U.S. Federal Regulations for Emergency Research: A Practical Guide and Commentary

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Abstract

Emergency medicine research requires the enrollment of subjects with varying decision-making capacities, including capable adults, adults incapacitated by illness or injury, and children. These different categories of subjects are protected by multiple federal regulations. These include the federal Common Rule, the Department of Health and Human Services (DHHS) regulations for pediatric research, and the Food and Drug Administration's (FDA) Final Rule for the Exception from the Requirements of Informed Consent in Emergency Situations. Investigators should be familiar with the relevant federal research regulations to optimally protect vulnerable research subjects, and to facilitate the institutional review board (IRB) review process. IRB members face particular challenges in reviewing emergency research. No regulations exist for research enrolling incapacitated subjects using proxy consent. The wording of the Final Rule may not optimally protect vulnerable subjects. It is also difficult to apply conflicting regulations to a single study that enrolls subjects with differing decision-making capacities. This article is intended as a guide for emergency researchers and IRB members who review emergency research. It reviews the elements of Federal Regulations that apply to consent, subject selection, privacy protection, and the analysis of risks and benefits in all emergency research. It explores the challenges for IRB review listed above, and offers potential solutions to these problems.

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Emergency medicine has a broad scope of practice. The spectrum of clinical research that is required to advance emergency care is correspondingly broad. To examine clinical problems ranging from minor to life-threatening conditions, emergency research enrolls subject populations with differing decision-making capacities, including capable adults, adults incapacitated by acute illness or injury, and children. These different categories of subjects are protected by several overlapping U.S. federal regulations. Investigators should be familiar with the federal regulations that govern emergency research. Knowledge of the regulations will facilitate the IRB review process by enabling researchers to design studies that comply with the rules and preserve the rights of vulnerable research subjects.

This article is intended as a guide for emergency researchers and for IRB members who oversee emergency research. It reviews the federal regulations that govern emergency research, examines necessary protections for subjects in research for which few regulations exist, and explores potential solutions to regulatory problems that present barriers to the conduct of emergency research.

U.S. FEDERAL REGULATIONS GOVERNING EMERGENCY RESEARCH

U.S. federal research regulations reflect the guiding ethical principles of respect for persons, beneficence, and justice articulated by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in the Belmont Report.[1]

Biomedical research in the United States is governed by regulations known as the Common Rule.[2] These regulations are so named because they govern human subjects research funded by all U.S. federal departments. This includes the Department of Health and Human Services (DHHS) and the Department of Defense, which frequently fund emergency research. The Common Rule details the structure and function of IRBs and sets out substantive requirements that cover informed consent, subject selection, privacy protection, and the assessment of risks and potential benefits.

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The DHHS has separate regulations for research involving vulnerable subjects, including children,[3] pregnant women, fetuses and neonates,[4] and prisoners.[5] These regulations apply to emergency research performed on these specific populations.

Regulations issued jointly by the DHHS and Food and Drug Administration (FDA) permit an exception from informed consent requirements for emergency research in life-threatening situations.[6] The exception from informed consent requirements is known informally as the ''Final Rule'' in the emergency research community. These regulations have principally been applied to trauma and resuscitation research, but pertain to research on any life-threatening condition when it is impossible to obtain consent from a subject or substitute decision-maker.

COMMON ELEMENTS AND TERMINOLOGY IN FEDERAL REGULATIONS

There is significant overlap between the federal regulations that govern emergency research. They commonly address respect for subjects' privacy, fairness in subject selection, and protection of vulnerable subjects. There are also important differences with respect to informed consent and the analysis of risks and potential benefits.

These regulations specifically govern research on human subjects. Human subjects are individuals about whom investigators obtain data through direct interactions, clinical interventions, or review of identifiable personal information.[2] Research, in the regulatory context, refers to any activity that is designed to develop generalizable knowledge. This includes clinical research, in which therapies or diagnostic tests are evaluated, basic science research, and observational or epidemiologic studies.[2]

All federally-funded research is subject to the Common Rule's requirements for the protection of subjects' privacy. IRBs expect similar assurances for privately-funded research. The Common Rule requires that subjects' privacy be protected and the confidentiality of data be safeguarded. IRB submissions typically require investigators to describe in detail the number and identity of individuals who have access to identifiable information, and how identifiable information will be safeguarded. Investigators must also document that their privacy protection and data storage mechanisms comply with the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA).[7] Shahan and Kelen, in a recent review article, further discuss privacy protections in emergency research.[8]

Federally-funded research must also comply with the Common Rule requirements for fairness in subject selection.[2] The Belmont principle of justice demands a fair distribution of the burden of research risks, and an assurance that the benefits of research will similarly be fairly distributed.[1] Subjects must be chosen from a patient population to whom the study is relevant. It is permissible to perform a study on a vulnerable or disadvantaged subject population only if the study's hypothesis requires their inclusion, and if similarly situated patients may benefit from the results of the study. This ensures that vulnerable subjects are not enrolled in research simply because they are a population of convenience. The principle of justice also requires that subjects not be excluded on the basis of gender, ethnicity, age, or any other characteristic, unless the reason for their exclusion is scientifically relevant. This ensures that the results of research may be applied to all who may benefit.

The Belmont principle of respect for persons requires that subjects who are vulnerable because of limited decision-making capacity or specific clinical circumstances be extended additional protections.[1] A common additional protection is a limit on permissible research risk. Regulatory limits on research risks revolve around the concept of minimal risk. Minimal risk, as defined in the Common Rule, means that ''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.''[2]

The concept of minimal risk is important to emergency research performed in a variety of clinical situations. Minimal risk serves as a baseline against which IRBs and regulators can compare the risks of research performed on vulnerable subject populations such as children. Examples of procedures posing only minimal risk are listed in an appendix to the Common Rule section on expedited IRB review,[9] and may also be found in the literature. They include such procedures as venipuncture, ultrasonography, electrocardiography, noninvasive bodily secretion collection, and review of medical records.[9] The incorporation of the concept of minimal risk into specific regulations addressing research on children, incapable adults, and patients with life-threatening emergencies will be discussed in detail below.

RESEARCH FOR NON–LIFE-THREATENING CONDITIONS, WITH SUBJECTS CAPABLE OF PROVIDING CONSENT

The majority of emergency research addresses medical conditions that are not life-threatening. Examples include trials of oral analgesics for fracture pain,[10] or comparisons of procedural sedation regimens for painful procedures.[11]

The criteria for IRB approval of such studies is outlined in subpart 111a of the Common Rule [46 CFR 46.111(a)]. The Common Rule outlines requirements for informed consent, subject selection, the protection of privacy, and the analysis of risks and potential benefits (Table 1).

Informed consent for research participation must be obtained from potential subjects who have the capacity to choose whether to participate. The Common Rule permits a waiver of consent for some types of epidemiologic and observational research, provided that the research poses only minimal risk to subjects [45 CFR 46.117(c)]. Most IRBs have developed their own requirements for what information must be included on consent forms for clinical research. However, the basic requirements for the disclosure of risks, potential benefits, and alternatives, and description of privacy protections are outlined in the Common Rule (Table 2).

Table 1
Requirements for Institutional Review Board Approval of Clinical Research for Non–Life-threatening Problems Involving Capable Adults

1. Risks to subjects are minimized: a. By using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk and b. Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes. 2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. 3. Selection of subjects is equitable. 4. Informed consent will be sought from each prospective subject. 5. Informed consent will be appropriately documented. 6. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects. 7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
Adapted from 45 CFR 46.111(a).

The Common Rule requires that the risks of research participation be reasonable in relation to potential therapeutic benefits or the importance of the knowledge expected to be gained. IRBs are now being advised to use a structured framework, known as Component Analysis, to make this determination.[12] The key feature of Component Analysis is that it recognizes the moral distinction between therapeutic procedures and nontherapeutic procedures, and applies different ethical tests to each.

Therapeutic procedures refer to the treatment regimens or diagnostic modalities being evaluated in a clinical trial. Therapeutic procedures must offer a reasonable relationship between risks and potential benefits, be consistent with competent medical care, and satisfy the conditions of clinical equipoise.[12] A state of clinical equipoise exists when there is disagreement in the expert clinical community as to the preferred treatment.[13] This state of disagreement is the very rationale for performing a clinical trial, and ensures that subjects are not subjected to substandard treatment by randomization.[13]

Nontherapeutic procedures are different from therapeutic procedures. They are the interventions used solely to gather data to answer the scientific question of a study, and represent the incremental risk of research participation beyond ordinary clinical practice. The risks of nontherapeutic procedures must be minimized, for example, by using blood drawn for therapeutic purposes to monitor drug levels rather than performing separate phlebotomies. The risks of nontherapeutic procedures must, in the judgment of the IRB, be justified by the importance of the potential knowledge to be gained. If a study's therapeutic

Table 2
Elements of Informed Consent and Requirements for Documentation of Informed Consent

The research subject will be provided with an information sheet that includes:
A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental;
A description of any reasonably foreseeable risks;
A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable;
A description of any potential benefits to the subject or to others;
A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
Contact information for individuals who can provide additional information about the study or address questions about research-related injuries;
A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits, and the subject may discontinue participation at any time without penalty;
Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
A description of additional costs to the subject that may result from participation in the research;
A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject; and
The approximate number of subjects involved in the study.
Adapted from 45 CFR 46.116 (a)–(b) and 45 CFR 46.117 (a)–(b).

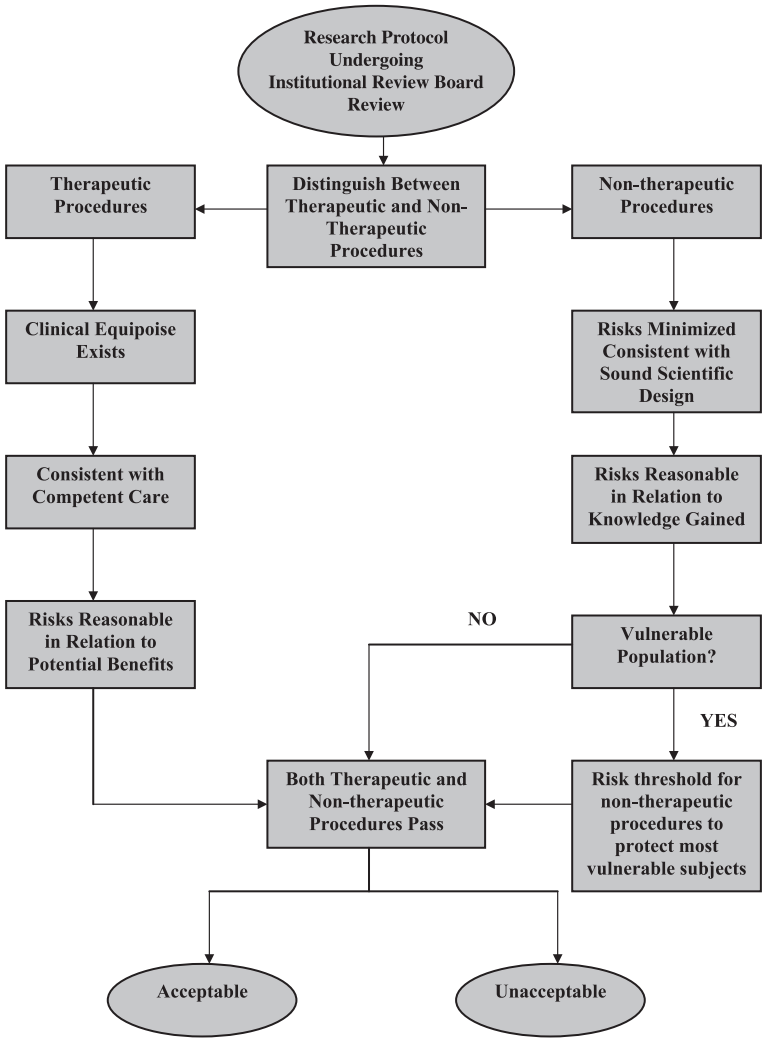

Figure 1. Algorithm for analysis of risks and potential benefits using component analysis. Adapted from Weijer C, When are research risks reasonable in relation to anticipated benefits? Nature Med. 2004; 10:570-3 (used with permission).[18]

and nontherapeutic procedures pass these ethical tests, then an IRB may approve that study[12] (Figure 1).

EMERGENCY RESEARCH INVOLVING CHILDREN

Pediatric emergency research is performed across a spectrum of disease severity. Examples include trials comparing parenteral antiemetics for viral gastritis[14] and comparisons of bronchodilator regimens for moderate to severe asthma exacerbations.[15]

Pediatric emergency research is subject to DHHS regulations for research on children.[3] The Common Rule's requirements for safeguarding subjects' privacy and equitable subject selection apply to pediatric research. Investigators must detail in their IRB submissions the study's privacy protections. The results of a study must be relevant to the class of subjects enrolled in that study. Investigators should enroll the least vulnerable possible subject population. In other words, if a study is feasible in healthy children, then ill or injured children may not be enrolled.

Enrollment of a pediatric patient in clinical research requires the permission of the child's legal guardian and, when possible, the assent of the child. Guardians are to be provided with the same information as is typically required on a consent form for research involving adult subjects (Table 2).

Obtaining parental consent may be challenging in situations where only one parent is present or if the parents disagree. DHHS regulations require the consent of only one parent if the research poses no more than minimal risk or if the research poses a minor increase above minimal risk but offers the possibility of direct benefit to the child. Enrollment of a child in research otherwise requires the consent of both parents.[2] If the parents have differing custodial responsibility, consent must be sought from the parent who has legal custody and authority to make health care decisions.[16]

Seeking the assent of a child is different from seeking parental permission for research enrollment. Assent refers to a child's agreement to participate in a study, after having discussed the risks and potential benefits with parents and investigators. The assent process allows the child to understand, as much as is

possible, the purpose, potential advantages, and potential consequences of study participation, and gives the child an opportunity to refuse to participate. The U.S. National Commission for Protection of Human Subjects of Biomedical and Behavioral Research suggests the age of 7 as an appropriate age to involve a child in discussions about study participation and to seek their assent for participation.[17] However, the complexity of the decision, the child's maturity, and the effect of a child's medical condition on their mental status will influence a child's capacity to provide assent. Therefore, the decision to seek a child's assent requires an individualized assessment of capacity.

Children are vulnerable because they lack decision-making capacity. Therefore, children enrolled in research are entitled to additional protections. In addition to requiring the consent of a child's guardian, the DHHS pediatric research regulations limit the degree of permissible research risk. The degree of permissible risk varies according to the design of a particular study. The concept of minimal risk, as discussed above, is used as a comparator for IRB decision-making as to the acceptability of the risks of procedures in pediatric research.[2]

Pediatric research whose therapeutic components pose more than minimal risk is permissible, provided that ''. . . such risk is justified by the anticipated benefits to subjects;'' and ''…the relation of anticipated benefit to such risk is at least as favorable to the subjects as that presented by available alternative approaches.''[2]

Research in pediatrics when nontherapeutic components pose more than minimal risk is permissible, provided that ''A) Such risk represents a minor increase above minimal risk; B) Such intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, psychological or social situations, and is likely to yield generalizable knowledge about the subject's disorder or condition; C) the anticipated knowledge is of vital importance for understanding or amelioration of the subject's disorder or condition.''[2] Pediatric research when nontherapeutic components pose more than a minor increase above minimal risk may only be approved with the permission of the secretary of the DHHS.[2]

The determination that a study's components pose more than minimal risk requires the IRB to make a qualitative and quantitative judgment about the probability and magnitude of potential harms. This is often done by analogy, comparing a study's interventions to other procedures that are felt to pose only minimal risk.[18]

The National Bioethics Advisory Commission (NBAC) has suggested that these regulations be replaced, using a simpler Component Analysis framework.[19] The proposed regulations would require that therapeutic procedures offer a reasonable relationship between risks and potential benefits, be consistent with competent medical care, and satisfy the conditions of clinical equipoise. The risks of nontherapeutic procedures should be minimized and be justified by the expected gain in generalizable knowledge. Applying a risk threshold of no more than a minor increase above minimal risk would optimally protect all children who are enrolled with the consent of a legal guardian.[19] To date, no move to alter the current regulations has been made.

EMERGENCY RESEARCH INVOLVING INCAPABLE ADULTS

Emergency research may require the enrollment of adults whose decision-making capacity has been acutely impaired by their illness or injury. A recently-published example is a comparison of imaging strategies in hemodynamically stable trauma patients that enrolled both capable subjects who provided informed consent and incapable subjects who were enrolled with the permission of a substitute decision-maker.[20]

Few federal regulations address the protection of incapacitated adults in clinical research. The Common Rule requires that informed consent for research participation be obtained either from the subject or from a legally authorized representative [45 CFR 46.111(a)]. Regulations pertaining to equitable subject selection and protection of subjects' privacy continue to apply. The Common Rule also requires that, ''When some or all of the subjects are likely to be vulnerable . . . additional safeguards have been included in the study to protect the rights and welfare of these subjects'' [45 CFR 46.111(b)]. There are no federal regulations that specifically define what additional safeguards are sufficient to protect these vulnerable subjects.

This paucity of regulation has presented problems for clinical researchers in geriatrics[21] and critical care[22] and may also pose a challenge for emergency research. IRBs have no guidance on what additional protections are owed to these vulnerable subjects. For this reason, research enrolling incapable adults is subject to unusually rigorous IRB examination. This meticulous scrutiny has led to delays in the approval of some geriatric and critical care research.[21,22]

In the absence of regulation, emergency researchers and IRB members may extrapolate appropriate protections for this kind of research from other research regulations. Incapacitated adults are similar to children in that they are protected by a substitute decision-maker, so it seems appropriate to use the DHHS pediatric research regulations as a model for additional protections. Following NBACs recommendations for pediatric research,[19] it seems appropriate to limit risks of nontherapeutic procedures to a minor increase above minimal risk. Consent procedures, privacy protections, and considerations related to subject selection should be documented as they would be for any study conducted under the Common Rule. These recommendations closely resemble regulations for research on incapable adults that were proposed by the Department of Health, Education, and Welfare in 1978, but were never enacted.[23]

RESEARCH FOR LIFE-THREATENING CONDITIONS WHEN PROXY CONSENT IS NOT FEASIBLE

Medical problems presenting an immediate threat to life are frequently encountered in emergency medicine.

For many of these conditions, including cardiac arrest and multiple trauma, treatments and outcomes remain unsatisfactory. There is a clear need for further clinical research to advance therapy for these problems.[24] Studies addressing these disorders often require the use of a waiver of informed consent to enroll research subjects. Well-known examples of this type of research include the evaluation of diasparin cross-linked hemoglobin in trauma[25] and a placebo-controlled study of amiodarone for out-of-hospital cardiac arrest.[26]

The Common Rule permits a waiver of informed consent when research poses no more than minimal risk.[2] Many commentators and regulators believed that this minimal risk threshold prohibited clinical research in life-threatening emergencies, leading to an effective moratorium on resuscitation and trauma research beginning in 1993.[27,28] The emergency research community spearheaded efforts to create new legislation for emergency research. These efforts led to the development of the DHHS/FDA exception from informed consent requirements for research in emergency situations, commonly known as the Final Rule.[6,24,28]

The Final Rule exception from informed consent may be used only for the study of life-threatening emergency medical conditions. Potential subjects must lack the capacity to provide informed consent, and it must be impossible to contact a substitute decision-maker in time to permit the use of time-sensitive investigational therapies. The Final Rule outlines additional protections for subjects enrolled in this type of research, including limitations on the degree of permissible risk, and a requirement for consultation with the community (Table 3).[6] This type of research remains subject to the Common Rule requirements regarding equitable subject selection and safeguarding subjects' privacy.

From 1996 to 2007, 60 applications were made to use the exception, with 21 studies being approved. Perceived barriers to the use of the Final Rule exception include variability in IRB familiarity and comfort with the Final Rule, inconsistent interpretation of the definition of ''life-threatening,'' and practical and philosophical challenges associated with community consultation.[29]

Emergency researchers are of the opinion that IRBs are interpreting the definition of ''life-threatening'' too narrowly, and restricting the use of the Final Rule to research in resuscitation situations.[30] The Final Rule was conceived to facilitate not only resuscitation research, but also research in other life-threatening situations, including head injury, multiple trauma, and cardiovascular emergencies.[24,28] The Final Rule applies to research on any ''. . . conditions where the likelihood of death is high unless the course of the disease or condition is interrupted,'' where intervention is required before authorization from a legally authorized representative is feasible.[6,31]

The Final Rule requires that the study be disclosed to the community and that investigators consult with the community regarding the study. The community

Table 3
Conditions for Institutional Review Board Approval of Clinical Research Using an Exception from Informed Consent for Emergency Research

1. The 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 particular interventions.
2. Obtaining informed consent is not feasible because:
   a. Subjects will not be able to give informed consent because of their medical condition;
   b. The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
   c. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.
3. Participation in the research holds out the prospect of direct benefit to the subjects because:
   a. Subjects are facing a life-threatening situation that necessitates intervention;
   b. Animal and preclinical studies support the potential for the intervention to provide a direct benefit to the individual subjects; and
   c. Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
4. The clinical investigation could not practicably be carried out without the waiver.
5. The protocol defines the length of the therapeutic window, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and to ask for consent within that window rather than proceeding without consent.
6. The institutional review board has reviewed and approved informed consent procedures and an informed consent document consistent with the Common Rule.
7. Additional protections will be provided, including, at least:
   a. Consultation with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;
   b. Public disclosure of plans for the investigation and its risks and expected benefits;
   c. Public disclosure following completion of the clinical investigation to apprise the community and researchers of the study and its results;
   d. Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and
   e. If a legally authorized representative is not available, the investigator will attempt to contact another family member for permission to enroll the subject.

Adapted from 21 CFR 50.24.

consultation process has become a barrier to the conduct of important research. It is a time- and resource-consuming process that has deterred some study sponsors from proceeding with studies in the United States.[32,33] It can be difficult to identify the community to be consulted, and there is no consensus as to the best method of consultation and disclosure.[32,34] Philosophical objections to community consultation include the opinion that consultation adds little to the protection of individual research subjects.[35] It is unclear as to what constitutes successful consultation, or how an IRB is to integrate a community's concerns into the review process.[32,34,35]

Although the problems with the requirements of the Final Rule are important, investigators and IRBs remain obligated to work within the Final Rule's regulatory framework. In 1998, the FDA issued an update to clarify the Final Rule requirements.[31] This document contains suggestions for appropriate means of consulting with the community, including public meetings, the appointment of a community advisory panel to the IRB, or the use of consultants from the community, including additional community members on the IRB. These methods have been used in several studies with varying degrees of success.[32,34]

The 2005 Academic Emergency Medicine Consensus Conference, ''Ethical Conduct of Resuscitation Research'' reviewed current methods of, and experiences with, community consultation and called for more research into the efficacy of current consultation methods. We refer investigators and IRB members to the November 2005 issue of *Academic Emergency Medicine*, and to a recent review of the literature on community consultation[34] for further elaboration. Because there is no consensus as to the ideal method of consultation and disclosure, and because the determination of the adequacy of community consultation rests with the IRB, investigators should collaborate with their local IRB to develop a community consultation process that best meets the needs of their particular study.[32]

In fall 2006, the FDA convened a hearing to elicit feedback on the Final Rule from the emergency researchers, study sponsors, and the public. Representatives from the emergency research community discussed many of the above-listed challenges. Presenters made several recommendations, including the establishment of a central review committee for Final Rule studies to assist local IRBs in the review process and the convening of further meetings between the FDA and stakeholders in emergency research to collaborate in the evolution of emergency research regulations. Presentations by members of the emergency research community are presented in the April 2007 issue of *Academic Emergency Medicine*.

CHALLENGES IN THE USE OF EMERGENCY RESEARCH REGULATIONS

Emergency researchers may find navigating federal research regulations challenging. Similarly, IRB members who review emergency research should be aware of potential pitfalls in applying research regulations. Especially important problems include the absence of regulations governing research enrolling incapable adults, difficulty protecting vulnerable subjects using the Final Rule, and problems applying conflicting regulations to studies that enroll subjects with differences in decision-making capacity.

Absence of Regulatory Guidance for Research Enrolling Incapable Adults

As discussed previously, there are no specific regulations governing emergency research that enrolls incapacitated adults with the consent of a substitute decision-maker. Furthermore, the legality of proxy consent for research in some states remains unclear.[36] There is no regulatory guidance as to the necessary additional protections for the vulnerable subjects enrolled in these studies. The Acute Respiratory Distress Syndrome Network (ARDSNet) studies, in particular, have been criticized for failing to offer any additional protections beyond proxy consent.[36]

In response to difficulties with IRB approval of geriatric research, investigators have suggested that specific regulations for research enrolling incapacitated adults be enacted.[21] New regulations should include the following basic elements: 1) a requirement that the use of incapacitated adult subjects be essential for answering the study's scientific question, 2) protections for subjects' privacy that are compatible with the Common Rule and HIPAA requirements, 3) requirements and procedures for obtaining consent from substitute decision-makers on behalf of incapacitated subjects, and 4) a limit of no more than a minor increase above minimal risk for nontherapeutic procedures. These requirements are similar to previously proposed regulations for research involving incapable adults.[23]

The adoption of such regulations would be in the interest of emergency researchers and research subjects. Clear regulations for research enrolling incapable adults would enhance subject protections while guiding the IRB review of emergency research that enrolls adults incapacitated by their medical condition.

Subject Protection in Final Rule Studies

The challenges posed by the community consultation process for studies performed under the Final Rule have been well documented. An important problem that is perhaps less obvious is that the wording of the Final Rule's threshold for research risk fails to adequately protect the vulnerable subjects that are enrolled in emergency research without their consent.

The Final Rule requires that risks be ''. . . reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.'' The degree of permissible risk in studies approved under the Final Rule is therefore inextricably linked to the severity of the subjects' medical condition. Taken literally, this means that there is effectively no limit on the degree of permissible risk of nontherapeutic procedures, provided that a subject's condition is sufficiently dire.[37] This seems at odds with the Belmont principle of respect for persons, which requires that vulnerable subjects be

protected in a manner that reflects the extent of their vulnerability.[1]

Protections for vulnerable subjects in Final Rule studies are improved through the use of Component Analysis, the structured framework for risk analysis described above and in the IRB handbook.[12] Therapeutic procedures must be consistent with competent medical care, have a reasonable relationship of risks to potential benefits and must satisfy the requirements of clinical equipoise. A meaningful risk threshold should be applied to nontherapeutic procedures, which present the incremental risk of research participation. The most appropriate risk threshold for Final Rule studies is minimal risk.[37] A limit of ''no more than a minor increase above minimal risk'' is suggested for pediatric research, where subjects are protected by a substitute decision-maker. Subjects enrolled using the Final Rule are not protected by a substitute decision-maker, so a stricter limit of minimal risk for nontherapeutic procedures seems appropriate.[37]

Emergency research could easily proceed using this framework, since the most important outcomes (survival, disability, and the like) are easily ascertained using minimally risky nontherapeutic interventions.[38] This approach to the analysis of risks and potential benefits, including the use of a limit of minimal risk for nontherapeutic interventions, complies with the current Final Rule requirements while providing stronger subject protection.

Inconsistency of Multiple Federal Regulations for Emergency Research

All emergency research is subject to the Common Rule's privacy protection and subject selection requirements. The requirements for informed consent, whether from a capable subject or a substitute decision-maker, are similar across federal regulations. However, rules for the analysis of risks and potential benefits in the Common Rule, Final Rule, and DHHS pediatric research regulations are very different.

Differences between federal regulations become especially challenging for the IRB review of emergency research that enrolls subjects with varying decision-making capacities. In these studies, different federal regulations would apply simultaneously to different subjects within the same study. For example, studies of laceration repair techniques often enroll both adult and pediatric subjects.[39,40] Adult subjects are protected by the Common Rule, while the pediatric subjects in the same study are protected by the DHHS pediatric regulations. Similarly, studies that enroll subjects using the Final Rule may also enroll incapable subjects with the consent of a substitute decision-maker, along with other subjects who are capable of providing consent.[41–44] The Final Rule protections apply to subjects enrolled without consent while subjects capable of providing consent are protected by the Common Rule.

IRBs have no guidance as to how they should apply potentially conflicting regulations for the analysis of risks and potential benefits to a single study. The use of Component Analysis by IRBs allows the harmonious adherence to multiple federal regulations while optimally protecting vulnerable subjects (Figure 1). Requirements that therapeutic procedures be consistent with competent care, offer a reasonable relationship of risks and potential benefits, and satisfy the conditions of clinical equipoise are consistent with all current federal regulations. Risk thresholds for nontherapeutic procedures should reflect the degree of vulnerability of the subjects rather than being related to the design of a study or the subjects' medical condition. A risk threshold should adequately protect the most vulnerable subject in a particular trial. For studies enrolling children or incapable adults, this threshold is a minor increase above minimal risk. In studies enrolling critically ill subjects using an exception from informed consent, nontherapeutic procedures should pose no more than minimal risk. This conservative strategy would both optimally protect vulnerable subjects and permit important emergency research to proceed while complying with all federal regulations.

CONCLUSIONS: NAVIGATING THE REGULATORY LANDSCAPE

Emergency researchers should be familiar with the content of the Common Rule, which applies to all human subjects research, as well as with specific regulations that may pertain to the subject population under investigation. Familiarity with relevant research regulations will allow emergency researchers to better prepare funding proposals and IRB submissions.

IRB members are challenged by the absence of guiding regulations for research involving incapacitated adults, and inconsistency in the treatment of research risk by regulations pertaining to different subject populations that may be enrolled in a single clinical study. The use of component analysis offers solutions to these problems. It provides a conceptual framework that allows the careful analysis of risks and potential benefits and assures additional protection to vulnerable subjects through the application of an appropriate threshold on the risks of nontherapeutic interventions that is consistent with the intent of current federal regulations.

Current regulations present barriers to the performance of important emergency research while potentially allowing excessively risky nontherapeutic interventions on vulnerable emergency research subjects. Regulators have a public responsibility to ensure that regulations offer adequate subject protections while allowing important research to proceed. We urge researchers, IRB members, and regulators to engage in an ongoing dialogue to create emergency research regulations that both facilitate important research and optimally protect vulnerable subjects.

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