

## Oregon Health & Science University Response to FDA Draft Guidance on Emergency Research with an Exception to Informed Consent

Research in the critically ill is ethically challenging. Researchers, Institutional Review Boards (IRBs), and sponsors must balance human subject protection with the compelling need to improve on existing therapies using the best scientific methods. One important area of significant clinical need is in the treatment of out-of-hospital sudden cardiac death when heart rhythm disorders may suddenly take the life of a patient who would otherwise live for many more years. Sudden cardiac death still kills hundreds of thousands of Americans each year<sup>1</sup> and the survival rate for out-of-hospital cardiac arrest remains low, about 5% nationally.<sup>2</sup>

Despite this pressing need, in the United States (U.S.) there has been a decrease in the number of resuscitation research trials being conducted over the last 20 years.<sup>3</sup> More telling is the observation that the number of sudden cardiac death treatment trials in Europe has significantly increased as compared to the U.S., particularly after 1993 when the U.S. temporarily suspended resuscitation research done without consent and Europe continued to allow it.<sup>3</sup> This disparity has occurred despite the FDA final rule being developed in 1996 to help with this ethically challenging research. Most of the standard therapies used to treat sudden cardiac death have never been tested to prove efficacy and little research and development has recently been done to determine if new therapies are superior. This is a research question that simply cannot be answered without human clinical trials in the out-of-hospital setting where informed consent is impossible.

We represent the Oregon Health & Science University IRB, a team of resuscitation researchers, and associated ethicists. Our group has participated in the Public Access to Defibrillation Trial, a protocol that implemented the emergency exception to informed consent. OHSU is also a site for the Resuscitation Outcomes Consortium (ROC) and in that capacity will be continuing to review and conduct protocols under the emergency exception to informed consent. We, therefore, have had extensive experience with the regulations. We have had some successes and some struggles with interpretation of the regulations. We are pleased that you are soliciting public comments to improve and clarify the process via a new guidance

document. We all see this research as ethically challenging but essential to improve patient survival from acute life threatening injuries and illnesses.

Our experience thus far in applying the regulations has left us with some questions regarding adequate community consultation and public notification. We would like further guidance about what is acceptable community consultation. We believe that an effective tool for community consultation would be to develop an advisory board of community leaders that convenes regularly to discuss all types of human subjects research, including research using exception to consent. The panel would include broad ethnic and minority representation, invited from a variety of established community groups.

Would this be an appropriate means of community consultation? In our past experience we have had real concerns about the quality of our consultation because of the difficulty we have had getting community members to meetings. We have had trouble with attendance even after extensive advertisement. At our institution we have used random digit phone surveying. This was supplemented with discussion at already scheduled meetings of targeted groups such as ethnic minorities or populations mostly to be enrolled a particular study. Since the phone survey utilizes a random sampling method we think it has provided meaningful feedback for our IRB. At the same time, the targeted meetings attempt to obtain the range of opinions and seek to determine if there are particular communities with specific concerns. A recent review of the responses from these methods for a ROC trial found that there were some differences in response from the various methods of consultation. Further clarification regarding the acceptability of this method of consultation would be helpful.

The concept of community is not adequately defined in the current guidance. Our current practice is to assess the public by a random survey and target certain geographic, vulnerable and/or minority populations, however the IRB has no guidance on whether this approach covers “community” as the regulations intend. Communities can be defined in many ways and the current guidance implies that community means public. It would be helpful to have clarification regarding the term community as well as guidance regarding defining the community per study or whether community is a less dynamic term.

It should be recognized that complete community consensus on the merits and/or desirability of resuscitation research may not be possible. We have found that some citizens are opposed to any clinical research and some are opposed to any research without advanced full consent, despite the potential of a proposed study for public good. Regardless of the process for obtaining community feedback, it seems advisable that the FDA support the ability of the local IRB through the community consultation process to weigh the overall benefit versus risk of the research on behalf of the general public.

In requesting this responsibility, our reading of the regulations for community consultation indicates that the IRB members are not expected to provide proxy consent for the public. Rather, their role is to weigh the risk and benefits in light of the public good, of which the community consultation is one aspect of such an important assessment. We would like to see a statement that clarifies the expectations for the local IRB, specifically as it relates to the question of proxy consent for the public. This is a confusing issue for our IRB members as some believe they must provide “consent” for the subjects. Our interpretation of the regulations is that IRBs are charged with ensuring that the regulations have been followed and that the public good is enhanced, rather than to provide proxy consent on behalf of the public.

Another aspect of the regulations that we find challenging is the concept of risk. We have wondered if there should be some gradation of the regulations based on the risk to the subjects. Should there be varying degrees of community consultation and notification as judged by the potential risk to subjects? There is inherently more risk in trying a novel cardiac drug in patients experiencing cardiac shock than for example testing public access defibrillation (i.e., testing a delivery system of a proven intervention) in victims of sudden cardiac death. Should these circumstances be governed by the same regulations? It would be more helpful to the IRB to have approvable categories similar to the Children’s categories in 45 CFR 46 part D (404 – 407).

To date there has been some research done on the regulations.<sup>4-15</sup> Little is still known about the public’s view of the regulations. In evaluating the regulations we believe that more information about applications of the exception should be available. We also would like to see further research that focuses on the process of emergency exception to informed consent. Specifically, the IRBs need to be able to better understand the public’s views

on research under a waiver and if the willingness to allow for a waiver varies by level of risk or if it is absolute.

In our experience working with the regulations we believe it can be done successfully, but it is time consuming. We approach this from multiple perspectives and as a group we are committed to the work of resuscitation researchers and to the improvement in the treatment of patients in acute life threatening situations. We believe that the rules are evolving and we welcome the guidance document as part of the evolution.

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