Research Conditions That Qualify for Emergency Exception from Informed Consent

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Abstract

Medical research involving critically ill and injured subjects unable to provide informed consent can only be conducted under federal regulations that attempt to balance the need to develop lifesaving treatments with protection of research subjects' rights. Regulators, researchers, and medical ethicists have all struggled to define the conditions under which an emergency exception from informed consent is appropriate. Although research has been successfully conducted under the current regulations, confusion remains regarding the meaning of the regulations, the applicable conditions, and the best ways to balance the needs of future patients and the rights of research subjects. In May 2005, at the *Academic Emergency Medicine* Consensus Conference ''Ethical Conduct of Resuscitation Research,'' a breakout session was held on the research conditions that qualify for the emergency exception from informed consent process. Several recommendations emerged: 1) The definition of ''life-threatening condition'' should be broadly interpreted to include serious disability as well as death. 2) Existing therapies should be considered ''unsatisfactory,'' even if partially effective, when serious risk of morbidity or mortality remains even with the best available treatment or when the adverse effects of the best available treatment are serious. 3) Research with the emergency exception should be performed only if sufficient evidence exists that the proposed intervention has a reasonable chance of benefit. 4) More evaluation is needed to determine the degree to which the current rules impede research. 5) Application of the current regulatory framework for abbreviated or waived consent in emergency research should be encouraged. 6) Further study should also address variability among institutional review boards, the goals of community involvement, and how best to engage and educate the public in research efforts using emergency exception from informed consent. **Key words:** exception; waiver; informed; consent; research; ethics. ACADEMIC EMERGENCY MEDICINE 2005; 12:1040–1044.

The development of lifesaving therapies for patients with critical medical emergencies sometimes requires clinical research in which subjects are not able to provide informed consent.[1] One reason that informed consent may not be possible is that the subject has an emergency medical condition for which effective treatment has to be initiated before the patient or a proxy can be educated about the proposed research and provide informed consent. Regulators developed the emergency exception from informed consent process because the benefit of the research to subjects and future patients with critical illness and injury must be carefully balanced with the protection of the rights of research subjects who did not volunteer to participate.[2] A fundamental difficulty in performing this research is determining and defining appropriate conditions for research with emergency exception from informed consent. Further difficulties involve understanding and implementing the methods used in lieu of informed consent to protect the rights of research subjects.

DIFFICULTIES IN DEFINING APPROPRIATE CONDITIONS FOR EMERGENCY EXCEPTION

United States federal regulations provide the rules that investigators and institutional review boards (IRBs) must use to decide whether a proposed study using emergency exception from informed consent can be performed.[3] Despite guidance in the preamble of the regulations and in a subsequent advisory statement, application of these guidelines is still limited by confusion regarding some of the described conditions for such research. These include the requirements that the illness or injury be ''emergent'' and ''life-threatening'' and that existing therapy be ''unsatisfactory.''

Determining the existence of a medical ''emergency'' in the emergency exception from informed consent process is one of the ethical challenges in this type of clinical research. Some problems are straightforward and clearly constitute an emergency. For

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example, a victim in cardiac arrest needs intervention within minutes, without time to obtain informed consent from a proxy if the treatment has any chance of being effective. Other medical conditions fall along a spectrum of urgency, the limits of which are unclear.

Current federal regulations provide broad guidelines that IRBs can use to help decide whether the research condition being studied justifies using the emergency exception from informed consent process. One of the criteria for applying the emergency exception regulations is ''The human subjects are in a life-threatening situation.''

The existing regulations do not intend the term ''life-threatening'' to mean immediately life-threatening. The preamble to the regulations, published in the *Federal Register* in 1996, states:

> The criteria contained in the rule do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before consent from a legally authorized representative is feasible. Life-threatening includes diseases or conditions where the likelihood of death is high unless the course of the disease or condition is interrupted. [See §312.81.] People with the conditions cited in the examples provided in the comments—e.g., long-term or permanent coma, stroke and head injury—may survive for long periods but the likelihood of survival is not known during the therapeutic window of treatment. People with these conditions are clearly at increased risk of death due to infection, pulmonary embolism, progression of disease, etc. The rule would apply in such situations if the intervention must be given before consent is feasible in order to be successful.[3]

As noted in this statement, disorders such as severe head injury, stroke, and major injury create a high risk for death unless the expected clinical course is altered. This explanation demonstrates an understanding by regulators that an overly restrictive interpretation of ''life-threatening'' would prevent important research activity. Although the term ''life-threatening'' is not to be interpreted narrowly, the definition of the phrase remains unclear.

The list of disorders that are life-threatening is fairly lengthy, but the list of combinations of conditions that are life-threatening while also clearly altering the subject's ability to provide informed consent is not as extensive. For example, in a patient with a major injury to the chest without coexisting brain injury, the combination of significant pain and a narrow therapeutic window limits the potential subject's ability to ponder the risks and benefits of participation in a research study.

UNDERSTANDING METHODS TO PROTECT RESEARCH SUBJECTS

The regulations for conducting clinical research with emergency exception use some novel methods in lieu of informed consent to protect the rights of potential subjects. Use of these methods, most notably the requirements for community consultation as a patient safeguard, is not within the experience of most IRBs. The rules were written in part with a goal to allow flexibility by IRBs to meet local preferences. The combination of flexible rules and scarcity of prior local experience makes consistent implementation of these regulations difficult. Variable levels of comfort among IRBs may create problems implementing emergency research beyond those indicative of the local community's willingness to participate in emergency research. Similarly, the IRBs likely have significant variation in interpretation of a clinical condition justifying the use of the emergency exception from informed consent process. Variable implementation creates a moving target for investigators that may unnecessarily impede valuable research, and it raises ethical questions of equity.

Federal regulations require community consultation and public notification about proposed research to be conducted with emergency exception from informed consent, but the usefulness of this requirement is unclear.[4] Several benefits of community involvement are possible. The openness of community involvement itself prevents researchers from even proposing studies they believe would be unacceptable to the public. Feedback from the community regarding their views of the proposal, relevant values in the community, and issues of trust may inform the investigators or the IRB on conduct of the study. Finally, the most ambitious goal of public notification would be to try to achieve sufficient educational penetration that any would-be subject is likely to know about the study before becoming an eligible subject. Poor understanding of these different possible roles of community involvement in the emergency exception from informed consent process makes it hard for investigators to design, and for IRBs to evaluate, the community feedback.

CONSENSUS PROCESS

In May 2005, the journal *Academic Emergency Medicine* convened a consensus panel on the research conditions that merit use of the emergency exception from informed consent process. The participants included bioethicists, administrators, lawyers, physicians, and researchers. Participants came from federal regulatory agencies, academic and community-based clinical research groups, and IRBs.

In this consensus process, broad areas of concern were introduced in a plenary session. Focus issues were then discussed in breakout groups that prepared consensus statements, which were then discussed again and revised in plenary session. Final drafts of recommendations were disseminated and commented upon through electronic messaging.

The purpose of the meeting was to determine consensus and make recommendations regarding the interpretation and application of current regulations, and to describe future efforts to improve the conduct of emergency research and the protection of subjects unable to consent.

CONSENSUS RECOMMENDATIONS

1. Institutional review boards should interpret the definition of "life-threatening situation" broadly so that research using an exception from informed consent process is available for research involving any anatomic or physiologic derangement that could result in loss of life or serious disability.

Interpreting the current regulations broadly to include the risk of serious disability as a life-threatening situation in the context of emergency exception from informed consent is appropriate for at least two reasons. First, serious disability is itself often directly life-threatening because it places the patient at risk for dangerous complications, such as infection or venous thromboembolism, which frequently shorten the patient's life. Second, serious disability is conceptually as profoundly threatening to the quality and nature of life as is the threat of death. When an experimental intervention needs to be applied quickly to effectively prevent loss of life or serious disability, then the research may qualify for the emergency exception from informed consent process, so long as all other conditions for using the emergency exception from informed consent process also apply.

The panel rejected a quantitative threshold value for defining ''life-threatening,'' noting a wide range of interpretation. For example, panel members agreed that a risk of death of less than 1 in 10,000 within 30 days would probably not be ''life-threatening,'' but a risk of death of more than 1 in 20 within 30 days would. The consensus view was that a qualitative threshold be used for each project, akin to the balancing of relative risks and benefits already performed by investigators and IRBs for individual projects on a case-by-case basis.

2. Existing therapies should be considered "unsatisfactory," even if partially effective, when serious risk of morbidity or mortality remains, even with the best available treatment or when the adverse effects of the best available treatment are serious. Emergency exception from informed consent should not be used to test experimental treatments that are expected to be no better than existing therapies.

The current federal regulations allow use of emergency exception from informed consent only when existing treatment for the condition to be studied is ''unsatisfactory.'' This is, appropriately, a higher standard than that required for other forms of clinical research. When there are no proven treatments for a condition, it is clear that existing therapy is unsatisfactory. Existing therapy may also be unsatisfactory, however, if it is known to be better than placebo but still results in high morbidity and mortality, or has a high rate of serious adverse effects. It is not appropriate to conduct research with emergency exception from informed consent to prove that an experimental therapy is just as good as existing therapy. The research must have the prospect of benefiting patients and society.

The panel considered the example of a study currently enrolling patients using the emergency exception from informed consent process that compares out-of-hospital administration of a hemoglobin-based oxygen-carrying solution with saline for the treatment of severe hemorrhagic shock.[5] Given the lack of oxygen-carrying capacity in saline and the lack of any other out-of-hospital treatment for hemorrhagic shock, the existing out-of-hospital treatments are clearly unsatisfactory.

Once the patient arrives at the hospital, the situation is a bit different. The study protocol requires that patients who were initially randomized to receive the investigational product continue to receive the investigational product until 6 units of the product have been given or 12 hours have passed. Patients randomly assigned to the normal saline control arm are to receive blood as soon as possible after hospital arrival. Most trauma centers have units of uncrossmatched packed red blood cells immediately available to accomplish that goal. Since victims of hemorrhagic shock have high morbidity and mortality even with the best existing therapy, and since blood transfusion can have dangerous adverse effects, this study design is appropriate if continuing the investigational product is hypothesized to be better than switching to blood after arrival at a trauma center. If the investigational product is, at best, only as good as blood, then the study should not, under an emergency exception, continue to expose patients to the investigational product instead of blood after blood is available.

As noted earlier, existing therapies may be unsatisfactory even if effective if they are associated with significant adverse effects or toxicity. The panel also considered the possibility that therapies may be unsatisfactory if they have substantial disadvantages such as prohibitive cost or limited availability.

Institutional review boards may wish to consult community representatives in some cases to determine whether the existing treatments are ''unsatisfactory'' to that community. The community consultation process can provide IRBs with input, helping weigh the severity of the ''life-threatening'' condition, the potential risks of the proposed treatment, and the loss of autonomy. Community representatives could be educated about the proposed study, including, if any, the currently available yet ''unsatisfactory'' treatments. The community representatives can be asked

to provide a judgment on whether the proposed research justifies using the emergency exception from informed consent process. Determining appropriate community representatives, however, represents a challenge in itself.

3. Available evidence about the proposed intervention should support a reasonable chance of delivering a direct benefit to the subject.

In addition to making a judgment about whether existing treatments are unsatisfactory, investigators and IRBs need to have sufficient evidence from laboratory, animal, or human studies that the proposed intervention has a reasonable chance to directly benefit the subject. The potential direct benefit can include increasing the likelihood of survival or reducing the risk of adverse effects.

4. Additional research is needed to determine whether the current rules create undue barriers to performing important resuscitation research.

The goal of federal regulations is to protect the rights of subjects enrolled without informed consent, while allowing important research to proceed. The regulations create both explicit and implicit barriers to conducting research with the emergency exception process. Limited use of emergency exception is acceptable and likely desirable, but regulatory barriers should not prevent the conduct of appropriate and valuable research. The panel encourages further research addressing barriers, the degree to which they protect patients, and the degree to which they impede research. Investigations might explore whether impediments result from the rules themselves, from variable implementation in local IRBs, from the disinclination of investigators, or from community feedback.

5. We encourage the appropriate, but expanded, use of the current regulatory framework for abbreviated or waived consent (rather than emergency exception) for minimal-risk studies in emergency conditions, with the understanding that randomization alone does not imply that a study is greater than minimal risk. We encourage federal regulators to provide definitive guidance to IRBs on this issue.

Distinct from the emergency exception from informed consent, federal regulations allow for waiver of consent or abbreviated consent in studies in which there is both minimal risk to subjects and no practicable way to obtain consent. This mechanism may be underutilized in certain forms of emergency research. Despite the high risk of morbidity and mortality in critically ill and injured patients, for example, nontherapeutic studies involving the recording of physical data or the analysis of surplus blood have minimal incremental risk to a patient unable to provide consent.

Abbreviated consent processes may be appropriate in emergency research when subjects' capacity to provide informed consent is limited but not absent. In such cases, subjects are initially given a simplified explanation of the study during the acute phase of their presentation, and offered enrollment. Those providing this abbreviated consent are enrolled and provided detailed information later when their decisional capacity has improved, continuing in the study only if they confirm their consent.

Finally, waiver of informed consent may be applicable in clinical trials of medical emergencies in which subjects cannot provide consent, but in which two distinct but accepted standard therapies are being compared. In such trials there is no experimental therapy, and all subjects receive standard care consistent with that provided to patients not enrolled in a trial, so that there is minimal incremental risk to being randomized to either group. Anecdotally, there is concern that most IRBs regard randomized research as inherently beyond the criterion of minimal risk. The panel believes that randomization itself does not create risk, and waiver of informed consent is an appropriate mechanism for emergency research when incremental risks of participation are minimal or absent and consent is not possible. Appropriate use of these alternative mechanisms will prevent unnecessary and inappropriate use of emergency exception from informed consent in trials with insignificant risk or in which some form of consent is possible.

We recommend that federal regulators provide more detailed guidance on acceptable criteria for waived or abbreviated consent in emergency conditions. Expanding appropriate use of these mechanisms depends on regulators' communicating directly with IRBs to address this issue and correct any misperceptions.

6. Further study should also address variability among IRBs, the goals of community involvement, and how best to engage and educate the public in research efforts using emergency exception from informed consent.

Variable or erratic IRB interpretation, implementation, and enforcement of regulations on research performed using emergency exception from informed consent are problematic. In multicenter studies, variable IRB behavior creates inequitable distributions of risk among communities. Variable implementation also suggests inconsistent understanding that may be remedied with improved regulatory guidance. Further study of variability may address these concerns and correct misconceptions held in the IRB community.

Community notification, a safeguard introduced in lieu of informed consent, is a likely element in variable interpretation of the emergency exception regulations. Studies of different models of community involvement, and of the different goals inherent in those models, should seek to determine those most effective at protecting the rights of research subjects. Because community involvement processes can be costly, lengthy,

yet limited in their reach, they must be studied to determine the most efficient methods of meeting the goals and requirements of this regulation.[6]

CONCLUSIONS

Research using human subjects without prospective informed consent is ethically challenging. Regulators, investigators, subjects, and other patients all benefit from a process that allows both development of life-saving treatments for medical emergencies and protection of the rights of research subjects when informed consent is not possible. Current federal guidelines have created such a process, and, not surprisingly, the process is complex. This consensus panel of investigators, regulators, and experts in medical ethics examined sources of confusion in the process and made recommendations and suggestions that are intended to improve the ability both to perform appropriate research and to protect subjects more effectively. We expect this work, and the ongoing cooperation of communities, researchers, and regulators, to promote more effective and ethical research in the future.

Breakout group participants: O. Hugli, Joseph Procaccino, Neal Dickert, Tasmeen Singh, Colleen Davis, Margaret Hsieh, Robert Niskanen, Fred Harchelroad, Tammie Quest, Jill Baren, Steven Birnbaum, James F. Holmes, and Lynne D. Richardson.

References

1. McRae AD, Weijer C. Lessons from everyday lives: a moral justification for acute care research. Crit Care Med. 2002; 30: 1146–51.
2. Biros MH. Research without consent: current status. Ann Emerg Med. 2003; 452:550–64.
3. Department of Health and Human Services. Protection of human subjects: informed consent and waiver of consent requirements in certain emergency research: final rules. (codified at 21 CFR §50, et al., 45 CFR §46). Fed Reg. 1996; 61(192):51500–33.
4. Shah AN, Sugarman J. Protecting research subjects under the waiver of informed consent for emergency research: experiences with efforts to inform the community. Ann Emerg Med. 2003; 41:72–8.
5. Northfield Laboratories, Evanston, IL. PolyHeme® pivotal phase III trial. Available at: http://www.northfieldlabs.com/amb_trial_des.html. Accessed Jun 28, 2005.
6. McClure KB, DeIorio ND, Gunnels MD, Ochsner M, Biros MH, Schmidt TA. Waiver of consent in research: community consultation and notification [abstract]. Acad Emerg Med. 2002; 9: 440–1.