Clinical research studies conducted in emergency settings under the waiver of consent provision outlined in federal regulations are uncommon, yet the importance of such research that may result in potentially lifesaving interventions is indisputable. Surgeons, as well as health care professionals in other disciplines of medicine, should be aware of the multiple challenges facing them if they contemplate conducting a research trial without the prospective informed consent of enrolled subjects. The challenges associated with conducting research studies using the exception from informed consent requirements for emergency research are numerous, beginning with ensuring an appropriate study design, understanding state and federal regulations that govern such emergency research studies, and continuing through a complicated and sometimes arduous institutional review board (IRB) process that is unique to these studies. This article will describe the challenges encountered when implementing the exception from informed consent requirements for emergency research and will provide surgeon researchers with an understanding of the ethical controversies surrounding such studies.

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The need for ensuring the protection of human subjects is a fundamental principle of human research, with its theoretical basis established by several key events following World War II. The atrocities of the Nazis during that war led, in 1947, to the Nuremberg Code, which outlined 10 principles of ethical research in humans (Figure 1). The Kefauver-Harris Act of 1962 amended the 1938 Food, Drug, and Cosmetic Act to include tighter federal regulations on the US drug industry. The birth defects induced by the antinausea and sedative drug thalidomide raised awareness of the inadequate preclinical and clinical testing of this drug prior to its widespread use, prompting the passage of this law requiring pharmaceutical companies to demonstrate safety and efficacy of a drug prior to marketing it. The Helsinki Declaration of 1964, and its subsequent revisions, set forth international ethical guidelines for biomedical research. Included in the Helsinki Declaration are statements that (1) research should be based on prior laboratory and animal studies; (2) research should be conducted by scientifically qualified persons; (3) research should be preceded by a careful risk-benefit analysis; (4) research should be conducted with the consent of the subject, legal guardian, or responsible family member; and (5) the specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. Consent to remain in a research study should be obtained as soon as possible from the individual or a legally authorized representative. The Belmont Report of 1978 identified 3 overarching ethical principles to guide medical research: (1) respect for

See Invited Critique at end of article

Author Affiliations: Division of General Surgery, Department of Surgery (Dr Vaslef), Division of Emergency Medicine (Dr Cairns), and the Institutional Review Board (Dr Falletta), Duke University Medical Center, Durham, NC.
The voluntary consent of human subjects is absolutely essential.

The experiment should be scientifically necessary and for the good of society.

The experiment should be so well designed and based on animal studies and knowledge of the natural history of the disease under study that the anticipated results will justify the research.

The experiment should be conducted so as to avoid unnecessary physical and mental suffering and injury.

The experimentation should not lead to death or disabling injury.

The risk of research participation should not exceed the humanitarian importance of the experiment.

Proper preparations should be made and adequate facilities provided to protect the research subject against even remote possibilities of injury, disability, or death.

Only scientifically qualified persons should be permitted to conduct medical experimentation.

Human subjects must be free to withdraw from the experiment at any time.

The investigator should terminate the experiment if continuation is likely to result in injury, disability, or death to the subject.

Figure 1. Basic principles of medical experimentation outlined in the Nuremberg Code (paraphrase of main points).

- Human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence is necessary to determine the safety and effectiveness of a particular intervention.

- Obtaining informed consent is not feasible because:
  - Research subjects will be unable to give their informed consent as a result of their medical condition
  - The research intervention must be administered before the consent of the subject’s legally authorized representative is feasible, and
  - There is no reasonable way to identify prospectively the individuals likely to become eligible to receive the research intervention.

- The research study offers the prospect of direct benefit to the research subject.

- The research study could not be practically carried out without the waiver.

- Attempts to contact the research subject’s legally authorized representative within a defined therapeutic window of time must be made.

- The IRB has reviewed and approved informed consent procedures and the consent document in accordance with federal regulations and has approved the plan for providing the opportunity for a family member to object to the subject’s participation.

- Additional protection of research subjects includes community consultation prior to initiation of the study, public disclosure of the plans for the research and its risks and benefits, public disclosure of the study results and demographic characteristics of the study population, and establishment of an independent data monitoring committee.

Figure 2. Conditions to be met under Part 50.24 of Title 21 of the Code of Federal Regulations (21 CFR 50.24) for waiver of consent emergency research studies. IRB indicates institutional review board.

- There are basically 4 events that must occur in sequence under the exception from informed consent requirements.

- A number of conditions must be met for the research activity to be conducted under 21 CFR 50.24 (Figure 2) or the DHHS waiver, and the IRB must review and approve the research protocol and ensure that all of the conditions outlined in Figure 2 are met.

Multiple challenges to both the investigator and the IRB are associated with conducting a research study under the exception from informed consent requirements. There are basically 4 events that must occur in sequential order prior to initiating accrual to a research study that falls under the exception from informed consent requirements: (1) design of the study; (2) preliminary IRB review; (3) community consultation; and (4) final IRB review and approval.

Persons, who are entitled to autonomy and the right to give their informed consent prior to research participation; (2) beneficence, an obligation to maximize the benefits, and minimize the risks, of research participation; and (3) justice, which implies equal access to the potential beneficial effects of the research.

Pertinent US regulations relating to the protection of human subjects in biomedical research have evolved along separate but parallel paths, depending on the federal agency providing the oversight for the research. Thus, Part 46 of Title 45 of the Code of Federal Regulations, hereafter referred to as 45 CFR 46, stipulates the US Department of Health and Human Services (DHHS) requirements for obtaining and documenting informed consent and outlines the procedures to be followed by IRBs as they conduct initial and continuing review of the research. In 1991, 16 federal agencies adopted the provisions found in 45 CFR 46, Subpart A, and this regulation has since become known as the “Common Rule.” The Food and Drug Administration (FDA) has similar regulations codified in 21 CFR 50 and 56.

In 1996, the FDA regulations were revised to include 21 CFR 50.24, which allows for an exception from informed consent requirements for a very limited class of research in emergency settings. This has become known as the “Final Rule.” In parallel, DHHS approved a waiver of the applicability of the 45 CFR 46 requirements of obtaining and documenting informed consent. Detailed accounts of the events leading up to the development of these federal regulations have been described by Biros’ and Birchler.

Some bioethicists had concerns about various provisions of the exception from informed consent requirements. These concerns included a potential blurring of the lines between research and therapy and the possibility that participants in emergency research studies, especially those involving major trauma centers, would include disproportional numbers of inner-city residents who might be unwilling or unable to participate in community research discussions.

As a consequence of the 1996 federal regulations, the added expense, burden, and difficulty encountered by investigators to comply with the newly required procedures resulted in a decrease in acute resuscitation research in the United States and a shift of such research overseas, particularly to Europe. Interestingly, a recent European Union directive on the conduct of clinical trials may halt European research on individuals who are unable to provide prospective informed consent. The directive contains no provisions for exceptions or waiver of informed consent and may hinder acute resuscitation research in Europe to an even greater degree than the 1996 regulations have in the United States. Thus, the US federal regulations of 1996 and the 2001 European Union directive combined have resulted in an extremely limited number of emergency research studies that have been completed or are ongoing under an exception from informed consent.
DESIGN OF THE STUDY

The design of the research study must conform to the requirements listed in Figure 2. The study must only enroll people who are in a life-threatening situation, although federal guidance associated with this requirement states that the subjects do not necessarily have to be in an “immediately life-threatening” situation. For example, a patient who nearly drowned who is now comatose may not be any longer in an immediately life-threatening situation, but he or she may be a potential research subject under the exception from informed consent requirements if the proposed intervention may provide some benefit to that person and all other requirements are met. In addition, for the intervention to offer potential benefit, it must begin before consent can be obtained from the person’s legally authorized representative or family member.

Another required condition is that available treatments are unproven or unsatisfactory. While the definitions of unproven or unsatisfactory are not provided in 21 CFR 50.24, the IRB must make this determination guided by the requirement that “clinical equipoise” must exist. That is, “at least a reasonable minority of medical professionals believes the experimental treatment would be as good as, or better than, the standard treatment.” Most studies that fall under the waiver of consent rule will likely have the experimental intervention added to standard therapy. However, those studies in which the experimental intervention is initiated in lieu of standard therapy may be permissible, but they warrant closer scrutiny by the IRB to determine that clinical equipoise exists.

The experimental intervention must also be shown to offer the prospect of direct benefit to the subjects. The experimental intervention must be promising, although it does not have to be proven to be effective. A research study to compare a new intervention vs standard therapy, designed to demonstrate noninferiority of the intervention rather than its superiority, may not meet this requirement. The prospect that an intervention will provide direct benefit to the subjects should be determined by a review of animal and other preclinical studies and, where feasible, human studies using the intervention in nonemergency settings. The risks and benefits of the intervention, as well as those of standard therapy, must be assessed in the process of determining the potential for direct benefit. Furthermore, while societal benefit from the results of the research is desirable, this so-called aspirational benefit should be distinguished from the potential direct benefit to the research subjects. Aspirational benefit alone does not justify the use of the exception from informed consent requirements for emergency research.

Finally, the study design should be such that the individuals likely to become eligible for participation in the trial cannot be identified prospectively in a “reasonable” way. The IRB is given some flexibility in its interpretation of what constitutes reasonable. It is likely that an IRB’s judgment in this regard will vary from one research study to another depending, for example, on how promptly the intervention must be initiated and whether eligible research subjects would be on hand and readily available to give their consent to research participation prior to the need for the research intervention. An assessment must be made based on the population from which the subjects will be drawn, the probability that any individual within that population at risk will become a potential subject, and whether it is feasible to obtain prospective consent from those individuals at risk.

PRELIMINARY IRB REVIEW

The IRB must review the proposed protocol and determine, point by point, if it meets the requirements of 21 CFR 50.24 or comparable DHHS requirements. As described earlier, the IRB must find and document that the proposed intervention must be administered because of a subject’s life-threatening situation but prior to obtaining consent of the subject, the subject’s legally authorized representative, or the subject’s family member. The IRB must also ensure that clinical equipoise exists, available treatments are unproven or unsatisfactory, there is potential direct benefit to the research subjects, and there is no reasonable way to prospectively identify the individuals likely to become subjects in the clinical investigation.

The IRB must also determine that the clinical investigation could not “practically” be carried out without the waiver of consent. If the IRB finds, for example, that the study could be conducted without biasing the science using consenting subjects, then the IRB must not approve the exception from informed consent requirements for emergency research. If the research, on the other hand, would be inappropriately delayed by restricting it to consenting individuals, then the waiver could apply.

The IRB, in conjunction with the clinical investigator, must make sure that procedures are in place to obtain consent at the earliest feasible opportunity from the subject, the legally authorized representative of the subject, or a member of the subject’s family. A potential therapeutic window of time, based on available evidence, should be defined as the time frame in which attempts to obtain consent are made and documented. For any given study, this period may necessarily be very short if the prospect of direct benefit is to exist, therefore precluding the feasibility of trying to obtain consent before the investigational intervention should be initiated.

Both the investigator and the IRB must consider whether a shortened written consent form (a so-called short form) should be presented to the subject’s legally authorized representative in instances where time is of the essence in initiating the study intervention. Such a shortened consent procedure may be far from ideal, but it also may represent the best option for ensuring that both the rights and the welfare of the subject are preserved.

Additional challenges associated with the consent process include defining the hierarchy of family members to ensure the validity of 1 person’s claim to be the subject’s legally authorized representative and establishing a process of mediation if family members are not in agreement about a subject’s participation in the research study. Clearly, a thorough understanding by both the investigator and the IRB members of the federal regulations governing the exception from informed consent require-
ments for emergency research is necessary. Nonetheless, the wording of 21 CFR 50.24 and comparable DHHS requirements do not leave much to the discretion of individual IRBs. Multi-institutional research studies, as a result, might be approved by some IRBs but not by others. While this lack of concordance across IRBs may be justified in some instances as a result of local societal factors, it is nevertheless desirable for all IRBs to interpret the regulations similarly and to exercise discretionary judgment using a common standard as presented in the federal regulations and the associated guidance documents.

State or local laws and regulations must also be considered by the investigator and the IRB. The state of North Carolina, for example, had a rule presented in its Patient’s Bill of Rights that, until recently, conflicted with the federal regulations that allow for an exception from informed consent requirements for emergency research. A rules change had to be effected to make the state rule coincide with the federal regulations. The federal regulations do not preempt state rule in cases where state rule sets a higher standard (in this case, to require voluntary informed consent for all research participation).

In addition, local regulatory agencies may have to approve a study if they provide oversight of a particular aspect of the study. For instance, if a proposed study involves a prehospital intervention by a county’s emergency medical services personnel and the county’s board of commissioners or equivalent oversight body, as well as any state board that oversees emergency medical services procedures, it may require that they approve the study before it accrues research subjects.

COMMUNITY CONSULTATION

Once an IRB reviews a research study and finds that it meets the exception from informed consent requirements for emergency research as outlined in the federal (and perhaps state) regulations, the IRB may issue an approval to initiate the required steps of community notification about the proposed research and community consultation to determine the community’s attitudes about the research. This process is intended to inform the IRB and to provide additional protection of the rights and welfare of individuals who might become study subjects.

The community consultation process is, perhaps, the least well defined of the requirements in the federal regulations that allow for the exception from informed consent requirements for emergency research. The methods of the community consultation, the extent of the consultation, the assessment of the adequacy and the effectiveness of the consultation process, and the decision to approve or not approve a study based on the community input are all issues that are left to the IRB to determine, with little guidance from the federal regulations. Investigators who have conducted community consultation for emergency research studies meeting the exception from informed consent requirements have expressed the need for more specific guidance to elucidate effective strategies for community consultation.

The mechanism of community consultation is likely to be multifaceted and may include radio and television spots, newspaper articles, informational Web sites, telephone “hotlines,” public meetings, establishment of community advisory boards, meetings with “captive” audiences like local Rotary or Lions Clubs, and meetings with groups whose members may be at higher risk than the population at large of becoming subjects in the research trial. The challenges for the investigator and the IRB are to determine how much community consultation is sufficient, without being unnecessarily burdensome on the community; to ensure that the potential risks and benefits of the proposed research study are adequately communicated to the community; and to ensure that the IRB is adequately informed about community attitudes surrounding the proposed research. It is highly unlikely that all the members of the community who are potential research subjects could be consulted during this community consultation process, no matter how much effort is expended during this process. But both the investigator and the IRB must ensure that a good faith effort has occurred to permit the community to be informed about the proposed research and to comment as to its appropriateness in that particular community.

The community consultation process must also include a dialogue of “opt-out” mechanisms for individuals who choose not to participate in the proposed research study. The establishment of effective opt-out mechanisms poses a challenge for the investigator and the IRB. Bracelets indicating a person’s desire not to participate have been used but have sometimes been found to be impractical. Maintaining an up-to-date database of individuals who have chosen to opt out may be feasible in some instances. But limitations of this approach include logistical difficulties if the list is extensive, if multiple nearby enrolling sites are involved in the study, and if prehospitalization enrollment of subjects will occur.

How does an IRB objectively assess the effectiveness of community consultation? Will it require written comments from the community? Does poor turnout at public meetings obligate the IRB to require additional consultation with the community, or does it reflect public apathy, tacit consent, or both? What will the IRB do with the aggregate community response? Should an IRB’s decision to approve a study rest with the community’s majority response? These are all challenges that individual IRBs must face and resolve without the benefit of specific federal regulation. However, each IRB must establish its own guidelines that address these issues.

FINAL IRB REVIEW AND APPROVAL

Once the community consultation phase is completed and the IRB is satisfied that it is adequately informed about community attitudes concerning the proposed research, final IRB approval may be given for the investigator to proceed with the research. Public disclosure of the IRB’s decision, including the anticipated date of study initiation, must occur so community members can be informed of the result of the completed community consultation process. Ordinarily, a reminder to the community of the plans for the investigation and the risks and expected benefits associated with the study would be provided at this stage, and it is the IRB’s responsibility to review and approve the information to be disclosed. Con-
sequences of this disclosure include reassuring the public about the careful review process completed by the IRB, reminding the community that the research study that is about to commence involves individuals from the community, and describing once again the opt-out mechanisms for individuals from the community who choose not to participate as research subjects.

CONCLUSIONS

The ethical principles outlined in the Nuremberg Code, the Helsinki Declaration, and the Belmont Report, and codified in 45 CFR 46 and 21 CFR 50 and 56, serve as the basis for the protection of human research subjects. Guided by these principles and encouraged by the prospect of advancing emergency medicine, investigators leading clinical research studies conducted under the exception from informed consent requirements for emergency research, as well as the IRBs that are empowered to review and approve such research, are faced with many challenges to assure the safety and welfare of potential research subjects. These challenges are present at every step in the process to initiate such a research study, including the phases of study design, initial IRB review, community consultation, and final IRB review and approval.

Federal and state regulations sanctioning such research are sufficiently imprecise in some regards that the process by which the review occurs must be guided by individual IRBs. While this is necessary to ensure that community attitudes are known by the IRB and are considered as the IRB decides to approve or disapprove the research, further guidance for investigators and IRBs would be helpful to ensure that the process is efficient, equitable, and not unduly cumbersome, costly, or time-consuming. Consensus guidelines could be established with the input of IRB members, investigators, ethicists, and community members. The Resuscitation Outcomes Consortium, recently established by the National Heart, Lung, and Blood Institute and others to conduct clinical research in the areas of cardiopulmonary resuscitation and traumatic injury, may facilitate the development of consensus guidelines.17 The Resuscitation Outcomes Consortium, which includes 10 regional clinical centers in the United States and Canada, will address the issue of waiver of informed consent use in their upcoming multicenter clinical trials. If these guidelines were established, then the challenges associated with conducting research under the exception from informed consent requirements for emergency research would become less daunting and the prospect of proceeding with much needed research would be realized.

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Correspondence: Steven N. Vaslef, MD, PhD, Section of Trauma and Critical Care, Duke University Medical Center, Box 102345, Durham, NC 27710 (vasle001@mc.duke.edu).

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