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**ARTICLE:** Waived Consent for Emergency Research

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**SUMMARY:**

... We would not say that the central problem of the Nazi experiments was their failure to obtain informed consent. ... Typically all patients would receive standard treatment and half would be randomized to receive the experimental treatment. ... The researchers interpreted minimal risk to refer to the differential risk in outcome from the experimental treatment as compared with the *standard treatment*, not as compared with the risks of daily life. ... In addition to the need to comply with the DHHS regulations, FDA regulations governed most studies, with different exceptions to the general informed consent rule. When investigational drugs were involved, the FDA permitted a waiver of informed consent if all four of the following conditions were met:

... While new treatments could be compared with standard treatment, the preferred experimental design is to give all patients standard treatment, and to randomize the experimental treatment using a placebo control. ... The fear of regulatory action against such research became real in 1994 when the FDA terminated a study in progress because of concerns about informed consent. ... Research is much more tightly regulated than standard treatment, with its succession of barriers from reviews of proposals for funding, approval of an IRB, detailed requirements for informed consent and review at the time of publication. ...

**HIGHLIGHT:** The voluntary consent of the human subject is absolutely essential. n1

**TEXT:****[\*163] I. INTRODUCTION**

Contrary to the first principle of the Nuremberg Code, the voluntary consent of the human subject is neither necessary nor sufficient for ethically and legally responsible research in the United States. That it is not sufficient has been well argued by Robert Burt <sup>n2</sup> and others. We would not say that the central problem of the Nazi experiments was their failure to obtain informed consent. <sup>n3</sup> Nor would the presentation of signed and witnessed consent forms change anyone's view on the moral justification for the experiments. <sup>n4</sup> For related reasons, institutional review boards (IRBs)

[\*164] sometimes reject or defer protocols for paternalistic or various other reasons, arguing that clinicians should not allow patients to consent to be subjects in a study. n5

It has also been recognized that the subject's informed consent is not always necessary for ethically acceptable research. The Declaration of Helsinki n6 and the U.S. Department of Health and Human Services (DHHS) regulations acknowledge that appropriate representatives may consent on behalf of a subject n7 and that in some circumstances consent may be waived altogether. n8 Fueled by advances in cardio-pulmonary resuscitation and the treatment of severe brain injury, interest has accelerated in conducting clinical trials on patients who are unable to consent because of their medical condition, and whose condition required initiation of treatment before an appropriate representative could be contacted to provide surrogate or proxy consent.

In the United States, an investigator seeking to conduct research on such patients was caught between the Scylla and Charybdis of two conflicting sets of regulations. The Food and Drug Administration (FDA) allowed for a waiver of consent for interventions that were necessary to save the life of the patient. n9 To waive consent, the DHHS regulations required, *inter alia*, that the experimental treatment present no more than minimal risk. n10 The FDA's emergency guideline, in contrast, required, that the research hold out the prospect of direct benefit to the patient. n11 The combination of these rules were considered by many to preclude placebo-controlled clinical trials on patients unable to consent, because a placebo is rarely necessary to save the life of a patient, n12 and DHHS regulations precluded experimentation, regardless of its possible life-saving implications, for all but the most trivial interventions. n13 As a result, innovative therapies either have not been developed, or have been tried without the benefits of well-designed trials, often resulting in long-delayed discoveries that innovative approaches were unacceptably toxic, inefficacious or both. n14

In response to these concerns, a coalition of critical care investigators, with the endorsement of many leading medical professional organizations, proposed a change in the federal rules that would allow for the expansion of the conditions under which

[\*165] consent could be waived in emergency research. n15 Following a conference sponsored by the National Institutes of Health (NIH) and the FDA, n16 proposed regulations were published, n17 and, after review of extensive comments, a final rule announced. n18

This Article reviews the history of waivers for informed consent in research involving human subjects; legal and regulatory aspects of the current rule; the ethical issues involved; and issues that will need to be addressed as the rule is applied in clinical studies.

## II. RECENT HISTORY OF REGULATIONS REGARDING WAIVED CONSENT

The World Health Organization's Declaration of Helsinki, while affirming the importance of consent from the subject, n19 departed from the Nuremberg Code's absolutism by acknowledging exceptions. First, it acknowledged that incompetent patients can be research subjects if consent is obtained from a "responsible relative . . . in accordance with national legislation." n20 But the Declaration goes farther, allowing consent to be waived under conditions that are less than clear; namely: "If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee." n21 This loophole transfers broad authority for waiving consent to the reviewing committee, because it offers no substantive criteria.

The DHHS policy, prior to the 1996 revisions, permitted waiver of informed consent only if all of the following were true:

- (1) The research involves no more than minimal risk to the subjects;
- (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- (3) The research could not practicably be carried out without the

[\*166] waiver or alteration; and

(4) Whenever appropriate, the subjects be provided with additional pertinent information after participation. n22

All of these conditions required interpretation by companies contemplating development of a product; by investigators; by IRBs; and by oversight agencies, particularly the FDA and the NIH Office of Protection from Research Risks (OPRR). Condition 4 raised no serious objections, and 2, in its lack of precision, seemed consistent with a wide range of proposed interventions.

Interpreting condition 3 posed more difficulty. Consider a proposal to test a new agent in the treatment of severe brain injury. The most efficient way to assess efficacy and toxicity would be in a prospective, randomized, placebo-controlled trial. n23 Typically all patients would receive standard treatment and half would be randomized to receive the experimental treatment. Because the major inclusion criteria would include unconscious patients, and the need for urgent treatment would often preclude obtaining proxy consent from appropriate relatives in a timely fashion, the investigator typically claimed that he could not practicably carry out the research without a waiver. Others suggested that the limits of the window of opportunity for beginning treatment n24 were unknown and that a delay sufficient to allow time to contact relatives would still provide enough subjects for an adequate trial. n25 A more extreme position, taken by some, was that prospective consent could be obtained from a very large cohort of healthy people who could then be included in a trial were they later to suffer a major head injury. n26 Whether the greatly increased time and cost of such a trial are practicable is and was a matter of opinion, and is difficult to resolve in an objective way.

The most significant controversy over the DHHS rules, however, focused on the requirement that the research involve no more than minimal risk, defined as: "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." n27 Interpreting and applying the minimal risk standard to other sections of the regulations had already been problematic, particularly sections regarding children, which restrict nontherapeutic studies to those posing no more than minimal risk. n28 This led

[\*167] some IRBs to question studies involving venipunctures, while other IRBs approved studies involving small bowel intubation, n29 and evoked controversy regarding the use of placebo injections in a trial of growth hormone. n30

This "no more than minimal risk" requirement seemed to preclude almost all research in emergency settings, because the majority of proposed interventions were likely to involve risks that would be more than minimal by the federal definition. But not everyone agreed, and some interpreted the rule differently.

In 1980, Norman Fost and John Robertson reported on a study comparing different steroid doses in treating acute head injury. n31 Although the risk of all three doses, if given repeatedly as planned, was presumably higher than the risks encountered in a routine visit to the doctor, the IRB concluded that the study would not expose patients to any risk beyond that of standard therapy because all three doses were used in standard practice. n32 The IRB was also concerned with the psychological burden to a relative being confronted within moments after a catastrophic injury, and being asked to consider "experimentation" on a loved one. n33 Because the interventions were in fact standard treatment and the only experimental aspect involved was randomization, which itself involved no risk, the IRB allowed the investigator to use what they called "deferred consent" for the initial dose, which means allowing treatment to begin without consent, and then approaching the relatives for consideration of continued treatment. n34 This was also predicated on the shared understanding that one administration of either dose met all interpretations of minimal risk, because the concern about adverse effects of the drug only arose after multiple doses. n35

In 1986, Norman Abramson, Alan Meisel and Peter Safar reported a study using thiopental sodium following cardiac arrest. n36 Patients were entered without consent into fifteen U.S. and European hospitals. n37 The researchers interpreted minimal risk to refer to the differential risk in outcome from the experimental treatment as

[\*168] compared with the *standard treatment*, not as compared with the risks of daily life. n38 They relied on another section of the regulations providing guidance to IRBs in reviewing studies: "In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research)." n39 For example, they pointed out that the experimental treatment using approved calcium-blocking drugs, though admittedly being used for an unapproved purpose, could be given outside of a clinical trial. n40 In fact physicians in emergency settings commonly use such innovative therapies. n41 Patients in this trial, therefore, were receiving treatment virtually identical to the treatment they would have received had they not participated in the research. n42 This line of reasoning also was followed by Ernest Prentice and his colleagues in a study of another agent, PEGSOD, which offered promise in treating severe brain injury. n43

In addition to the need to comply with the DHHS regulations, FDA regulations governed most studies, with different exceptions to the general informed consent rule. When investigational drugs were involved, the FDA permitted a waiver of informed consent if all four of the following conditions were met:

- (1) The human subject is confronted by a life-threatening situation necessitating the use of the [drug];
- (2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.
- (3) Time is not sufficient to obtain consent from the subject's legal representative.
- (4) There is no alternative method of approved or generally recognized

[\*169] therapy available that provides an equal or greater likelihood of saving the life of the subject. n44

Conditions 1-3 raised few obstacles, n45 but the fourth condition seemed terminally murky at worst, and ambiguous at best. By definition, the likelihood of an experimental treatment offering equal or better outcomes is unknown -- if it is known to be superior, there is little reason to study it. More important, conditions 1 and 4 seemed to preclude placebo-controlled studies, because a placebo would not be considered "necessary" to save the life of a patient. n46 While new treatments could be compared with standard treatment, the preferred experimental design is to give all patients standard treatment, and to randomize the experimental treatment using a placebo control. This avoids the ethical dilemma of withholding standard treatment, as well as offering more statistical power for the study, for example, the opportunity to demonstrate an effect using the least number of patients necessary.

Not surprisingly, it was difficult to justify a randomized clinical trial using the FDA exceptions, because they seem to be crafted to allow a patient to receive experimental treatment when the attending physician believes it would serve that patient's interests. n47

These ambiguities and differences in interpreting the regulations would have several consequences. First, they would lead to concerns that some studies were being conducted "outside of the rules." Second, because some IRBs were rejecting studies which others approved, such arguably permissible studies would not be carried out. Third, some companies and investigators would be inhibited from even considering studies. Fourth, prospective consent at the time of hospital admission would allow for studies on patients with medical emergencies while in the hospital, but would preclude studies of the much larger number of patients whose medical emergencies arose outside the hospital. Finally, the variation in application of the standards suggested they needed clarification, if not modification. n48

[\*170] The IRBs' reluctance in part was based on their awareness that the FDA had the authority to disqualify an IRB, effectively curtailing the ability of an entire institution to conduct any research involving human subjects. The FDA had exercised this authority for violations that involved arguably less substantive matters. n49 In 1993, the Director of the OPRR at the NIH warned IRB chairs in a "Dear Colleague" letter that using "deferred consent" was not in compliance with the DHHS rules regarding waiver of consent, n50 and was reported as saying that "DHHS is not allowing resuscitation research using deferred consent." n51 Two high-ranking FDA officials took the same position. n52

The fear of regulatory action against such research became real in 1994 when the FDA terminated a study in progress because of concerns about informed consent. n53

[\*171] The study involved comparing a hand-held suction device resembling a plunger with standard external cardiac massage in treating out-of-hospital cardiac arrest. n54 An IRB had approved the trial, and there were no apparent adverse effects at the time of suspension. n55 The FDA had earlier suspended an IRB approved study involving the use of PEG-SOD. n56

In response to industry concerns about the inhibiting effect of confusion, Rep. Ron Wyden (D-Ore.), then chairman of the House Subcommittee on Regulation, Business Opportunities, and Technology, held public hearings eliciting a wide range of opinions, including a proposal to expand the waiver for a narrow category of emergency research, with added safeguards and oversight. n57 In January 1995, the FDA and NIH cosponsored a public meeting to discuss the issue, n58 at which a consensus statement from a coalition of researchers and numerous professional societies attracted wide support. n59 The FDA published a proposed revision of the rules in September 1995, n60 and a final rule in October 1996. n61

The central elements of the final rule are: (1) the patient has a life-threatening situation; n62 (2) available treatments are unproven or unsatisfactory; n63 (3) consent from the patient is not feasible because of the patient's condition, and because treatment must be initiated before an appropriate representative can be reached; n64 (4) research cannot reasonably be conducted otherwise; n65 (5) risks and benefits of the experiment are considered reasonable in light of the patient's condition and what is known about other therapies; n66 and (6) participation in the research holds out the prospect of direct benefit to the subject. n67

The following new procedural protections are required, in addition to previous requirements under the federal rules: (1) consultation with the community in which

[\*172] the research will occur; n68 (2) public disclosure of the study design and attendant risks prior to its commencement; n69 (3) public disclosure of study results when completed; n70 (4) use of an independent data safety monitoring board; n71 and (5) approval of the study by the FDA. n72

### III. ETHICAL CONSIDERATIONS INVOLVING THE REVISED REGULATIONS

Although the majority of those who submitted written comments to the proposed rule were supportive, there was strong opposition to the revisions. Jay Katz, one of the founding thinkers of the modern bioethics movement, and author of a landmark text on human experimentation, n73 lamented the violation of the first principle of the Nuremberg Code n74 and suggested the new rule would be seen as a throwback to the Tuskegee study. n75 Others expressed concerns about randomization, the implicit loss of having one's doctor make an individualized decision, and ridiculed the claim that it might be in a patient's interest to receive experimental treatment. n76

[\*173] Even Jack Kevorkian weighed in. n77

Criticisms of the rule generally focus on three claims: (A) consent is an absolute principle; (B) the standard for consent should be higher in research than in standard care; and (C) patients would not want to be enrolled into a clinical trial without their consent; and that there is no justification for giving a placebo without consent. I will examine each of these in turn.

## A. CONSENT IS AN ABSOLUTE PRINCIPLE IN MEDICAL TREATMENT

Informed consent is a central principle in contemporary thinking about medical ethics and law, serving as one mechanism for protecting patients from harm, but primarily as a way of allowing patient autonomy to express itself. n78 Nonetheless, like all principles, it is certainly not an absolute. It is neither necessary nor sufficient for ethically responsible research involving human subjects.

### 1. Proxy Consent

In ordinary clinical treatment, exceptions to requiring the patient's informed consent are widely recognized. *Proxy consent*, increasingly recognized as a misnomer, actually bypasses consent of the patient and authorizes treatment due to the patient's incapacity. n79 The proxy provides authorization or permission to proceed, ideally based on a best guess as to what the patient would have wanted. This is called substituted judgment. If the patient's wants are unknowable, as in infancy, the parents and the doctor base the decision on an estimate of what would be in the patient's interests. n80

### 2. Implied Consent

*Implied consent* refers to situations in which the physician bypasses the usual requirements of disclosure and affirmative consent because the patient consents implicitly, not explicitly. n81 Examples include the myriad of routine tests that occur during hospitalization, such as blood chemistries, x-rays and urinalyses. While implied consent to such tests is a variation of consent, it is rarely informed in any meaningful sense.

### [\*174] 3. Waived Consent

*Waived consent* refers to circumstances in which a patient waives his right to be informed or involved in decisions regarding either his standard health care or his participating in research. n82 Even in the United States, where informed consent is the cultural norm, n83 a patient may choose to delegate decision making to the physician. n84 In other cultures, delegation of such authority to a community leader may be the norm. n85

### 4. Presumed Consent

Most relevant to the present discussion is *presumed consent*, commonly cited in emergency situations where support is widespread for providing treatment without any consent or authorization from the patient or a proxy, on the presumption that the patient would consent if he could. n86 Two aspects of this presumption are important to note.

First, the presumption is not predicated on an absolute assurance that the patient would consent if he could. It is understood that some patients would refuse even standard treatment. The presumption is therefore predicated on a "reasonable person" standard. n87 One implication of this standard is that some patients will be treated contrary to their wishes. However, because a decision to treat or not to treat will unavoidably offend someone's desires, using this standard is the lesser of two evils.

Second, the presumption allows the physician to use his best judgment as to how to treat the patient. In many instances, particularly in emergency settings, treatment may involve unproven and untested interventions; I will address this point later in this paper.

Finally, messages sent do not correspond to messages received. Even in the conventional paradigm where an apparently competent patient consents to a standard treatment, for example, an appendectomy, the consent is often lacking with respect to the key element of being informed. n88 Despite a physician's best efforts, fully competent patients commonly do not understand, in any meaningful sense, the likelihood of benefit or risk, or the pros and cons of alternative approaches. n89 F.J. Inglefinger characterized the process of informed consent as "an elaborate ritual." n90 In the real world, these everyday breaches of the principle of informed consent reflect

[\*175] widespread understanding and support for the moral legitimacy of treating patients without meaningful consent. The patient may give spoken or written authorization, sufficient to protect the physician against malpractice claims for proceeding without consent, but we should not mistake these authorizations for truly informed consent. n91 In emergency settings in particular, the physician is expected to make an educated guess as to what the patient's autonomous wishes might be, or if they are unknowable, to assess what course of action would be in the patient's interests.

#### B. THE STANDARD FOR CONSENT SHOULD BE EVEN HIGHER IN RESEARCH STUDIES

Just as consent is not an absolute principle in standard treatment, research settings justify similar ethically and legally valid exceptions. Proxy consent, for both therapeutic and nontherapeutic studies, is recognized in the federal regulations. n92 As discussed above, this provides legally valid authorization, though the moral basis for proxy consent remains controversial. n93 However we resolve the controversy, we cannot claim that physicians adhere to the first principle of the Nuremberg Code.

The question, therefore, is not *whether* informed consent from the patient or representative can ever be waived in ordinary treatment or research settings; rather, the question is *when* and *under what circumstances*. n94

It has long been accepted that the standards for consent should be higher in the research setting than in ordinary care. n95 Research is much more tightly regulated than standard treatment, with its succession of barriers from reviews of proposals for funding, approval of an IRB, detailed requirements for informed consent and review at the time of publication. n96 There are several reasons for this, including the history of serious transgressions, particularly the horrific disclosures of the Nuremberg trials. n97 Laws are not written until they are first broken. In addition, compared with standard care, experimentation is reasonably convenient to regulate due to its limited frequency and the existence of "tollgates," such as FDA approval and NIH funding.

This elaborate and generally effective regulatory infrastructure provides more protection to a patient in a clinical trial than a patient receiving routine care. In contrast, a physician providing routine care has considerable liberty to experiment on his patients. n98 This experimentation is commonly termed "innovative therapy." n99

[\*176] The central differences between innovative therapy and research are that, in the former, there is relatively no regulatory oversight and a minimal likelihood that generally applicable knowledge will result. n100 In the trenchant words of Paul Lietman, "As long as you promise not to learn anything from what you're doing, you don't have to go through an IRB." n101

For several reasons, the likelihood of patient exposure to innovative therapy -- essentially unreviewed, uncontrolled experimentation -- as compared with regulated research is arguably higher in the emergency and critical care settings than elsewhere. n102 The pressure of clinical work leaves little time for physicians to design and implement research studies. Physicians attracted to emergency and critical care may be more inclined to action than scholarly activities. Moreover, the difficulties of obtaining IRB consent, coupled with complying with the federal regulation, have long been seen as barriers to conducting well-designed prospective studies in emergency settings. n103

Innovative therapy often had disastrous consequences. Many invasive, dangerous interventions were used for decades before physicians realized that such procedures were unacceptably toxic, ineffective or both. Thousands of children were killed or injured by these therapeutic misadventures. n104 Although systematic comparisons are difficult, comparable examples of such widespread harm rarely result from well-designed, peer-reviewed clinical trials. Prospective review reduces the possibility for harm, filtering out many poorly thought out research designs through requiring researchers to satisfy particular requirements. Such requirements may include literature reviews and animal studies when appropriate; screening investigators for competence to conduct proposed studies; requiring justifications for sample size to reduce the number of potential subjects exposed to risk; interim review, by either an IRB or a data monitoring committee; and disseminating results through presentations at scientific meetings and publication. n105

These mechanisms reduce the relative degree to which consent actually protects research subjects from harm. In the emergency setting, where the efficacy of consent is reduced even further, a well-reviewed clinical trial seems to offer better protection

[\*177] from risk and a greater likelihood of benefit than using the same treatment under the guise of innovative therapy. Furthermore, studies conducted under the new FDA waived consent requirements establish additional protections, including requirements for community consultation prior to initiating a trial; independent data monitoring committees; and the requirement for FDA review before a trial is begun, even if the experimental intervention is already approved but is being studied for a new indication. n106

An example is the recently suspended U.S. trial of diaspirin cross-linked hemoglobin (DCLHB) for treating shock, n107 one of the first multi-center trials using the new procedures for waiver of consent. n108 The protocol called for patients brought to emergency departments in shock to receive all standard treatments and then randomized to receive either DCLHB or a placebo. n109 The researchers wanted to enter over 850 patients, most of whom would need to be entered before doctors could obtain consent from either the patient or a proxy. n110 The sponsor terminated the study following a recommendation from the data monitoring committee after, approximately 100 patients had been entered, due to higher mortality in the group receiving the experimental treatment. n111 Some may conclude that the study shows the dangers to patients from being entered into the trial without consent. A more plausible interpretation is that, even if investigations reveal that the drug caused the excess mortality, n112 far fewer patients were harmed than would have been had the drug been used under the guise of innovative therapy, which affords much less opportunity to discover ill effects of experimental use.

If this analysis is correct, then it follows that the standards for consent should be highest in those settings in which other mechanisms for protecting patients from harm are absent; namely, innovative therapy.

It might be said in response that the researcher has a conflict of interest in serving two masters: future patients versus the patient before him. It is this conflict that leads the physician/investigator to compromise the interests of his patient in the name of science, society and perhaps personal advancement. But the potential for these conflicts has been largely buffered in recent decades by the many layers of oversight in clinical research. The egregiously unethical practices that were common thirty years ago are now rare, n113 presumably because of this extensive multi-layered oversight. n114 For reasons such as undue confidence in technology, an impulse to action, and the absence of sufficient brakes on a physician's enthusiasm, an innovative

[\*178] therapist in the emergency setting has neither consent nor oversight to protect the patient from unwarranted experimenting.

### C. PATIENTS WOULD NOT WANT TO BE ENTERED INTO A RESEARCH STUDY WITHOUT CONSENT

Good ethics starts with good facts. If the purpose of consent is to increase the likelihood that patients are treated according to their preferences, then it would be helpful to know how patients and their representatives feel about waivers of consent. The most extensive study of this question is worth describing in detail. It supports the view that properly designed, properly reviewed clinical trials using waiver of consent, as outlined in the new rule, can be consistent with the preferences of the great majority of patients.

In 1990, the Brain Resuscitation Clinical Trial II Study Group reported the results of a randomized, placebo-controlled trial of calcium channel blockers given to comatose survivors of cardiac arrest. n115 The NIH-funded study enlisted twenty-four hospitals in eight countries, although two hospitals ultimately withdrew from the study due to malpractice concerns, n116 and included procedures for what was called *deferred consent*. n117 Five hundred and fifty-eight patients were entered into the study. n118 Physicians had to initiate treatment within thirty minutes of restoring spontaneous circulation, precluding prospective consent in virtually all cases. n119 Within eight hours, and prior to administering the second dose of medication (or placebo), physicians contacted a patient's family members to provide them with full information and invite them to consent to continued participation in the trial. n120 Detailed reports of these interactions were compiled. n121

Reports on reactions to the consent process are available from 78% of the American families and patients (266 of 343) and 47% of the European patients (102 of 215). The deferred consent mechanism was used for 95% (326 of 343) of the patients. n122 In twelve instances, the families refused to consent to continue. n123 In all cases, the refusal was based on a belief that the patient would be better off dead because of an underlying medical condition, not because of the experimental nature of the intervention. n124 Six negative reactions to the use of deferred consent were documented, three of which were related to concerns about survival, not about experimentation *per se*. n125

The results show that the overwhelming majority of families were in agreement with what was done, and presumably would have provided ethically and legally valid consent had they been contacted prior to the administration of the first dose. This

[\*179] suggests that in this study, for this population, enrolling patients in a randomized trial, which gave them the opportunity to receive a promising experimental treatment, was consistent with their surrogates' understanding of what the patients would have wanted. The responses suggest that relying on standard treatment, with its known poor outcome, would have been inconsistent with what these families preferred. There is no evidence that waiving consent was perceived as morally problematic for the great majority of families. n126

#### D. PLACEBOS CANNOT BE JUSTIFIED WITHOUT CONSENT

Even if opponents of the waived consent rule concede that physicians may justifiably administer an experimental drug without valid consent, on the grounds that it is the physician's judgment that such treatment has the best possible chance of helping the patient, some argue that there is no justification for giving a *placebo* in such circumstances, n127 because there is no conceivable benefit for the patient.

While conceding the possibility of placebo effect, its purpose in the critically ill patient is almost certainly not based on the possibility of direct benefit. Its purpose is not as treatment, but as nontreatment. Nontreatment, of course, is not the same as not helpful. 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. The historical record suggests that an attitude of agnosticism would have saved many patients from serious harm. n128 Apart from considerations of consent, the physician who claims to be acting in the interests of his patient may best serve both present and future patients by enrolling them into controlled trials when evidence for preferring a possibly risky treatment is lacking. n129

Similarly, a decision to enter a patient into a placebo-controlled trial is not inconsistent with the notion of presumed consent. The responsible physician must be able to answer the late-arriving relative, or a late-awakening patient, who asks why he was given a placebo. n130 A reasonable response would be as follows:

I am reasonably certain the standard treatment will not help. I don't

[\*180] know if the experimental treatment will help, but I think it is reasonable to try. If you were able to consent, I would offer it to you, and my best guess is that you would be interested in and willing to try it. However, my own conscience tells me it would not be responsible to give it to you in an uncontrolled way, because neither you, nor I, nor future patients would ever know whether it helped or hurt. As part of a controlled trial, therefore, I am administering your treatment in precisely the same way that I would if you were awake, or if your relatives were here. I am basing this on a presumption -- shared by many other disinterested, dispassionate, knowledgeable people with no stake in the out-come of this experiment who have reviewed this proposal -- that a reasonable person would more than likely consent to such treatment, and I therefore also presume you would consent to a 50% chance of receiving such treatment. If you tell me you would insist on receiving the experimental treatment, without being part of a well-designed study, then I regret to inform you that I can not accommodate that request. I believe it is irresponsible to give potentially dangerous treatments, of unknown benefit, without appropriate review, oversight and efforts to learn from the experience, so that lethal mistakes will not be repeated.

This presumption does not depend on a requirement that all patients enrolled would have consented if they could. Even an explicit complaint from a relative or patient after discovering he was enrolled in such a trial without consent does not show that it was wrong to treat the patient in this way. The same possibility exists for any unconscious patient treated in an emergency without consent, whether with standard or innovative treatments. Available data suggests that the number of people who would object is extremely small. n131 The alternative is to withhold treatment from all unconscious patients, to avoid offending the small minority who would not consent to be treated. This, of course, would fail to respect what would have been the wishes of the majority. Absent certainty about the patient's wishes, whether by concurrent consent, an advance directive or the credible representations of a proxy, the physician who wants to respect the most likely preferences of his unconscious patient has no choice but to make an informed guess as to what the patient's wishes would have been. n132

#### [\*181] IV. RESIDUAL CONCERNS ABOUT THE NEW REGULATIONS

While the new regulations can be justified on ethical and legal grounds, their implementation presents potential pitfalls and unresolved questions.

##### A. COMMUNITY CONSULTATION

The new rule requires "consultation . . . with representatives of the communities in which the research will be conducted and from which the subjects will be drawn," and "public disclosure to the communities in which the research will be conducted." n133 Who qualifies as a representative is unavoidably ambiguous, and the rule provides no guidelines. Theoretically, it would be possible to set up a *de minimis* procedure for community involvement, but this is unlikely to happen. Plans for community involvement must be disclosed to the FDA as part of the new investigational new drug application that is required for each study using the waiver, and these materials will be publicly available. n134 Early experience with such protocols suggests that involved parties have a high level of concern, in some cases fear, regarding a backlash from minorities, even if there is enthusiastic implementation of the requirement for community involvement. n135 There is already a high level of distrust in the African American community, even for research conducted under traditional standards of informed consent. n136 Thus, for researchers to set up *de minimis* procedures would require them to have a special kind of political naivete or insensitivity to risk backlash against a study, an institution, as well as against the rule itself.

Many questions regarding the details of community consultation and disclosure remain to be worked out. Where and how should public disclosure occur? How should "representatives" be identified? How should "communities" be defined? Should representatives sit on IRBs, special committees or simply speak in public meetings? If these procedures are perceived as inadequate, the consequences are that more detailed regulations may be needed, or support for the rule may weaken.

##### B. OPPORTUNITIES TO OPT OUT

The rules require that the subject, his representative or family member be informed "at the earliest feasible opportunity . . . that he or she may discontinue the subject's participation at any time." n137 Presumably this refers to discontinuing any experimental intervention or invasive monitoring that is occurring solely as part of the research project. It is less clear whether this provision is intended, or should be interpreted, to allow a patient or relative to exclude his or her data from analysis. Such an option could cause difficulties in statistical analysis, particularly if deaths are excluded from the database. A patient or family might be so outraged at the recruitment of a loved one into a research project without consent that they would not want anyone to benefit from the information obtained from the research.

[\*182] Although the analogy overstates the issue, this problem has sometimes been compared to the use of data illicitly obtained in the Nazi experiments. n138 The central principle is that people should not benefit from ill-obtained gains. The Nazi experiments were, of course, nontherapeutic and widely perceived as immoral, n139 whereas an unconsenting patient under the DHHS waiver will be treated with an intervention that his physician believes to be in his interest, according to rules that were created by a thorough democratic process. n140 Post-hoc regret about the manner of treatment cannot be equated with condemnation of the rules on moral grounds.

There is another issue regarding opting out that is not stipulated by the regulations, but has been raised by some studies; namely, whether potential subjects should be given an opportunity to exclude themselves before the recruitment begins. This could be accomplished through the community disclosure process, by making available a mechanism for individuals to identify themselves as not eligible for the study, through either the use of bracelets or lists accessible to those who would be enrolling or assigning patients.

Opting in, or prospective consent, n141 should not be an issue, because the rule explicitly requires that the waiver can only be used when "the research could not practicably be carried out without the waiver." n142 Accordingly, if patients who may be candidates for the experimental treatment could be identified on admission to the hospital or earlier, it would be obligatory to obtain prospective consent.

### C. RESTRICTION TO LIFE THREATENING CONDITIONS

In view of the controversial nature of the new rules, they should be limited appropriately to patients with serious conditions in which irreversible damage could occur if access to experimental treatments is not available. 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. Loss of a limb, eye or a replaceable organ also are feared, but many patients faced with those dangers are able to consent or, if the patient is incapacitated, the danger may not be so immediate that next of kin cannot be contacted to provide proxy consent.

A more serious concern is for patients with acute brain injury for whom the greater fear may not be death, but rather survival with a severe disability. In fact, among the small minority of surrogates who said they would not have consented to the experimental treatment of brain injury in a relative, the most common objection was not with respect to the treatment's experimental nature, but instead with treatment of any kind; the concern was not that their relative would die, but that he would survive with a permanent severe disability. n143 For these individuals, the appropriate

[\*183] treatment goal was not simply to preserve life, but also brain function. n144 The justification for treatment without consent, therefore, is not that the patient has a life-threatening condition, but that he has a brain-threatening condition.

Although treatments that aim to preserve brain function may result in higher rates of survival, as well as higher rates of intact survival, these two may not be linked. It would be desirable to separate these goals, if for no other reason than to clarify in the review process that mere survival may not be an appropriate goal.

## V. CONCLUSION

Informed consent is not an end in itself. It is a means, an instrument designed to achieve the end of protecting patients from harm and protecting their right to self-determination. In the emergency setting, the unconscious patient, in need of urgent treatment, often depends on the physician to make judgments in the absence of consent. In these circumstances, the physician must proceed either on what he or she believes to be in the best interest of the patient, or on the basis of a best guess as to what the patient would want. If a patient would trust his physician to use unproven therapies without consent under the rubric of innovative therapy, then such trust would presumably extend to unproven therapies that are part of well-designed, well-monitored, controlled trials. It is not plausible to presume that a patient would want his physician to use an innovative treatment, never properly tested for safety or efficacy in that situation, with no prior review, no monitoring, no post hoc review, but would object to the same physician using the same treatment with all the safeguards of a controlled trial.

Physicians who work in emergency settings have often used untested, unproven therapies in the belief that such therapies offered the best chance for helping the patient. This practice of innovative therapy has resulted in extensive harm, often with little or unknown compensating benefit, because it is commonly unknowable whether new treatments used in uncontrolled ways were in fact beneficial.

This pattern fails to serve societal interests, because it results in little progress in treating conditions that kill or disable large numbers of people, and it does not do honor to traditional notions of consent. Because consent is not available as a tool to protect patients from harm in such settings or to provide information about the patient's autonomous wishes, some other mechanism for advancing those interests must be found.

The revision of the federal rules for waiver of consent in research on life-threatening conditions seeks to correct all of these problems. It aims to improve the rate of progress in treating these conditions, to the benefit of future patients. More important, it aims to improve the likelihood that a presently identifiable patient will be treated in a manner in which he or she would approve if given the opportunity to consent. Incidentally, the new rules may also improve the present quality of care in emergency settings by reducing the amount of unreviewed, uncontrolled, unsupervised innovative therapies, and replacing such therapies with well-conceived, well-designed, properly monitored, publicly accountable protocols.

### **Legal Topics:**

For related research and practice materials, see the following legal topics:

Healthcare Law Treatment Incompetent, Minor & Mentally Disabled Patients General Overview  
 Healthcare Law Treatment Patient Consent Consent by Guardians & Parents Healthcare Law Treatment Patient Consent Informed Consent

## FOOTNOTES:

n1 *The Nuremberg Code*, in 2 U.S. GOV'T PRINTING OFFICE, TRIALS OF WAR CRIMINALS BEFORE THE NUERNBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL NO. 10 (1946-1949), *reprinted in 276 JAMA 1691, 1691 (1996)*.

n2 Robert A. Burt, *The Suppressed Legacy of Nuremberg*, HASTINGS CENTER REP., Sept. -- Oct. 1996, at 30, 33 (suggesting that the self-determination principle which emerged from the Nazi doctors' trials masks the fact that the Nuremberg judges could not provide a reassuring answer to the question, "whether physicians and/or state officials can be trusted to protect rather than abuse vulnerable people").

n3 See Jay Katz, *The Consent Principle of the Nuremberg Code: Its Significance Then and Now*, in THE NAZI DOCTORS AND THE NUREMBERG CODE: HUMAN RIGHTS IN HUMAN EXPERIMENTATION 227, 227-31 (George J. Annas & Michael A Grodin eds., 1992) [hereinafter THE NAZI DOCTORS] (discussing the first principle of the Nuremberg Code).

n4 This observation, of course, will evoke the response that consent under the conditions of incarceration in a concentration camp would unavoidably be coercive; therefore it could never be voluntary and would not be morally valid consent. A full consideration of this claim would require, *inter alia*, a discussion of the meaning of coercion and challenges to the claim that prisoners under a death threat are incapable of making morally valid choices presented by the state. Under existing federal regulations, prisoners are allowed to make choices regarding their involvement as subjects in certain kinds of experimentation. See Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners As Subjects, 45 C.F.R. §§ 46.301-.306 (1997).

n5 Examples include experiments that are so poorly designed as to make it unlikely that any useful information will emerge; nontherapeutic studies involving risks which, in the opinion of the institutional review board (IRB), are excessive; or studies in which the investigator has conflicts of interest that raise concerns about his ability to recruit subjects fairly.

n6 World Med. Ass'n, *Declaration of Helsinki: Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects*, *reprinted in 277 JAMA 925, 925-26 (1997)* [hereinafter *Declaration of Helsinki*] (as amended by the 48th General Assembly, Somerset West, Republic of South Africa, 1996).

n7 See 45 C.F.R. § 46.116 (1997).

n8 *See id.* § 46.116(c) (describing conditions under which an IRB may waive some or all of the elements of informed consent); *see also id.* § 46.117(c) (describing waiver of the requirement that a subject sign a consent form).

n9 *See 21 C.F.R. § 50.23(a)(1) (1997).*

n10 *See 45 C.F.R. §§ 46.116(d)(1), 46.117(c)(2).*

n11 *See 21 C.F.R. § 50.24(a)(3).*

n12 *See id.* § 314.126(b)(2)(i) (describing placebo concurrent controlled trials).

n13 *See 45 C.F.R. § 46.116(d)(1)* (stipulating that the research must present "no more than minimal risk to the subjects").

n14 *See generally* ROBERT J. LEVINE, *ETHICS AND REGULATION OF CLINICAL RESEARCH 202-07* (2d ed. 1986) (critiquing placebo-controlled clinical trials).

n15 *See* Michelle H. Biros et al., *Informed Consent in Emergency Research: Consensus Statement from the Coalition Conference of Acute Resuscitation and Critical Care Researchers*, 273 *JAMA* 1283, 1286 (1995).

n16 *See* Charles Marwick, *Research in Emergency Circumstances*, 273 *JAMA* 687, 687-88 (1995).

n17 Protection of Human Subjects; Informed Consent, 60 *Fed. Reg.* 49,086 (1995) (to be harmonized with 45 C.F.R. pt. 46 and 21 C.F.R. pt. 50) (proposed Sept. 21, 1995).

n18 Protection of Human Subjects; Informed Consent, 61 *Fed. Reg.* 51,498 (1996) (to be codified at 21 C.F.R. pts. 50, 56, 312, 601, 812, 814) (effective Nov. 1, 1996).

n19 Basic Principle number 9 states: "In any research on human beings, . . . the physician should . . . obtain the subject's freely-given informed consent, preferably in writing." *Declaration of Helsinki, supra* note 6, at 926.

n20 *Id.* Paul Ramsey, William Bartholome and others have noted that this so-called "proxy consent" may constitute legally and perhaps ethically sufficient permission to use an incompetent patient as a subject, but is not the moral equivalent of true consent. *See, e.g.,* William G. Bartholome, *A New Understanding of Consent in Pediatric Practice: Consent*,

*Parental Permission, and Child Assent*, 18 PEDIATRIC ANNALS 262, 262 (1989). The primary purpose of true consent is to respect the autonomy of the subject. *See id.*; *see also* Paul Ramsey, *The Enforcement of Morals: Nontherapeutic Research on Children*, HASTINGS CENTER REP., Aug. 1976, at 21, 21 (stating that even though medical codes since the Nuremberg Code have allowed surrogates to give consent for children and other incompetent persons, "no attempt was made to argue that the validity of the proxy consent could be grounded in the subject's presumable consent"). Because the patient is often not participating in this decision, and his willingness to do so is unknown at best, we should not use the term *consent* in such situations.

n21 *Declaration of Helsinki*, *supra* note 6, at 926.

n22 45 C.F.R.  $\beta$  46.116(d) (1997).

n23 *See* 21 C.F.R.  $\beta$  314.126(a), (b)(1)-(2)(i) (1997) (describing characteristics of an "adequate and well-controlled" study, which is the primary basis on which to determine "substantial evidence" of effectiveness for new drugs; characteristics include a clear statement of a study's objectives and intended methods of analysis, as well as use of a placebo concurrent control group, one of five recognized types of controls).

n24 *See generally* Protection of Human Subjects; Informed Consent, 61 Fed. Reg. 51,498, 51,507 (1996) (discussing the definition of the "therapeutic window" relative to obtaining consent and relative to the likelihood of survival after head injury).

n25 The major problem with such an approach is that failure to demonstrate a benefit would leave unanswered the question of whether earlier institution of treatment would have shown a benefit. Animal studies of treatment of brain injury generally showed that earlier institution of treatment had a greater likelihood of showing benefit.

n26 *See id.* at 51,120 (discussing prospective consent).

n27 45 C.F.R.  $\beta$  46.102(i).

n28 *Compare* 45 C.F.R.  $\beta$  46.404 (describing "no greater than minimal risk" research with children), *with id.*  $\beta$  46.406(a) (describing "minor increase over minimal risk" in nontherapeutic research under certain conditions).

n29 Jeffrey Janofsky & Barbara Starfield, *Assessment of Risk in Research on Children*, 98 J. PEDIATRICS 842, 844-45 (1981).

n30 Ernest D. Prentice et al., *Can Children Be Enrolled in a Placebo-Controlled Randomized Clinical Trial of Synthetic Growth Hormone?*, IRB: REV. HUMAN SUBJECTS RES.,

Jan./Feb. 1989, at 6, 6 (reviewing the safety and efficacy of hormone therapy in connection with Turner's syndrome).

n31 See Norman Fost & John Robertson, *Deferring Consent with Incompetent Patients in an Intensive Care Unit*, IRB: REV. HUMAN SUBJECTS RES., Aug./Sept. 1980, at 5, 5.

n32 See *id.*

n33 See *id.*

n34 See *id.* (describing how consent must be obtained within 48 hours).

n35 The term *deferred consent* was appropriately criticized by Tom Beauchamp for reasons which, in retrospect, seem correct. See Tom L. Beauchamp, *The Ambiguities of 'Deferred Consent'*, IRB: REVIEW HUMAN SUBJECTS RES., Aug./Sept. 1980, at 6, 7. It would have been better to acknowledge that *no* consent was obtained for the initial dose and that this should have been called *waived* consent. See *supra* note 8 and accompanying text (describing waiver of informed consent). The waiver could have been justified under the existing regulations, in ways that are explicated more fully by Norman Abramson and others. See Norman S. Abramson et al., *Deferred Consent: A New Approach for Resuscitation Research on Comatose Patients*, 255 JAMA 2466, 2467-70 (1986). The problematic nature of this term emerged again in a Food and Drug Administration (FDA) challenge of a study involving head injury. See Ernest D. Prentice et al., *IRB Review of a Phase II Randomized Clinical Trial Involving Incompetent Patients Suffering from Severe Closed Head Injury*, IRB: REV. HUMAN SUBJECTS RES., Sept. -- Oct. 1993, at 1, 1.

n36 See Abramson et al., *supra* note 35, at 2466.

n37 See *id.* at 2467.

n38 See *id.* at 2468. This position is supported by Charles McCarthy, director of Office of Protection from Research Risks (OPRR), who reported that the Drafting Committee of the Department of Health and Human Services (DHHS) regulations intended for "minimal risk" to be interpreted in this way. See Charles R. McCarthy, *To Be or Not To Be: Waiving Informed Consent in Emergency Research*, 5 KENNEDY INST. ETHICS J. 155, 158 (1995) (stating that "a waiver of informed consent . . . was justified provided that the *increment of risk associated with the subject's participation in a clinical trial was minimal* and that the research offered the prospect of significant benefits to the subjects").

n39 45 C.F.R.  $\beta$  46.111(a)(2) (1997).

n40 See Abramson et al., *supra* note 35, at 2468.

n41 *See id.* at 2468 (distinguishing "'research' on the one hand and 'experimental' or 'innovative' therapy on the other").

n42 One of the ironies of this position is that Abramson was unusual among emergency physicians in his commitment to studying innovative therapies as part of rigorously designed prospective clinical trials. Patients in the author's hands, therefore, were *less* likely to receive thiopental than at some other institutions, because there was a placebo arm in the study. *See id.* at 2466. The other irony is that the physicians in the study could legally have given thiopental to all the patients without having to consider any of the constraints of the research regulations. *See* R.W. Smithells, *Iatrogenic Hazards and Their Effects*, POSTGRADUATE MED. J., 1975 Supp. 2, at 39, 41 ("I need permission to give a new drug to half my patients but not to give it to all of them.").

I will return to this problem -- innovative therapy outside of a research trial. *See infra* notes 98-114 and accompanying text (describing innovative therapy and discussing an example).

n43 *See* Ernest D. Prentice et al., *An Update on the PEG-SOD Study Involving Incompetent Subjects: FDA Permits an Exception to Informed Consent Requirements*, IRB: REV. HUMAN SUBJECTS RES., Jan.-Apr. 1994, at 16, 16 [hereinafter Prentice et al., *Update on the PEG-SOD Study*]; Prentice et al., *supra* note 35, at 1 (describing a Phase II safety and efficacy study of PEG-SOD as a treatment for severe closed head injury).

n44 21 C.F.R.  $\beta$  50.23(a)(1)-(4) (1997).

n45 They did raise other questions, however. First, the requirement that the intervention be aimed at saving the patient's life caused problems for those who were candid enough to realize that death was not always the major concern in patients with severe head injuries. Particularly when relatives were the source of consent, the major concern was not that the patient would die, but that he would survive with severe impairment. *See* Prentice et al., *supra* note 35, at 4 (describing the possibility of post-traumatic vegetative state). The primary purpose of the treatment, therefore, was not to save the life, but to improve the prospects for quality of life. There are some emergencies in which consent is not feasible, life is not in jeopardy and the goal of experimental treatment is to save a limb, an eye or some other important but not vital structure. Second, the reference to a "legal representative" raised questions about whether spouses or adult children, generally not legal guardians, had legal authority to consent for research. State law is often murky on this subject. *See id.* (discussing the availability of a legal representative or next of kin).

n46 There are cases in which a placebo could be life-saving; namely, studies in which therapies that had become standard practice without scientific evidence, come under question. The progression from innovation to standard practice is common, particularly in critical care settings; when careful studies are done, long-established practices have often been shown to

cause more harm than benefit, so that assignment to the placebo arm of a study can be life-saving. See Norman Fost, *Distinguishing Experimentation from Practice*, SEMINARS PERINATOLOGY (forthcoming 1998).

n47 See Carin M. Olson, *The Letter or the Spirit: Consent for Research in CPR*, 271 JAMA 1445, 1445 (1994) (comparing "compassionate use" and "emergency use" and stating how in both, an "article is employed in a life-threatening situation for which no standard treatment is available").

n48 See Marwick, *supra* note 16, at 687 (quoting Ernest Prentice, Associate Dean for Research, University of Nebraska Medical Center), which states:

A literal and strict interpretation of these regulations essentially prohibits the conduct of most emergency research where obtaining consent or a proxy consent is not possible. The IRBs are forced to disapprove such research or use a very flexible interpretation of the regulations. But a convoluted justification strips the regulations of their ethical validity, so it is important that they be revised and re-interpreted.

Prentice wrote a very thoughtful analysis of his own IRB's approval of the much-discussed PEG-SOD study, in which the IRB relied on a flexible interpretation of the regulation. See Prentice et al., *supra* note 35, at 1. Prentice and his colleagues interpreted the "minimal risk" rule to refer to the incremental risk of being in the study, as compared with standard treatment. See *id.* at 2 (describing "minimal differential [incremental] risk"). This approach is similar to the "flexible" interpretation of Abramson and his colleagues. See Abramson et al., *supra* note 35, at 2468 (describing "minimal differential risk"); see also McCarthy, *supra* note 38, at 161 (observing "the research community's confusion about the permissibility of waiving consent in emergency research").

n49 The Stanford University institutional review board was suspended in 1994 by the FDA for various procedural violations, such as lack of written procedures for determining which projects require review more often than annually, and lack of written procedures for ensuring prompt reporting of problems to the FDA. See Food and Drug Admin., Department of Health and Human Servs., FDA Form 483 (FDA inspectional observations made of the Administrative Panel on Human Subjects in Medical Research at Stanford University, May 3, 1994) (on file with author) [hereinafter FDA Form 483]; see also Letter from Paul W. Goebel, Jr., Chief, Institutional Review Board, Center for Drug Evaluation and Research, to Charles H. Kruger, Vice Provost and Dean, Stanford University (Sept. 28, 1994) (on file with author) (lifting the FDA sanction on the Stanford University IRB, empowering it once again to approve studies regulated by the FDA). There were no claims of violations of subjects' rights or harm to subjects. See FDA Form 438, *supra*.

n50 Gary B. Ellis, *Informed Consent -- Legally Effective and Prospectively Obtained*, in OPRR REP. (Office for Protection from Research Risks, National Institutes of Health No. 93-3, Aug. 12, 1993).

n51 See Olson, *supra* note 47, at 1446 (citing written communication from Gary B. Ellis, director of OPRR to institutional officials and IRB chairs (Aug. 12, 1993)). Former OPRR Director Gary B. Ellis acknowledged that such research would be acceptable if it involved "no more than minimal risk," but the interpretation of minimal risk varied widely. See *id.* (citing written communications from Gary B. Ellis (Aug. 12, 1993 and Oct. 21, 1993)). The effect of these warnings was to make at least some IRBs very uneasy about the risk of legal sanctions if they interpreted the rules in the wrong way. See *id.* (noting that "current regulations do not relate to resuscitation research in humans"; "IRBs are confused"; and "the FDA and DHHS regulations are inconsistent").

Charles McCarthy, director of OPRR, questioned OPRR's authority: "OPRR, however, seems determined to uphold a strict interpretation of the HHS regulations that, despite the intent of the Drafting Committee, rules out waivers of informed consent in virtually all cases of emergency research. OPRR has provided little justification for its position . . ." McCarthy, *supra* note 38, at 160.

n52 See Olson, *supra* note 47, at 1446 (citing oral communication with Susan Alpert, M.D., Mar. 29, 1994 and written communication with Robert Temple, M.D., Mar. 31, 1994).

n53 See Keith G. Lurie et al., *Evaluation of Active Compression-Decompression CPR in Victims of Out-of-Hospital Cardiac Arrest*, 271 *JAMA* 1405, 1407 (1994); Olson, *supra* note 47, at 1445 (discussing Lurie's study).

n54 See Lurie et al., *supra* note 53, at 1405.

n55 See *id.* at 1407 (noting that the FDA, in light of no adverse outcomes, granted permission for the study to continue to the end of the second completed crossover period).

n56 See Prentice et al., *Update on the PEG-SOD Study*, *supra* note 43, at 16. The FDA allowed the study to resume provided the protocol was revised in accordance with *ad hoc* guidelines approved by the FDA. See *id.*

n57 See *Problems in Securing Informed Consent of Subjects in Experimental Trials of Unapproved Drugs and Devices: Hearings Before the Subcomm. on Regulation, Business Opportunities, and Technology of the House Committee on Small Business*, 103d Cong. 49 (1994) (testimony of Dr. Norman Fost) (describing three such safeguards: (1) review by focus groups comprised of nonsubject patients and relatives; (2) debriefing of subjects after they have been informed of the initial experimental treatments; and (3) independent review by the NIH or DHHS of study designs before the study begins).

n58 See Marwick, *supra* note 16, at 687.

n59 "By the end of the forum, it had become clear that there was widespread agreement that the existing regulations regarding the conduct of research under emergency circumstances need to be revised and the NIH and FDA rules harmonized." *Id.* at 688.

n60 Protection of Human Subjects; Informed Consent, *60 Fed. Reg.* 49,086 (1995).

n61 Protection of Human Subjects; Informed Consent, *61 Fed. Reg.* 51,498 (1996).

n62 *See 21 C.F.R. § 50.24(a)(1)* (1997).

n63 *See id.*

n64 *See id.* § 50.24(a)(2).

n65 *See id.* § 50.24(a)(4).

n66 *See id.* § 50.24(a)(3)(iii).

n67 *See id.* § 50.24(a)(3).

n68 *See id.* § 50.24(a)(7)(i).

n69 *See id.* § 50.24(a)(7)(ii).

n70 *See id.* § 50.24(a)(7)(iii).

n71 *See id.* § 50.24(a)(7)(iv).

n72 *See id.* § 50.24(d)-(e). Existing rules do not require FDA oversight of studies involving new applications of a previously approved drug or device. *See 21 C.F.R. § 312.2(b)(1)*; *see also* David A. Kessler, *Regulating the Prescribing of Human Drugs for Nonapproved Uses Under the Food, Drug, and Cosmetic Act*, 15 *HARV. J. ON LEGIS.* 693, 707-08 (1978) (describing nonapproved uses of FDA-approved drugs). In industry-sponsored trials, there would generally be an interest in obtaining prospective FDA approval for the research design, because marketing of a drug for the new indication would require FDA approval. *See 21 U.S.C.A. § 355(a), (d)* (West Supp. 1998) (requiring FDA approval before a new drug can be introduced into interstate commerce and setting forth the grounds for refusing an application). Some studies, however, could be funded by hospitals, medical schools, private foundations and others who would not necessarily be interested in or need FDA approval. *See id.* (describing substantial evidence from clinical investigations).

n73 JAY KATZ, *EXPERIMENTATION WITH HUMAN BEINGS* (1972).

n74 See Gina Kolata, *Ban on Medical Experiments Without Consent Is Relaxed*, N.Y. TIMES, Nov. 5, 1996, at A1 (quoting ethicist and attorney Jay Katz while he was at a conference in Nuremberg, marking the 50th anniversary of the Code). "It's a fateful step,' said Jay Katz, lamenting the fact that 'we are making exceptions' to the first principle of the Code." *Id.*; see also Katz, *supra* note 3, at 235 (praising the Nuremberg Code because it "stands alone in its unequivocal declaration of rights, perhaps even inalienable rights, of subjects to consent to participation in research").

n75 "Many [African Americans] will wonder what's different about this latest abrogation of informed consent. Is this yet another opportunity to force African Americans to be guinea pigs for 'white' science? . . . The Tuskegee experiment is the emblem of experimentation without consent. . . ." Annette Dula, *Bearing the Brunt of the New Regulations: Minority Populations*, HASTINGS CENTER REP., Jan.-Feb. 1997, at 11, 12. Annette Dula goes on to describe other atrocities in the history of human experimentation on minorities, *see id.*, none of which would be permissible under the new rule. See generally JAMES H. JONES, *BAD BLOOD: THE TUSKEGEE SYPHILIS EXPERIMENT 2* (1993) (describing the Tuskegee Study, which in no way involved treatment, but was instead "a nontherapeutic experiment, aimed at compiling data on the effects of the spontaneous evolution of syphilis on black males"); Vanessa N. Gamble, *Under the Shadow of Tuskegee: African Americans and Health Care*, 87 AM. J. PUB. HEALTH 1773 (1997) (discussing the legacy of Tuskegee).

n76 In the words of George Annas, ethicist and health lawyer at Boston University:

Most people would not want a doctor to flip a coin when they come into an emergency room. . . . They would want the doctor to do what is best for them. . . .

. . . For most people, research is not an opportunity . . . . The average person wants treatment, not an opportunity to be researched on. . . . The idea that people might be denied new treatments is silly. . . . If we knew it would work, it would be a treatment.

Kolata, *supra* note 74, at A1.

n77 Jack Kevorkian, *At Least My Patients Gave Consent*, L.A. TIMES, Feb. 12, 1997, at B9.

n78 See Burt, *supra* note 2, at 30; Jay Katz, *Informed Consent -- Must It Remain a Fairy Tale?*, 10 J. CONTEMP. HEALTH L. & POL'Y 69, 71 (1994).

n79 See Committee on Bioethics, American Academy of Pediatrics, *Informed Consent, Parental Permission, and Assent in Pediatric Practice*, 95 PEDIATRICS 314, 315 (1995); Bartholome, *supra* note 20, at 262.

n80 See Protection of Human Subjects; Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 44 *Fed. Reg.* 23,192, 23,193 (1979) (stating that subjects with diminished autonomy may "require protection," the extent of which "should depend upon the risk of harm and the likelihood of benefit" to the subject).

n81 See Bartholome, *supra* note 20, at 262-64 (discussing assent, consent and dissent by the child); Committee on Bioethics, *supra* note 79, at 315-16 (same).

n82 See *supra* note 8 and accompanying text (discussing federal regulations regarding waiver of informed consent).

n83 See RUTH R. FADEN & TOM L. BEAUCHAMP, A HISTORY AND THEORY OF INFORMED CONSENT 38-39 (1986).

n84 See generally Katz, *supra* note 78, at 72-81 (describing the physician's role in medical decision-making).

n85 See Robert J. Levine, *International Codes and Guidelines for Research Ethics: A Critical Appraisal*, in THE ETHICS OF RESEARCH INVOLVING HUMAN SUBJECTS: FACING THE 21ST CENTURY 235, 239 (Harold Y. Vanderpool ed., 1996) [hereinafter ETHICS OF RESEARCH].

n86 "Consent . . . is a means to an end. . . . [The goal] is to do what the patient would want." Kolata, *supra* note 74, at A1 (quoting Dr. Norman Fost).

n87 "It seems to me that a reasonable person [with severe head injury] would very much want to be in [an emergency research] study," especially if standard treatment would provide little help. Kolata, *supra* note 74, at A1 (quoting Dr. Norman Fost).

n88 See Katz, *supra* note 78, at 69.

n89 See F.J. Ingelfinger, *Informed (but Uneducated) Consent*, 287 *NEW ENG. J. MED.* 465, 465 (1972) ("The trouble with informed consent is that it is not educated consent.").

n90 See *id.* at 466.

n91 *See id. at 465; see also* JAY KATZ, THE SILENT WORLD OF DOCTOR AND PATIENT 48-84 (1984) (describing the history and evolution of the legal doctrine of informed consent).

n92 *See 45 C.F.R. § 46.116 (1997).*

n93 *See supra* note 20 (discussing how proxy consent, although perhaps ethically sufficient, is nonetheless not equivalent to true consent).

n94 *See 45 C.F.R. § 46.116(d).*

n95 "The doctrine of informed consent, as currently articulated, imposes similar disclosure and consent obligations for therapy and research, with the only difference being that for research the informed consent process is subjected to review by IRBs." Jay Katz, *Human Experimentation and Human Rights*, 38 *ST. LOUIS L.J.* 7, 13-14 (1993).

n96 *See id. at 14* (noting that research is subject to IRB scrutiny).

n97 *See Burt, supra* note 2, at 30; Katz, *supra* note 3, at 227.

n98 *See* Protection of Human Subjects; Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 44 *Fed. Reg.* 23,192, 23,193 (1979) (noting that when a clinician makes a significant departure from standard practice in an often "new, untested or different" way, it does not automatically constitute "research," and is therefore subject to formal protocols setting forth specific objectives and procedures).

n99 *See id. at 4* (defining "innovative therapy" as a type of "nonvalidated practice"). "Therapy" here is intended to encompass innovative diagnostic and monitoring techniques, intended primarily for the benefit of the patient with no intent to advance knowledge for the general welfare. *See, e.g.,* Robert J. Levine, *Informed Consent in Research and Practice: Similarities and Differences*, 143 *ARCHIVES INTERNAL MED.* 1229, 1231 (1982), *cited in* Katz, *supra* note 95, at 25.

n100 *See* Katz, *supra* note 95, at 12 (stating that "every medical intervention, therapeutic or investigative in intent, constitutes an experiment").

n101 Personal communication with Paul Lietman, M.D., Ph.D. (1971).

n102 Much of this discussion is drawn from Fost, *supra* note 46.

n103 *See, e.g.*, Olson, *supra* note 47, at 1447 (observing that the "only honest approach is to recognize that truly informed prospective consent is not possible for some research"); *see also* Biros et al., *supra* note 15, at 1284-85 (discussing regulatory issues applicable to emergency research).

n104 These misadventures include the inappropriate use of exogenous oxygen to minimize hypoxic brain damage, infant mortality due to sulfisoxazole use, excessive administration of Vitamin K, overdosages of chloramphenicol, bicarbonate therapy for the acidemia of "respiratory distress syndrome" and the use of gentamicin for gram negative infections. *See* Gerard B. Odell, *Therapeutic Misadventures in Neonatal Care*, in MODERN PERINATAL MEDICINE 323, 323-31 (Louis Gluck ed., 1974); Fost, *supra* note 46.

n105 *See generally* Charles R. McCarthy, *Challenges to IRBs in the Coming Decades*, in ETHICS OF RESEARCH, *supra* note 85, at 127, 142 (discussing a variety of ethical issues in research and noting that the resolution of which is necessary to preserve the integrity of the research community).

n106 *See supra* notes 68-72 and accompanying text.

n107 *See* Baxter Healthcare Corp., *Hemoglobin Therapies* (May 8, 1998) <[http://www.baxter.com/www/Biotech/hemoglobin\\_ther.html](http://www.baxter.com/www/Biotech/hemoglobin_ther.html)>.

n108 *See id.*

n109 *See id.*

n110 *See id.*

n111 *See id.*

n112 It is important to keep in mind that a difference between the treatment and control groups could be due to factors besides a difference in drug effect, including nonrandom assignment; chance; and other nondrug factors. A European trial with the same drug is still in progress, *see id.*, suggesting that serious toxicity has not been seen in that study.

n113 *See* Henry K. Beecher, *Ethics and Clinical Research*, 274 *NEW ENG. J. MED.* 1354 (1966) (describing unethical medical research).

n114 *See supra* notes 62-72 and accompanying text (describing DHHS and FDA oversight).

n115 *See* Norman S. Abramson & Peter Safar, *Deferred Consent: Use in Clinical Resuscitation Research*, 19 ANNALS EMERGENCY MED. 781, 782 (1990).

n116 *See id.*

n117 *See id.* at 781-82.

n118 *See id.*

n119 *See id.* at 782.

n120 *See id.*

n121 *See id.*

n122 *See id.*

n123 *See id.*

n124 *See id.* at 783.

n125 *See id.*

n126 It cannot be inferred that the results would be the same for all trials. There are many variables, including the results of standard treatment; the expected risks of the experimental treatment; the particular population; the level of trust in the treating institution and physicians; and so on. More empiric work is needed and should be available from the trials conducted under the waiver. The Abramson study only shows that waived consent can be compatible with the informed desires of the great majority of those who would be asked to consent prospectively.

n127 Some have argued, unconvincingly in my view, that placebos are never justified, even with consent. *See* Kenneth J. Rothman & Karin B. Michels, *The Continuing Unethical Use of Placebo Controls*, 331 NEW ENG. J. MED. 394, 397 (1994) (claiming, *inter alia*, that placebo controls almost always violate the *Declaration of Helsinki*). *But see* Harold Varmus & David Satcher, *Ethical Complexities of Conducting Research in Developing Countries*, 337 NEW ENG. J. MED. 1003, 1004 (1997) (stating that the "most compelling reason to use a

placebo-controlled study is that it provides definitive answers to questions about the safety and value of an intervention . . . [which] are the point of the research"). For an analysis of the deficiencies of the *Declaration*, see Levine, *supra* note 85, at 250-53.

n128 See Rothman & Michels, *supra* note 127, at 395 (describing clinical trials in which some patients did not receive the "best proven" treatments).

n129 See *id.* at 397 (discussing recommendations regarding placebo controls).

n130 This discussion assumes a study in which all patients receive standard treatment, and are randomized to receive either an experimental treatment or placebo. The argument changes if standard treatment is withheld.

n131 See Abramson & Safar, *supra* note 115, at 783 (describing generally positive reactions from families' participation in a "deferred consent" study and concluding that "participation . . . was refused only when families thought, because of the patient's *underlying* state of health, that further lifesaving therapy should be withheld" (emphasis added)).

n132 Recall that even concurrent so-called informed consent is commonly only a window into what the patient might want if fully informed. See, e.g., Ingelfinger, *supra* note 89, at 465 (discussing problems with truly informed consent). Present standards for legally valid consent fall far short of confirming that the patient's consent is truly informed and freely chosen. See, e.g., Katz, *supra* note 95, at 24 ("The U.S. federal regulations on informed consent . . . do not go far enough in emphasizing the centrality of the inviolability of the human rights of research subjects, if not as an ethical obligation than surely as a societal obligation in a democracy."); see also Katz, *supra* note 78, at 84 (stating that "informed consent in today's world, is largely a charade which misleads patients into thinking that they are making decisions when indeed they are not").

n133 21 C.F.R.  $\beta$  50.24 (1997).

n134 See *supra* notes 68-70 and accompanying text; see also Protection of Human Subjects; Informed Consent, 61 Fed. Reg. 51,498, 51,513, 51,517 (1996) (discussing community consultation and public disclosure).

n135 See Gamble, *supra* note 75, at 1773.

n136 See *id.*

n137 21 C.F.R.  $\beta$  50.24(b).

n138 See Marcia Angell, *Editorial Responsibility: Protecting Human Rights by Restricting Publication of Unethical Research*, in *THE NAZI DOCTORS*, *supra* note 3, at 276, 276.

n139 See Katz, *supra* note 3, at 227, 228.

n140 See Protection of Human Subjects; Informed Consent, *61 Fed. Reg. at 51,498*; Protection of Human Subjects; Informed Consent, *60 Fed. Reg. 49,086, 49,086 (1995)*.

n141 See Jon F. Merz & Arthur L. Caplan, *Informed Consent for Emergency Research*, *274 JAMA 1196, 1196 (1995)* (discussing advance directives in the context of emergency research).

n142 See *21 C.F.R. § 50.24(a)(2)(iii)* (allowing deferred consent if there is no reasonable way to identify patients prospectively); *id.* *§ 50.24(a)(4)* (allowing deferred consent if there is no practical way to carry out the research without a waiver).

n143 See Prentice et al., *supra* note 35, at 4 (discussing the risk of vegetative state after severe head trauma).

n144 See *id.* (observing that the experimental treatment might "theoretically[] reduce the risk of brain damage and/or mortality").