

# Food and Drug Administration Public Hearing on the Conduct of Emergency Clinical Research: Testimony of Pediatric Emergency Care Applied Research Network

James M. Chamberlain, MD, Tasmeen Singh, MPH, Jill M. Baren, MD, MBE, Ronald F. Maio, DO, MS

**E**mergency 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 was organized in 2001 with the goal of conducting high-quality, scientifically rigorous research in pediatric emergency care. We are currently involved in a study that will utilize the exception from informed consent (EFIC).

We applaud the Food and Drug Administration in publishing the July 2006 guidance document and providing the opportunity for public comment. The guidance document provides greater clarity to the process of obtaining an EFIC under 21 CFR 50.24. We thank the Food and Drug Administration for an opportunity to comment on those portions of the guidance document where we believe further clarity or change is needed.

First, we agree with comments from our colleagues from the Neurological Emergencies Treatment Trials and the Resuscitation Outcomes Research networks and will not repeat their cogent arguments contained in their submitted abstracts. We will instead focus on areas that have not been addressed or require pediatric input.

## ETHICAL FRAMEWORK FOR THE EFIC

Neither the regulation itself nor the 2006 guidance document recognizes the personal loss of autonomy that is inherent in every emergency encounter. While the research community has begun to understand the concept of “incremental risk” (i.e., 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” (i.e., 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 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

---

From the Department of Emergency Medicine (JMC), Children’s National Medical Center (TS), Washington, DC; Department of Emergency Medicine and Pediatrics, University of Pennsylvania School of Medicine (JMB), Philadelphia, PA; and Department of Emergency Medicine and Office of Human Research Compliance Review, University of Michigan (RFM), Ann Arbor, MI. Dr. Chamberlain is principal investigator and Mr. Singh is project coordinator for the Pediatric Off-Patent Drug Study. Contact for correspondence and reprints: Ronald F. Maio, DO, MS; e-mail: [ronmaio@umich.edu](mailto:ronmaio@umich.edu).

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, deserves 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 document 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 with 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 with 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 document 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 bidirectional 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 document does not provide institutional review boards with input on what to do with negative community input. Although the spirit of the guidance document suggests that institutional review boards 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 document 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, because 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 Food and Drug Administration 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 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.