

Conduct of Emergency Clinical Research: Public Hearing
Abstract Submission for Presentation

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Introduction:

Emergency research is complicated by the need to balance patient autonomy while conducting the research needed to improve patient care. The Pediatric Emergency Care Applied Research Network (PECARN) organized in 2001 with the goal of conducting high quality, scientifically rigorous research in pediatric emergency medicine. We are currently involved in a study that will utilize the exception from informed consent.

We applaud the FDA in publishing the July 2006 Guidance and providing the opportunity for public comment. The Guidance provides greater clarity to the process of obtaining an exception from informed consent (EFIC) under 21 CFR 50.24. We thank the FDA for an opportunity to comment on those portions of the Guidance where we believe further clarity or change is needed.

First, we agree with comments from our colleagues from the Neurological Emergencies Treatment Trials (NETT) and Resuscitation Outcomes Research (ROC) networks and we will not repeat their already cogent arguments. We will instead focus on areas that have not been addressed or require pediatric input. Additionally, appendix A provides responses to the specific questions asked in the federal docket.

Ethical Framework for the EFIC:

Neither the regulation itself nor the 2006 Guidance recognize the personal loss of autonomy that is inherent in every emergency encounter. While the research community had begun to understand the concept of “incremental risk” (that is, the additional risk associated with performing a research study), we believe that we also need to begin to incorporate the concept of “incremental loss of autonomy” (that is, the additional loss of autonomy associated with research). In general, patients in emergency situations do not have personal autonomy. They do not have the luxury of discussing clinical treatment options with their physicians, nor do their family members. There is simply not enough

time to have these discussions. Patients and their families trust that their emergency physician will provide the best care available. **But what if the best care is unknown?** As a nation, we are faced with an ethical choice: We can choose to allow every emergency encounter to be an uncontrolled experiment at the hands of the individual physician, and hence fail to advance the science, or we can choose to enroll patients in a systematic manner into rigorously controlled clinical trials with well regulated treatment arms and safety monitoring aimed at determining the best treatments. The former approach, caused in part by the difficulties in implementing this type of research, has been described ethically as follows: “As the treating doctor, you are free to do whatever you want as long as you promise not to learn anything.” The latter approach is more ethical because it maximizes the likelihood of benefit to not only the individual patient but also to society. **The take home point is this: well conducted emergency research itself poses no additional loss of autonomy beyond that of standard care.** What this research does do is 1) ensure the highest quality of care by requiring the most intense levels of scientific review, 2) provide safety monitoring above that of normal clinical care, and 3) ensure that we can improve the care of patients to the maximum extent possible.

Requirements for use of EFIC:

Life Threatening Condition:

We believe that the use of the term “life threatening condition” is restrictive in that it precludes study of conditions that are not immediately life-threatening but have significant morbidity. Pediatric emergencies are rarely life-threatening but may have the potential for serious long-term morbidity and there is little research to determine optimal treatments in the emergency setting. Surely loss of limb, or loss of vision, or loss of neurologic function, for example, deserve the same benefits of carefully controlled research as loss of life. We believe that the regulation should be aimed at emergency conditions, that is, conditions that must be addressed immediately and without the delays inherent in a meaningful discussion about informed consent.

Current Treatments Unproven or Unsatisfactory: the Guidance is not clear about what constitutes “unsatisfactory or unproven therapies.” The term “unsatisfactory” is meaningless unless it is placed in the context of the question: “unsatisfactory compared to what?” We believe that the threshold test for allowing a study under the Exception should be clinical equipoise; that is the preponderance of evidence to date suggests that the two treatments are equal but there is a suggestion that a new treatment may be better. For example, current survival rates for out-of-hospital pediatric cardiac arrest are approximately 5% with epinephrine. Is this satisfactory? It is compared to placebo. But what if a new medication shows promise in animals? Why should we accept 5% survival when the new therapy might provide 8% survival? Then we would argue that epinephrine is unsatisfactory. What if survival for near-fatal asthma, for example, is 70% with current therapy but animal studies suggest 80% survival for a new medication? We believe that, in this context, the status quo of 70% survival is “unsatisfactory.” We believe that the Exception should be allowed whenever there is clinical equipoise and therefore the direct prospect of improving the care of patients.

Protections for Human Subjects:

Community Consultation:

Definition of Community: The Guidance implies that community consultation should attempt to include both the geographic population from which the subjects will be drawn as well as subjects who have the disease of interest. Prior studies utilizing the EFIC have shown that many methods of consultation with the general community (such as public meetings) have not been effective in achieving the bi-directional input that is intended in the spirit of these guidelines. We believe that targeted and focused community consultation should occur in groups who are vested in the study (such as community leaders or patients who have the disease) to obtain meaningful input. Particularly for pediatric studies, parents are constantly bombarded with information about potential diseases or concerns for their children; messages regarding one particular study will not receive their attention if their child does not suffer from the particular disease. People, in general, cannot relate to the abstract; it is only when such research is relevant to them personally or is relevant to their constituents that we will achieve meaningful input.

Documentation of consultation: the Guidance does not provide IRBs with input on what to do with negative community input. Although the spirit of the Guidance suggests that IRBs need to take community input into account, the message may be perceived as a need to obtain community consent.

Special Populations (Children)

We believe that the Guidance should be more explicit about the applicability of the regulations to trials involving children. There may be an assumption that children are more vulnerable under resuscitation circumstances than adults. In truth, all patients in a life-threatening situation are equally vulnerable. Excluding children on this basis would be unjust. In addition, many assume that children automatically have a parent or guardian who can decide on research participation. This is often not the case in the emergency department, as children often present with school personnel or babysitters. Even when parents or other family members are present, the emotional distress experienced during a medical crisis precludes meaningful discussions about informed consent during the therapeutic window.

Opportunity to Object:

Finally, we would like to applaud the FDA on its emphasis of the need to provide opportunities for family members or patients to object to their participation in clinical research protocols. Despite the arguments we have made in favor of emergency research, we recognize the tainted history of research in the United States and the fundamental distrust that some communities, most notably African Americans, have in our medical system. By providing families and patients several options for refusing participation, we go a long way in restoring this trust and ensuring that future generations can reap the benefits of participation in clinical research trials

Appendix A: Responses to Specific Questions

The following are specific responses to the questions posed in the consent notice.

1. Are the criteria for allowing studies conducted under §50.24 adequate to protect human subjects and to promote scientifically rigorous research?

The criteria are rigorous but provide a good balance between conducting rigorous research and assuring patient autonomy. As articulated in the testimony, the criteria for “life threatening” need also to consider “emergency” conditions that are associated with high morbidity but may not be life threatening.

Are any additional criteria warranted? ***Additional criteria are not needed.***

2. Are the following criteria easily understood and, if not, how can they be clarified?
 - a. "Available treatments are unsatisfactory or unproven" (§ 50.24(a)(1))
 - b. "Prospect of direct benefit" (§50.24(a)(3))
 - c. "Practicably" (§50.24(a)(4))

We believe the criteria for “unproven” and “unsatisfactory” are not clear and need to be further clarified. We believe that the word “practicably” should be interpreted as meaning “logistically feasible and scientifically appropriate.” For example, it might be possible to conduct a study using 50 hospitals over 20 years to enroll 100 patients in a clinical trial. This is not scientifically feasible and therefore is not practicable.

3. Are there other criteria in the regulation, besides those identified in criteria (2)(a) through (c), that need to be clarified?

No.

4. Are there challenges that have not been explicitly addressed in the regulation in designing scientifically rigorous and ethically sound emergency research protocols (e.g., pediatric protocols)? If there are such challenges, should they be addressed and how?

Please consider the comments provided in the testimony.

5. What are the costs, benefits, and feasibility of community consultation as currently required under § 50.24?

We believe that the major costs associated with community consultation are associated with the personnel needed to perform the consultation and plan activities and meetings. These costs can be difficult for pediatric studies for

which funding is limited. The major costs of public disclosure occur when IRBs require newspaper, radio or TV advertisements. These costs can be prohibitive.

6. What aspects of community consultation as currently practiced are effective mechanisms for human subject protection? Are there additional practices that could enhance human subject protection?

After working with community groups and reviewing the literature on prior experiences with community consultation, we believe the most effective bi-directional exchange is achieved through targeted consultation with community leaders or in populations that have the disease of interest. General public meetings generally are too large to provide meaningful exchange or do not have significant attendance. Targeted meetings bring together vested individuals who can provide thoughtful input.

Further, for multi-center research, some local community consultation may be conducted after the scientific protocol has been finalized. A central mechanism for doing some of the community consultation may be helpful in generating bi-directional dialogue that can be incorporated into the protocol. Local community consultation would then enhance the dialogue and address any local concerns. Such central consultation could be in the form of targeted focus groups or meetings with community leaders.

7. Are there elements of community consultation, both procedural and substantive, that should, at a minimum, be required (e.g., types of information presented, number and types of meetings or interactions, number of people reached)?

Guidance on the minimum amount of community consultation would be helpful. Please refer to the comments from the ROC network.

8. Would opt-out mechanisms (e.g., advanced directives, jewelry similar to medical alert bracelet/necklace, and driver's license indicators) to identify individuals who do not wish to be included as subjects in particular emergency research studies provide a necessary protection for human subjects? If so, are they feasible?

We agree with our colleagues from the ROC network that opt out jewelry is not always effective as individuals do not wear the jewelry or it is not easily identified by emergency workers. Similarly, maintaining lists in the ED or ambulances may not work as patient identity is not always known at the time of treatment. We believe that if a family member is present during the emergency, they should be told of the research study and allowed to refuse at the time of enrollment. For those without a family member present, opt-out jewelry may be the only option.

9. Who should use the information obtained from the community consultation process

and how should they use it? Should the regulation be more specific on this point, and if so, what should it provide?

We believe the information should be used by the local IRB.

10. Are there others besides the IRB (e.g., sponsors, clinical investigators, community leaders, advisory committees, ethicists) who should play a role in determining the adequacy of the plan for community consultation and the material to be publicly disclosed?

We believe that the IRB should play the central role in review.

11. The community consultation process typically includes meetings and discussions about the study with the community. Should the regulation require documentation of meeting activities and discussions in sufficient detail to show the information that was disclosed and the community reaction to the clinical investigation? If so, who should be responsible for such documentation (e.g., clinical investigator, sponsor)?

The new Guidance specifically identifies a role for the IRB and encourages the IRB to be involved in the community consultation process. Documentation of the process should therefore be left to the local IRB.

12. The regulations (see 21 CFR 312.54(a) and 812.47(a)) currently require the sponsor to submit the information publicly disclosed prior to study initiation and after completion to FDA Docket Number 1995S0158 (formerly 95S-0158). Should the regulation also require that documentation of community consultation activities be submitted to FDA, for example by being placed in the public docket? If so, who should be responsible for doing this?

Please see responses above. We believe this is the responsibility of the IRB.

Should this information also be available elsewhere such as on clinicaltrials.gov?² ***No, however, it would be useful to identify studies that use the exception from consent regulations in clinicaltrials.gov.***

13. Are there certain types of information (e.g., adverse event reports, study protocol, informed consent document) that should, at a minimum, be publicly disclosed to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn?

Any information that would otherwise be disclosed to participants that consent to the study should be publicly disclosed. Thus if there is information that the IRB deems necessary to inform participants of, should also be disclosed to the general public.

14. Should the full protocol, or other information such as the investigator's

brochure, for emergency research be available (e.g., through FDA's public docket, clinicaltrials.gov) to the general public before initiation of the clinical investigation?

Although we do not oppose this idea, we agree with the ROC investigators that “issues of proprietary concern will be difficult to address were this to happen and could be perceived as a significant barrier to research.”

15. Is there information regarding study results that, at a minimum, should always be disclosed after the clinical investigation is completed? If so, what is that information?

The major findings of the research study should be disclosed to the public as well as any significant adverse effects. Again, the local IRB should determine the exact content of the disclosure.

16. How can this disclosure best be accomplished? Who should be responsible for this disclosure?

The investigators should take responsibility for this disclosure and identify a mechanism for doing so with their IRB as part of the initial planning for the study. However, it should be recognized that some results may not be able to be publicly disclosed before they are published in a peer review journal.

17. When should a clinical investigation be considered "completed?" How soon after a clinical investigation is completed should the results be disclosed?

We agree with the ROC investigators that “the investigation should be considered ‘completed’ after all primary data are collected, analyzed, and published in a peer-reviewed journal. The results should be disclosed to the scientific community by publication in an appropriate peer-reviewed journal at the earliest feasible date.”

18. How can we assure timely disclosure of study results after completion of a study?

We do not foresee a role for the FDA in facilitating public disclosure.

19. What type of venue would be best for this additional review and public discussion?

A system is currently in place to present research results at scientific meetings and publish in peer review journals.

20. What information should be included in this review?

See response above.

21. Are there any additional challenges to the conduct of emergency research that have not been identified in the preceding questions? If so, what are they and how should they be addressed?

Please see discussion in the main body of this document.