

For Docket No. 1978N-0065

Contact Information

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Re: Conduct of Emergency Clinical Research, Draft Guidance

Dear Members of the FDA,

Thank you for the opportunity to comment on the recently published Draft Guidance for application of the Exception from Informed Consent regulations.

I attended the public meeting in Rockville, and while I think that the speakers thoroughly addressed many of the questions posed by the FDA, I would like to respond to question #4, “Are there challenges that have not been explicitly addressed in the regulation in designing scientifically rigorous and ethically sound emergency research protocols?”

I believe that the application of the regulations to emergency research conducted in the *inpatient setting* needs to be briefly addressed in the final guidance. An example of the type of inpatient research that I believe would be covered under 21 CFR 50.24 is the trial (conducted in Brazil) comparing low to high dose epinephrine as rescue therapy in children with cardiac arrest refractory to initial low dose epinephrine.¹ Many other potentially life-saving therapies may be best evaluated in the inpatient setting, including therapies for cardiac arrest, cardiac dysrhythmias, and acute respiratory failure, among others. I fear that without specific guidance in this area, IRBs will hesitate to approve research with an exception from informed consent in the inpatient setting. Further, such guidance will be helpful to investigators conducting inpatient emergency research.

With the support of a K award from the NIH, I have spent the last several years studying the practical aspects of applying the exception from informed consent regulations to inpatient research, specifically, research in the pediatric intensive care unit setting. Research I have conducted with others shows that parents, ICU nurses, and physicians all agree that obtaining meaningful prospective informed consent for inpatient resuscitation research is not plausible. Barriers to seeking informed consent for an ongoing trial from all patients/families admitted to an ICU include the burden on families, the small number of patients who would go on to be eligible for study participation, and concern that consent obtained before a patient developed an emergency condition would not be properly considered by families.²

Emergency research in the ICU setting offers opportunities and challenges that differ from those encountered when conducting research in the pre-hospital or emergency room setting. I believe that the FDA guidance should address the following points.

1. *The appropriate community with which to consult is largely contained within the hospital itself.*

In a survey of 91 parents of pediatric ICU patients, parents unanimously identified other parents of pediatric ICU patients as the most important group with whom to consult regarding inpatient emergency research with an exception from informed consent. Seventy-five of 91 (82%) felt that other parents represented the entire relevant community, with other suggestions including parents of healthy children, clergy, and parents of children with heart disease.³

I suggest that the guidance recommend focusing the community consultation process for inpatient resuscitation research on patients and families who have been or are in an intensive care unit. This group represents the community in which the research will take place and the community from which the research subjects will be drawn. Investigators may also choose to involve the greater geographic community, focusing on at-risk populations, e.g. support groups for individuals with conditions that put them at risk for requiring intensive care.

2. *Opt-out mechanisms can and should be maximized in the inpatient setting.*

While it is not possible to obtain meaningful informed consent from all patients admitted to an intensive care unit, it may be very possible to inform virtually all patients/families that a research study is ongoing and to provide a real opportunity to opt-out. For example, notices (posters) can be prominently displayed announcing the ongoing research, providing a *brief* description of the research, and indicating where more information can be obtained. Supplementing these posters with brochures distributed to all patients/families would go a long way to ensuring that patients or their families have the opportunity to learn as much as they like about a study prospectively, and to opt-out of participation if they so choose. Our research indicates that a concise, “bulleted” format is received more favorably by families than a prose description of the proposed study.

Thank you again for seeking input from the emergency research community as you develop this important document.

Sincerely,

Marilyn Morris, MD

References

1. Perondi M, Reis A, Paiva E, Nadkarni V, Berg R. A Comparison of High-Dose and Standard-Dose Epinephrine in Children with Cardiac Arrest. *NEJM* 2004;350(17):1722-30.
2. Morris M, Nadkarni V, Helfaer M, Nelson R. Exception from informed consent for pediatric resuscitation research: Community Consultation for a Trial of Brain Cooling After In-Hospital Cardiac Arrest. *Pediatrics* 2004;114(3):776-81.
3. Morris M, Fischbach R, Nelson R, Schleien C. A paradigm for inpatient resuscitation research with an exception from informed consent. *Crit Care Med* 2006;34(3):2567-75.