."¹⁵⁸ Prior to amendment of the statutory definitions on September 1, 1999, a "health care decision" was defined as a "treatment, service, or procedure to maintain, diagnose, or treat an individual's physical or mental condition."¹⁵⁹ Thus, the durable power of attorney for health care did not include allowing a patient's agent to consent to an experimental intervention. Nothing guarantees that a particular patient will receive the new intervention, in light of the fact that the protocol may include a placebo. In fact, the condition of those in the treatment arm may actually be worsened.¹⁶⁰

In the absence of a health care directive, most states' laws designate a hierarchy of individuals whom the patient's physician may contact to make treatment decisions if the patient is incapacitated. For example, under the current Texas statute, the attending physician and one person from a prioritized list, beginning with the patient's spouse and moving to the patient's adult children, parents, or nearest living relative, must agree to the treatment.¹⁶¹ Still, however, the statute refers to a "treatment decision," which would, under most statutory definitions, not include experimental interventions — or at least certainly would not be presumed to include participation in experimental protocols in the same manner that an incapacitated patient may be presumed to want to receive standard treatment.¹⁶²

In December 1998, a panel of experts, the Human Research Ethics Group, members of the Project on Informed Consent at the University of Pennsylvania Center for Bioethics, issued a report suggesting certain amendments to the federal regulations governing experimentation on human subjects. The panel proposed that state statutes allowing for durable powers of attorney for health care be amended to allow surrogate consent for research that may potentially benefit individual subjects, or that presented no more than a small increase over minimal risk to the subject.¹⁶³ The panel reasoned that allowing patients to express their wishes with respect to research participation promotes patient autonomy, as well as allows a designated surrogate to act for the potential benefit of the patient should the patient become incompetent.¹⁶⁴ In addition to decisions about participation in research, the panel suggested that a durable power of attorney or other advance directive should allow the named surrogate to withdraw the subject from the research, considering the subject's known preferences and the actual benefit the subject continues to receive as the research continues.¹⁶⁵

158. TEX. HEALTH & SAFETY CODE ANN. § 166.152(a) (West Supp. 2000).

159. TEX. CIV. PRAC. & REM. CODE § 135.002 (West 1997) (repealed 1999) (definition of "health care decision" omitted in recodification).

160. See Jonathan Moreno et al., *Updating Protections for Human Subjects Involved in Research*, 280 JAMA 1951 (1998).

161. See TEX. HEALTH & SAFETY CODE ANN. § 166.039(b).

162. *Id.*

163. See Moreno, *supra* note 160, at 1952.

164. See *id.*

165. See *id.*

H. Physicians and Drug and Device Companies Will Seek to Expand the Waiver Concept to Non-Emergency Investigations

Some physicians believe that requiring different standards of informed consent for standard care, innovative treatments, or research threatens the physician's ability to advance the care of the critically ill.¹⁶⁶ These physicians say such requirements are not realistic.¹⁶⁷

Some physicians would use the rationale behind the waiver of informed consent to support proposals that go far beyond the emergency life-threatening situation and would extend the waiver to the physician's everyday practice.¹⁶⁸ One group of physicians made such a proposal recently in an article they coauthored in the *New England Journal of Medicine*.¹⁶⁹ These authors comment that what they have described as "clinical and practical realities"¹⁷⁰ were recently recognized and embodied in the waiver of informed consent for emergency research.¹⁷¹ The FDA and DHHS endorsed the waiver on the ground that it would allow the seriously ill access to new therapies. This endorsement could be of benefit to future patients.¹⁷² The authors further postulate that this rationale should extend to a physician who, for example, wishes to conduct a randomized controlled trial to determine which of two antibiotics is more effective at treating bronchitis.¹⁷³ In addition, the authors recognize the paradox that allows a physician under a general consent for treatment to try a novel, unproven treatment on his patient that she may only have read about recently. But if the same physician wanted to determine which of two widely used drugs was better at treating a particular condition, she must prepare a formal protocol, obtain IRB approval, and seek written informed consent from potential subjects.¹⁷⁴ In their analysis, the authors distinguish between the general consent to treatment a patient gives as part of the physician-patient relationship, which includes standard medications and routine tests, and the specific informed consent necessary whenever the proposed intervention involves more risk as compared to the benefit, or when patient preferences or values are expected to influence the decision.¹⁷⁵ The authors propose that if an intervention could be offered outside a trial without the patient's informed consent, then the physician ought to be able to include the patient in a controlled trial *without consent* provided some additional protections exist.¹⁷⁶

166. See Ronald B. Hirschl & Robert Bartlett, *Ethics of Proxy Consent for Research Involving Patients With Adult Respiratory Distress Syndrome*, 276 JAMA 949 (1996).

167. See *id.*

168. See Robert Truog et al., *Is Informed Consent Always Necessary for Randomized, Controlled Trials*, 340 NEW ENG. J. MED. 804 (1999).

169. See *id.*

170. *Id.* at 806.

171. See *id.*

172. See 61 Fed. Reg. 51,498-51,533 (1996).

173. See Truog, *supra* note 168, at 804.

174. See *id.*

175. See *id.* at 805.

176. See *id.*

These protections, the authors explain, would include requiring no more than minimal additional risk in comparison with alternatives, that the investigator should have honest uncertainty about which treatment is better (clinical equipoise), and an assurance that no reasonable person should have a preference for one treatment over another.¹⁷⁷ The authors recognize, however, that some communities, such as racial minorities who may be particularly sensitive to being part of an experiment based on a history of abuse (rather than for any reason related to the study), may require specific informed consent.¹⁷⁸ Finally, the authors propose that patients should be informed that the setting in which they are being treated uses the standards described in determining the need for specific, instead of general, informed consent, thus allowing patients to seek additional information or go elsewhere for care.¹⁷⁹ The authors claim that if a clinical treatment meets the proposed standards, informed consent is unnecessary because patients are unlikely to prefer one medication over another, and it is unlikely that the process of obtaining specific consent would serve the patient in any meaningful way.¹⁸⁰ If this is so, what is the harm in providing the information and, out of respect for the patient, allowing the patient to decide? It seems more likely that the authors fear that informing the patient merely would allow patients to opt out for subjective reasons unconnected to the study and that medicine cannot advance at the proper speed if patients are involved in this way. This attitude is patronizing and disturbing. The authors recognize that their controversial position would have little support among ethicists.¹⁸¹

I. Other Ambiguities

At least four other ambiguities arise with respect to the waiver.

(1) A waiver may be issued so long as the research "could not practicably be carried out without the waiver."¹⁸² The question that arises is how narrow must the treatment window be in order for it to be impractical for the researcher to obtain surrogate consent. The rules require that surrogate consent be obtained whenever possible, even when the waiver has been issued.¹⁸³ Researchers have expressed their concern over this requirement; they want to know how many telephone calls constitute an adequate effort to obtain surrogate consent and what else is expected.¹⁸⁴

(2) Although the FDA regulations are restricted to situations where available treatments are unproven or unsatisfactory,¹⁸⁵ it is not clear whether "unproven" means not proved by rigorous scientific evidence, or whether it merely means

177. *See id.*

178. *See id.*

179. *See id.*

180. *See id.* at 804.

181. *See id.*

182. 21 C.F.R. § 50.24(a)(4) (1999).

183. *See id.* § 50.24(a)(5)-(a)(6); *see also* Brody, *supra* note 51, at 8.

184. *See* Marwick, *supra* note 148, at 1393.

185. *See* 21 C.F.R. § 50.21(a)(1) (1999).

unproven in the clinical judgment of physicians who have observed therapeutic benefits.¹⁸⁶ Similarly, the question arises whether the available treatment is "unsatisfactory" unless it improves the patient's condition by 100%, or whether it is "unsatisfactory" if the patient's condition improved by only 50%.¹⁸⁷ Clearer guidelines and definitions could eliminate subjective differences.

(3) The waiver requires that the patient or her family members be informed as soon as is feasible, and that the patient or family may "discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled."¹⁸⁸ What the rules do not address, however, is what becomes of the subject's data if the family opts not to continue in the trial.¹⁸⁹ Exclusion of the subject's data could affect the validity of the trial results, particularly when a patient dies.¹⁹⁰

(4) The waiver of informed consent requirement for emergency research applies only to subjects in a "life-threatening situation."¹⁹¹ For patients with acute brain injury, however, the fear of surviving only to be left with permanent, severe brain disability, may in fact be greater than the fear of death.¹⁹² Although the patient technically may not have a "life-threatening" condition, the rules were clearly meant to include those with acute brain injury as well. The rules should be limited to "serious conditions in which irreversible damage could occur."¹⁹³

V. Recommendations

A. Establish a National Human Investigation Board

The morality and legality of human research ought to be subjected to intensive public scrutiny and congressional mandate.¹⁹⁴ For decades, Jay Katz has advocated the need for a National Human Investigation Board.¹⁹⁵ The need for a national body is especially critical given the responsibility that the federal regulations vest in IRBs. Katz argues that the IRBs are not able to make the ethical judgments required of them given their time limitations, the composition of the boards, and the pressure for approval from peers at their own institution.¹⁹⁶ Under the current system, many IRB members are on the faculty of the institutions to which the investigators belong; thus, IRB members face an inherent conflict of interest when called upon to protect research subjects when

186. See Katz, *Blurring the Lines*, *supra* note 66, at 9.

187. *Id.* at 10.

188. 21 C.F.R. § 50.24(b) (1999).

189. See Fost, *supra* note 72, at 181.

190. See *id.*

191. 21 C.F.R. § 50.24(a)(1) (1999).

192. See Fost, *supra* note 72, at 182 ("Death is the most irreversible of harms, but it is not the only one; and for many patients it is not the one most feared . . .").

193. *Id.*

194. See Katz, *Human Experimentation*, *supra* note 1, at 39.

195. See JAY KATZ, *EXPERIMENTATION WITH HUMAN BEINGS* 856-954 (1972).

196. See Katz, *Blurring the Lines*, *supra* note 66, at 12.

to do so could impede the research and affect their colleagues in decisive ways.¹⁹⁷ The primary responsibility of the National Human Investigation Board would be to formulate clear, detailed research policies and to serve as a resource to which IRBs can turn for guidance and advice.¹⁹⁸ The Board, Katz proposes, would establish review procedures that would allow for publication of Board decisions which would be a step toward case-by-case development of policies governing human experimentation.¹⁹⁹

B. Amend the Current Regulations

Under the current regulations, a waiver may be issued for research that could not *practically* be carried out without the waiver.²⁰⁰ That provision should be amended to require investigators to give specific assurance that a study cannot be conducted without using subjects who are unconscious or otherwise incapacitated.²⁰¹ A waiver should not be granted in those cases where the research could go forward using subjects capable of consenting in advance. This recommendation would eliminate the cases where use of the waiver would allow research to proceed faster; the research would still proceed, but at a slower pace. For example, a waiver may be necessary in cases of traumatic brain injury resulting from a motor vehicle crash; on the other hand, repeat myocardial infarction may lend itself to recruitment through advance consent.²⁰²

Perhaps the most compelling recommendation for safeguarding the interests of the incapacitated subject is the appointment of an independent physician to assess continued participation of the subject if no surrogate consent could be obtained within reasonable time. For example, if surrogate consent could not be obtained within twelve hours, the protocol would require that a physician unconnected to the research evaluate the risks and benefits of allowing the patient to continue in the research. Such an amendment would provide incentive to the study team to locate a relative in order to avoid involving another physician.²⁰³

The regulations further should be amended to clarify that "life-threatening" situations include "brain-threatening" emergencies as well. The waiver should include serious conditions in which irreversible brain damage could occur. Finally, no waiver should be issued in investigations with a placebo arm.²⁰⁴

C. Amend State Laws

State statutes that currently limit the authority of an agent acting under a durable power of attorney for health care to "treatment" decisions, should be amended. These statutes should allow agents and other surrogate decision makers

197. See Katz, *Human Experimentation*, *supra* note 1, at 41.

198. See *id.* at 39.

199. See *id.* at 40.

200. See 21 C.F.R. § 50.24 (1999).

201. See Moreno, *supra* note 160, at 1952.

202. See *id.*

203. See *id.* at 1953.

204. See *supra* Part IV.D.

to decide whether to allow a subject's participation in an experimental protocol. In addition, the authority of agents and surrogates should be extended to allow an agent to withdraw a subject from the research when it is in the subject's best interest.

VI. Conclusion

The doctrine of informed consent is at the heart of respect for individual autonomy, and ethical research requires obtaining the informed consent of the subjects who participate. But many potentially life-saving interventions can be studied and tested only under emergency conditions, when the patient-subject is incapacitated and unable to consent to participate in the study. Often, the test drugs must be given, or other interventions must occur, within a window of time too brief to locate family or others who consent on behalf of the patient. The medical and legal communities must, however, remain vigilant so that medicine is not advanced through an ambiguous waiver of informed consent that is subjectively interpreted or that is disproportionately applied to minorities. Additional regulatory guidelines are needed, and are already too long in coming.

APPENDIX

CODE OF FEDERAL REGULATIONS TITLE 21 —
FOOD AND DRUGS CHAPTER 1 —
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A — GENERAL PART 50 — PROTECTION OF HUMAN
SUBJECTS SUBPART B — INFORMED CONSENT OF HUMAN SUBJECTS

§ 50.24 Exception from informed consent requirements for emergency research.

(a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

(2) Obtaining informed consent is not feasible because:

(i) The subjects will not be able to give their informed consent as a result of their medical condition;

(ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and

(iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:

(i) Subjects are facing a life-threatening situation that necessitates intervention;

(ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and

(iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(4) The clinical investigation could not practicably be carried out without the waiver.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each

subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with § 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of

benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with § 56.115(b) of this chapter.

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under §§ 312.30 or 812.35 of this chapter.

(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

[61 FR 51528, Oct. 2, 1996]

