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Waiver of Informed Consent for Emergency Room Research

INTRODUCTION

Emergency medicine involves the treatment of a highly diverse and critically ill population of patients. A number of physicians consider many standard treatments for emergency conditions to be inadequate. Efforts to assess new treatments in this field are uniquely constrained by the limitations on consent for research participation by seriously incapacitated patients. Treatment of many severe emergency conditions, including myocardial infarction, stroke, head injury and hypothermia, must rely on long-established practices which produce less-than-satisfactory results in many patients. The American College of Emergency Physicians notes that “we have an obligation to ensure that the American public receives the benefit of improvement in acute care medicine. Such improvement can only come about through continued biomedical research into the causes of and treatments for injury and illness.”¹

Research involving human subjects requires obtaining informed consent from patients or their surrogate decision-makers prior to enrollment in any clinical trial. This is designed to safeguard patient autonomy and protect vulnerable populations from assuming undue research risks. Existing federal regulations had allowed an Institutional Review Board (IRB) to approve a waiver of informed consent only when the research involved minimal risk. Investigators, arguing that this limitation unduly hinders scientific advance, petitioned the federal regulatory agencies (*i.e.*, the Food and Drug Administration (FDA) and Department of Health and Human Services (HHS)) to revise their stance. The FDA released proposed rules in the fall of 1995 and final regulations on October 2, 1996.

To date, the American Medical Association has endorsed application only of standard treatment in emergency cases when consent cannot be secured for clinical investigation.² In this report, the Council recognizes the need for improved emergency treatments and acknowledges the considerable safeguards that investigators and regulators can put in place to make emergency research involving human subjects, in the absence of informed consent, safe and effective. Initially, it is important to distinguish between research conducted on emergency patients, and the use of emergency treatment. The latter is permitted in most cases – emergency situations constitute an established exception to informed consent requirements. The former, research involving emergency patients, is the concern of this report.

CURRENT STATE OF EMERGENCY MEDICINE

Emergency care, by its very nature, sometimes involves poor odds for recovery from a serious event. The efficacy of standard therapies often has gone unproven because of the great challenge involved in designing a protocol to assess them. Physicians have become increasingly frustrated with treatment modalities resulting in generally poor outcomes. Some have even adopted innovative treatment methods independently of any opportunity to assess them. In one instance, an IRB was forced to reject a randomized clinical trial comparing high-dose epinephrine with standard-dose epinephrine in cardiac arrest, even though some of the clinicians in the institution were already using the high-dose “test product” on a regular basis.³ Given the public’s high expectations for the medical profession in this context, it is essential that a good means is sought for both assessing present standard treatments and developing new improved ones.

In addition to its urgent nature, emergency care differs from other forms of care in many important ways. The array of conditions encompassed by this field is diverse, including

cardiac arrest, severe head injury, stroke, drug overdose and other catastrophic medical events. Several different practice environments exist, from out-of-hospital emergency response settings, to hospital emergency departments, to inpatient hospital units. In addition, patients receiving this care almost never have an established relationship with the physician providing the care. The often instantaneous response required of emergency physicians places them in the unique position of presuming that all possible treatment should be provided. Traditionally, life-saving treatment in the event of an illness or injury which incapacitates the patient is assumed to be in compliance with patient preferences.

PAST PROFESSIONAL AND REGULATORY REQUIREMENTS

Emergency research involves a small but crucial portion of the clinical research currently being conducted. Consistent with its concern for the individual patient and its objection to enrolling patients in research against their will, the Council on Ethical and Judicial Affairs has stated that: “Where emergency treatment is necessary, the patient is incapable of giving consent, and no one is available who has the authority to act on the patient’s behalf, consent for standard treatment only is assumed.”⁴

Emergency clinicians, researchers and institutional review boards (IRBs) have long called for revision of federal guidelines which failed adequately to recognize the unique situation of emergency research.⁵ Previous guidelines from the FDA and HHS were too incongruous with one another to make research possibilities clear to those reviewing proposed protocols.⁶ FDA guidelines allowed for the emergency use of a test article (*i.e.*, experimental treatment) – waiving both the consent requirement and prospective IRB review (retrospective approval is required) – when 1) the subject is confronted by a life threatening situation, 2) informed consent cannot be obtained, 3) there is no time to obtain surrogate consent, and 4) there is no approved alternative treatment available that provides an equal or greater likelihood of saving the subject’s life.⁷ This does not constitute authorization to conduct a research study, but only permits a single use of an intervention (although in theory there may be multiple “single-uses”). Because these regulations were designed for emergency treatment situations, they were not applicable to most research involving emergency patients. In the latter situation, although the standard treatment may have an equal or greater possibility of saving the subject’s life, the experimental treatment may have the potential to greatly increase the subject’s level of functioning (condition 4). For example, the standard treatment may have a 50% chance of saving the subject’s life, but a 90% chance that the subject will be severely disabled. The experimental treatment may have an equal or lower chance of saving the subject’s life, but offer only a 60% possibility that the subject will be severely disabled. This balancing of risks (greater chance to live with lower functioning vs. less chance to live, but a high level of functioning associated with survival; or extremely low chance of survival vs. unknown chance of survival) is exactly the kind of thing the subject or surrogate is supposed to consider when making a decision about entering the study. In the absence of informed consent, the question raised by this policy is whether researchers can presume consent under certain circumstances. For instance, can researchers apply a “reasonable person standard” in deciding which risks potential subjects would agree to?

Unlike the FDA rules, the HHS policy did not allow any waiver of prospective IRB approval, but did allow a waiver of informed consent requirements when 1) the research involved no more than minimal risk, 2) the rights and welfare of the subjects would not be adversely affected, 3) the research could not be carried out without the waiver, and 4) the subjects would be informed after participation.⁸ This position reflected a balance between the need for advances in scientific knowledge, and protection of individual inviolability. Thus, where minimal risk was involved, the regulations were in effect allowing subjects to be enrolled without informed consent, whether or not a reasonable person would have agreed to participate. Since the risks were small, the need for scientific advance in this context was

thought to outweigh autonomy concerns. In fact, one could argue that most people (or the hypothetical reasonable person) would agree to minimal risk research, and thus that this was just another case of presumed consent. Although the rule seemed straightforward on its face, it was more difficult to apply than first appears. Minimal risk was incurred when “the probability and magnitude of harm or discomfort anticipated in the research [were] 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.”⁹ No additional guidance was given on how to establish which risks are ordinarily encountered in daily life (*e.g.*, the probability and magnitude of the risks associated with driving a motor vehicle are quite high), nor whose life we should consider (*e.g.*, a critically ill patient who may be exposed to a number of high risk treatments on a daily basis, or the average non-ill person). Notwithstanding the lack of explanation regarding “minimal risk”, many researchers and clinicians felt that the severe conditions and treatments represented in emergency medicine were incompatible with this concept. Therefore neither the FDA rules nor the HHS guidelines nor some combination of the two, since they actually appeared to be incompatible with each other, allowed for research with emergency subjects.

Moreover, agency clarification of the rules surrounding waiver of informed consent were somewhat inconsistent. The National Institutes of Health (NIH) and FDA both halted studies due to concerns over the consent process.¹⁰ In contrast, in July 1995, the Secretary of HHS approved a waiver of existing rules for the National Acute Brain Injury Study, funded by the NIH. Although the study involved greater than minimal risk, the secretary recognized that the research was of such importance as to exempt the trial from the usual requirements.¹¹ Also, in 1990, the FDA approved a waiver for military combat circumstances, allowing the use of investigational drugs in circumstances when obtaining informed consent is unfeasible and withholding the treatment would be contrary to the best interests of the military personnel.¹² Additionally, in 1994, the FDA permitted enrollment of incompetent patients in a high risk trial of polyethylene glycol-conjugated superoxide dismutase treatment for severe closed head injury without any explanation for the apparent exception to the waiver rules.¹³ The inadequacy of the past rules not only resulted in inconsistent judgments by the regulatory agencies, but also forced the research establishment to develop creative justifications for granting approval to emergency research protocols.

Unsatisfied with the ambiguous existing guidance, researchers and IRBs began to develop their own paradigms within which they could assess proposed research modalities. Adherence to the principle of deferred consent, where a proxy would authorize continued participation in the protocol subsequent to the patient’s enrollment, prevailed for several years, permitting some research to go forward. More recently, the term “ratification” has been applied to reflect this reasoning more genuinely. In 1993, however, the NIH Office for the Protection of Research Risks (OPRR) discredited this rationale by questioning its legality. In a letter to IRB chairs, OPRR reiterated its policy of prospective informed consent for research participation and referenced the language of the waiver provision as the only exception. It also declared that deferred consent or ratification did not constitute informed consent under the HHS regulations.¹⁴

Other methods of meeting the regulatory informed consent requirements have been proposed. One possibility, advance consent, involves securing permission for research participation in the event of future incapacitation. This proposal may seem unwieldy, but might be supported by widespread completion of advance directives documenting preferences on such research. However, this is likely to be hindered by the fact that only a relatively small percentage of the population complete an advance directive, as well as by the need to indicate with a high degree of specificity the type of research in which one would be willing to participate. Moreover, generic advance directive legislation is designed for use in directing future treatment and thus may not apply to the research context. Alternatively, there may

be research particular to a specific condition for which the patient population in a given geographic area could be targeted for advance consent. This, however, is more likely to work with non-emergency research where it is easier to identify the target population. Another option is to require consent for potential critical research upon hospital admission.¹⁵ This may allow some emergency research to occur (*e.g.*, that which is done in pre-specified inpatient units) but would exclude many emergency patients. Obtaining advance consent from the majority of emergency patients, who by definition are unlikely to have anticipated an emergency event, would require some mechanism for widespread authorization. In theory, integrated health plans could solicit preferences for emergency research participation in the course of enrolling patients. However, given the present difficulties in providing full information on health plans to new enrollees, it may be unlikely that the discerning of research preferences will be given a high priority. Even if it were, the informed consent might be compromised by the circumstances. In general, then, advance consent is an impractical means of surmounting the informed consent difficulties in this context. Proxy consent, although a more accepted means of achieving consent, is also problematic. Proxy consent often cannot be secured within the short time before the research treatment is necessary. Such consent is also not always reliable since there is evidence that relatives may be more cautious about consent to unproven treatment than the actual patient would have been upon presentation of treatment alternatives.¹⁶

NEW REGULATIONS

On October 2, 1996, new regulations were put forth by FDA creating an exception from informed consent requirements when:

- (1) subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and a controlled investigation is necessary;
- (2) obtaining informed consent is not feasible;
- (3) research participation offers the possibility of direct therapeutic benefit to the subjects;
- (4) the investigation could not practicably be carried out without the waiver; and
- (5) additional protections of the rights and welfare of the subjects are provided.¹⁷

An IRB must be assured that each of the conditions is met. Moreover, a licensed physician who is not involved in the investigation must concur with the IRB's approval of the waiver of informed consent. Additional protections must include, at minimum, community consultation prior to IRB approval, public disclosure of intent to begin the study and of results following completion of the study, creation of an independent data monitoring committee to oversee ongoing research, and provision of an opportunity for family members to object to the subject's participation.¹⁸ HHS has issued an assurance that researchers who comply with the FDA regulations will not be in violation of HHS regulations. Moreover, future revisions of the HHS regulations will be congruent with the new guidelines.

ETHICAL ARGUMENTS

The ethical debate surrounding waiver of informed consent for research participation is based upon a concern with protecting patient autonomy. The prospect of enrolling critically ill patients into research protocols without explicit consent certainly raises concerns about exploiting certain vulnerable populations in pursuit of scientific data. Indeed, in every group of individuals enrolled in research without explicit consent, it is likely that some would have wanted only standard treatment. However, many standard treatments in the realm of emergency medicine are inadequate and untested. In this situation, there may be new treatments which, though also unproven, offer the prospect of improved therapy. In such instances, where the comparative efficacy of the standard and experimental treatments is

unknown, it may be appropriate to randomize patients to one treatment or another in a clinical trial.¹⁹

The argument can be made that a reasonable patient presented with less than good outcomes from standard treatment or unknown outcomes from experimental treatment would choose to have the opportunity for the experimental treatment. In fact, it has been argued that depriving these emergency patients of the experimental treatment because of their inability to consent or give timely proxy consent is discriminatory, preventing this vulnerable group from receiving the best available potential treatment. There is also concern that the unproven standard treatments may, in fact, be harmful. The Belmont Report noted that the principle of beneficence supports research that “makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous.”²⁰

For this argument to be valid, it is essential that any experimental treatment undergoing clinical trials is anticipated to be at least on par with the standard treatment. The existence of clinical equipoise is essential to any research, but more vitally in cases involving waived informed consent for participation.²¹ Clinical equipoise has been described as existing “whenever at least a reasonable minority of medical professionals believe the experimental treatment would be as good as, or better than the standard treatment.”²² Establishing that equipoise exists between standard treatment and an experimental treatment can be a challenge. One good example of the tenuous balance of risks and benefits is trials of tissue plasminogen activator (t-PA) for acute ischemic stroke.²³ In perhaps the most comprehensive study conducted thus far, investigators found that patients who received t-PA were at least 30 percent more likely to have minimal or no disability at the end of a three month period than those who received the placebo. However, the value of this impressive benefit was challenged by a high rate of symptomatic intracerebral hemorrhage in cases where t-PA was administered – 6.4 percent of patients compared with 0.6 percent of patients receiving placebo. Earlier studies of t-PA treatment had been stopped prematurely because of an unacceptable rate of hemorrhage. In this instance, substantial benefits over standard treatment were accompanied by increased risk of a high magnitude.

To what risks is it permissible to expose an unknowing subject? As noted previously, the regulations referred to “minimal risk.” The new rules refer to “reasonable risk,” a concept which depends on what is known about the experimental treatment, the alternative treatments, and the medical condition.²⁴ Other commentators, including the Coalition Conference of Acute Resuscitation and Critical Care Researchers (hereinafter “Coalition”), call for the use of a category of so-termed “appropriate incremental risk,” which is defined as “any potential risk associated with participating in the research protocol relative to the natural consequences of the medical condition, or any potential risk associated with receiving the experimental treatment relative to receiving the standard treatment for the medical condition.”²⁵ This balancing of risks and benefits particular to a clinical situation is the crux of the justification for permitting more than minimal-risk research without consent. In essence, the patient’s prognosis must be so unfavorable that the potential harms associated with the investigational agent are not much greater than the possible outcome from either the standard treatment or no treatment (*e.g.*, death or severe disability). Thus if the standard treatment involves high risk, or even if with treatment there is a high risk of death or disability from the medical condition, then a high-risk investigational treatment may be applied.

REQUIREMENTS FOR WAIVER

Patients in emergency situations are among the vulnerable populations requiring special research protections. In order for this population to be eligible for research participation

without consent the Council requires the following: First, the subject must enter into the critical emergent state suddenly and unexpectedly. If the physician could have anticipated the emergent state (because the subject was critically ill) and thus would have had time to obtain advance consent to research but failed to, consent cannot be waived.²⁶ Physicians should make efforts to discuss appropriate research options with patients while they still have decision-making capacity. Second, the experimental treatment must have a realistic possibility of benefit at least equal to or greater than standard care. Only where equipoise exists should individuals be deprived of potentially beneficial treatment, or subjected to potential risk of harm. Third, the subject must lack the capacity to give consent. Fourth, the window of opportunity in which to apply the experimental treatment must be so narrow as to preclude obtaining proxy consent. Fifth, the risk associated with the research should be reasonable in light of what is known about the critical nature of the medical condition and the possible alternative treatment options. Sixth, the proposed treatment must be at a sufficient stage of investigation that it is appropriate for use in human trials. Seventh, the research in question must not have been able to be carried out without the informed consent waiver.

Finally, despite the informed consent waiver, the subjects, or their legally authorized representatives, must be informed of their inclusion in the protocol and consent obtained for continued participation as soon as possible after the intervention. The subject, or the proxy, should be assured that he or she may withdraw from the study without repercussions for care. In an instance where withdrawal from the protocol might endanger the subject, the investigator should take steps to ensure that the subject or proxy is instructed about the potential harms and possible alternative treatments so that the decision to withdraw is fully informed. In addition, when a subject dies in the course of the traumatic event, whether or not the death is thought to be related to the research, surviving relatives must be informed that the patient had been enrolled in a research protocol. Previous studies have shown that individuals and their families generally are grateful for having been included in emergency research. It is important to make this disclosure, regardless of the outcome of the particular treatment, since trust in the profession could be undermined by later discovery of participation.

INSTITUTIONAL SAFEGUARDS

It is the responsibility of the investigator to ensure that all ethical requirements are met. Although not all research is covered by the federal regulations that require IRB oversight, the Council strongly recommends that all investigators and institutions develop similar committees to review and approve investigational protocols. In addition, where informed consent requirements will be waived, there should be community input prior to the initiation of the trial. Sources for input might include local public officials and community groups, in addition to members of identifiable populations most likely to be eligible for the research.

An independent data monitoring board should be created to assess the ongoing research. This body would track preliminary study data evaluating whether the risks involved are greater than anticipated, or whether the resulting benefits do not justify the risks.²⁷ Discrepancies from initial estimates of risks or benefits may result in modification of protocol design or termination of the trial.

CONCLUSION

The general public has high expectations regarding the quality of care to be provided in an emergency medical event. The Coalition Conference of Acute Resuscitation and Critical Care Researchers states: “Patients deserve and expect modern, safe, and effective medical care when they are acutely ill or injured. We believe the public desires advances in acute emergency and critical care and understands that research is required to improve medical

care.”²⁸ The current state of emergency medicine and research has resulted in the application of standard treatments that often have not been scientifically evaluated for safety and effectiveness and may render unsatisfactory outcomes. Given the insufficiency of standard treatment alternatives it is appropriate, with certain safeguards, to provide experimental treatments without obtaining the informed consent of the subject. However, in order to protect the rights and welfare of the subjects several conditions must be met.

RECOMMENDATIONS

The Council makes the following recommendations with respect to waivers of informed consent for emergency research:

- 1) The proposed research may be conducted only in emergency, life-threatening situations, and only when the experimental treatment is ready for trials involving human subjects.
- 2) The subject must lack the capacity to give informed consent for participation in the research.
- 3) The window of opportunity for intervention must be so narrow as to make obtaining surrogate consent unfeasible.
- 4) Obtaining prospective informed consent for the protocol must not be feasible (*i.e.*, the life-threatening emergency situation could not have been anticipated).
- 5) The experimental treatment must have a realistic possibility of benefit equal to or greater than standard care.
- 6) The risks associated with the research should be reasonable in light of the critical nature of the condition and the risks associated with standard treatment.
- 7) Where informed consent is waived, subjects or their representative must be informed as soon as possible about inclusion in the study and asked to consent to further participation. Subjects, or their representatives, may choose to discontinue participation at any time after being fully informed about the possible consequences. Additionally, if a patient dies while participating in the research protocol, the patient’s family or representatives must be informed that the patient was being treated with an experimental protocol.
- 8) Community input should be sought prior to approval of the protocol, and public disclosure should be made of study results. Fair randomization of research subjects should be given thorough consideration. An independent data monitoring board should be established to oversee the ongoing trial.

REFERENCES

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2. American Medical Association, *Code of Medical Ethics*, Opinion 2.07.
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5. Statement of the American College of Emergency Physicians, FDA/NIH Public Forum; Biros, MH, et al., "Informed Consent in Emergency Research: Consensus statement from the coalition conference of acute resuscitation and critical care researchers," *JAMA* 273(16): 1283- 1287 (1995).
6. Levine RJ: "Editorial: Research in Emergency Situations; The Role of Deferred Consent," *JAMA* 273:1300-1302, 1995.
7. The regulations described in this section are still in effect. The new regulations were simply added on to the old ones. However, emergency research is now presumably covered by the new sections, rather than the original guidelines described here.
8. 21 C.F.R. § 50.23(a).
9. 45 C.F.R. § 46.116(d).
10. 45 C.F.R. § 46.102(I).
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17. See, e.g., Warren JW et al., "Informed Consent By Proxy," *New Eng. J. Med.* 315(18):1124-1128 (1986).
18. 61 Fed. Reg. 51498, 51528 (October 2, 1996 to be codified at 21 C.F.R. § 50.24).
19. 21 C.F.R. § 50.24(a)(7)(i)-(v) (1996).
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21. 44 Fed. Reg. 23192 at 23194.

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25. 60 Fed. Reg. 49086 at 49092.
26. Biros, MH et al., “Informed Consent in Emergency Research: Consensus statement from the coalition conference of acute resuscitation and critical care researchers,” *JAMA* 273(16): 1283- 1287 (1995).
27. Of course, the federal regulations have an exception allowing for a single use of a test article for treatment purposes in the absence of consent when the subject meets certain specific requirements. See footnote 7 and accompanying text.
28. 60 Fed. Reg. 49086 at 49096.
29. Biros, MH et al., “Informed Consent in Emergency Research: Consensus statement from the coalition conference of acute resuscitation and critical care researchers,” *JAMA* 273(16): 1283- 1287, 1286 (1995).