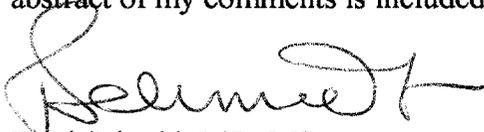


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Division of Dockets Management (HFA-305)
Docket Number 2006D-0331
Emergency Research
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville MD 20850

I would like to make public comment at the hearing scheduled for October 11th Docket number 2006D-0331 on the topic of Exception from Informed Consent in Emergency Research. An abstract of my comments is included and I plan to address questions 1,5 and 18 in particular.



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Thank you for convening this important meeting and working to develop the draft guidance related to FDA's Rule on the Exception from Informed Consent Requirements for Emergency Research. This meeting and discussion are important because the need to perform resuscitation research poses a true ethical dilemma. I will comment from the point of view of both a resuscitation researcher and an ethicist. As a resuscitation researcher, I have worked closely with several IRBs in the Portland metropolitan area to implement studies according to the FDA's Rule. Our investigative group participated in one completed multicenter study implementing requirements of the Rule (i.e., the NIH-sponsored Public Access to Defibrillation [PAD] trial) and the group is completing IRB requirements for several studies in accordance with the Rule as part of the NIH-sponsored Resuscitation Outcomes Consortium (ROC). As an ethicist I have conducted several studies related to the Rule. Much of what follows is based on the empirical research that my colleagues and I have conducted on the Rule.

An ethical dilemma exists when two important ethical interests appear to be in conflict. In this case, the need to develop treatments for certain acute medical conditions competes with our core ethical principal of obtaining informed consent before enrolling any person in a clinical trial. On the one hand, respect for autonomy would suggest that studies should not enroll subjects without their consent. However, when patients are not able to give consent because of their acute medical condition other principles including beneficence apply. As one example, it is estimated that between 250,000 - 450,000 Americans over the age of 35 die from sudden cardiac death annually.¹ Despite advances in healthcare, there has been little improvement in survival from out-of-hospital cardiac arrest (OOHCA), which is estimated to be 5% nationally.² In fact, the proportion of cardiac deaths attributable to OOHCA increased by 23.5% between 1989 and 1998.¹ Thus, well-designed studies testing new treatment interventions in cardiac arrest are critical. For treatments to be effective, they must be administered early.^{3,4} This often makes it impossible to obtain informed consent from the patients before enrolling them in studies of new, potentially beneficial treatments. Legally authorized representatives are not commonly available at the scene and when they are, the emotional nature of the situation and the imperative to treat immediately often make obtaining consent from these surrogates impossible.⁵

This dilemma can be summarized as follows; "[c]onsent of human subjects for participation in research requires that they fully understand their role and risk, not be coerced, and be allowed to withdraw at any time without penalty. In an emergency situation, informed consent is not always possible but the need for good research data is very high. Here is the ethical difficulty, and a real conflict of values: a population that might ultimately benefit from research cannot consent to the research and are thus excluded from the potential for therapeutic advances. Patients at high risk of morbidity or death, with cardiac arrest, shock, head injury, or altered mental status, are evidently

incapable of providing an adequate consent, but nevertheless are often in the greatest need of innovative therapy and might be willing to assume some risk for potential benefit.”⁶

While studies using these rules have the potential to find new treatments that may save lives, the burdens and risks of these studies fall to the subjects enrolled in the studies. Thus, it is appropriate that special care be taken to protect these vulnerable subjects.

In 1996, the Final Rule, 21CFR50.24, required two safeguards to protect human subjects: community consultation and public disclosure. Since that time researchers, IRBs and the public have all had an interest in the implementation of the rules.

Researchers have raised concerns that these regulatory requirements hinder their ability to perform resuscitation research and IRBs have struggled to interpret them. At the same time, there is also little known about subjects’ actual experience in these studies and whether they are adequately protected.

From the researchers’ perspective, although challenging, a number of studies have successfully used exception to informed consent.⁷⁻¹³ However, a recent study suggests that the new rules may be limiting the ability of United States researchers to perform resuscitation research. Nichol and colleagues found a decrease in cardiac arrest trials in the past decade and suggest that this may be due to the regulations.¹⁴ Researchers report that complying with the rules is complex. For example, the Public Access to Defibrillation Trial (PAD Trial) found that the study was reviewed by a total of 101 IRBs and median interval from submission to approval was 108 days.¹⁵ Another study found that the disclosure process required in excess of 80 hours of investigator time.¹⁶ Another found that the process leading to waiver added \$5600 to a study that was terminated after 4 persons were enrolled.⁷

A recent survey of United States medical school IRBs found that a significant number of IRBs at medical schools have reviewed at least one study under the Final Rule and that the more funding a site receives from NIH, the more likely it is to have reviewed a study.¹⁷ Of particular note to the current discussion is a recent study we completed interviewing IRB members about their experience with applying the rules.¹⁸ We found that emergency exception to consent studies take a long time to review and community consultation and public notification provisions are hard to interpret, but that if the guidelines are followed, IRB members believe that human subjects are protected. We also just completed a survey of the Chairs of the IRBs at all United States allopathic medical schools.¹⁹ We found that 46% of respondents had reviewed studies under the rules and 42% of those had rejected at least one study. The most common reasons for rejection were that there were concerns for the study design and that the study did not meet the criteria for exception to consent. Most of the respondents (68%) felt adequately trained to review these studies and 70% thought the rules adequately protect subjects. Only 27% thought the rules created excessive barriers to research. However, most pertinent to this meeting, 63% thought the rules did not give enough guidance.

A study of sixteen IRBs from the institutions participating in a multicenter trial found variability in several areas. One IRB waived the requirement for informed consent, five IRBs permitted telephone consent, and three IRBs allowed prisoners to be enrolled.²⁰ Because multi-center trials require the approval of so many IRBs, some have suggested the establishment of a central IRB.²¹ Such an IRB could be composed of ethicists with expertise in the regulations surrounding exemption from informed consent research, resuscitation researchers and a diverse spectrum of community representatives. However, most IRB chairs do not support such a centralized IRB. In our study, only 6% endorsed the idea of a national IRB for these studies.¹⁹

Little is known about public perception in this area. However, surveys of public willingness to be involved in research without consent has shown that willingness depended on income and the perceived risk of harm. These studies also found many respondents had concerns about studies performed without consent, but most subjects would personally be willing to be enrolled in such a study.²²⁻²⁴ No studies to date have evaluated the experience of subjects that have been enrolled in a study using exception to informed consent. We do not know whether or not these subjects believe that the process protected their rights. Such studies may help determine better means of community consultation notification.

With that introduction, I will specifically comment on several questions that you have posed.

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

When asked this question, the majority (70%) of Chairs of IRBs around the country stated that the criteria provide sufficient protection.¹⁹ Of course, this means that nearly a third of those that responded were less confident that the rules provide adequate protections.

The *Academic Emergency Medicine Consensus Conference on Ethical Conduct of Resuscitation Research* was convened in New York City in May of 2005.²⁵ The objectives of this conference were to provide an overview of the current status of the regulations in order to increase understanding of how the rules are currently and to explore areas of consensus on issues important to subjects, researchers, and regulators surrounding these regulations. Approximately 80 individuals representing 49 organizations participated in the day-long conference. Participants included resuscitation researchers, ethicists, and members of the regulatory community. The participants of one of the breakout sessions discussed the issues surrounding subject protection and advanced the following recommendations²⁶:

1. There are no outcome measures that define "protection"; therefore, it is not currently known whether or not subjects are protected under the current rules.
2. Care must be taken to protect not only the individual from harm during research but also to protect society from unregulated research in other countries and an inability to appropriately advance medical knowledge.

3. Some surrogate markers/methods of protection whose efficacies are debatable include data safety monitoring board activity, the community consultation and public notification (CC/PN) process, and institutional review board approval.
4. Minimal-risk studies should be held to different standards of protection than those that involve more significant risk to the subject.
5. A handful of studies have been published regarding community consultation and notification, and the majority are case studies. Those that are specifically designed to discover the most successful methods are hindered by a lack of formal outcomes measures and tend to have negative results.
6. Follow-up data from the CC/PN process should be disclosed to the Food and Drug Administration and incorporated into study designs.
7. Focus groups and/or random-digit dialing have been suggested as promising methods for fulfilling the CC/PN requirements.
8. Studies need to be funded and performed that formally investigate the best means of CC/PN.
9. More funding for this research should be a priority in the emergency medicine and critical care communities. More data regarding terminated studies should be made available to the research community.
10. Quantifiable markers of success for CC/PN must be validated so that research may determine the most successful methods.
11. Data regarding subjects' and family members' experiences with exception from informed consent studies need to be obtained.

Other areas of consensus can be found in the proceedings from the meeting.²⁷ Attendees demonstrated consensus regarding the need to further refine the Final Rule. However, they agreed that current regulations provide adequate and appropriate protection to safeguard patients. There was general agreement that current efforts to safeguard human subjects are effective, but participants agreed that refinements to and standardization of the FDA Final Rule would facilitate resuscitation research and enhance patient safety.

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

And

Question 18: What type of venue would be best for this additional review and public discussion?

As noted above, published reports note that the Public Access to Defibrillation Trial (PAD Trial) found that the study was reviewed by a total of 101 IRBs and median interval from submission to approval was 108 days.¹⁵ Another study found that the disclosure process required in excess of 80 hours of investigator time.¹⁶ Another found that the process leading to waiver added \$5600 to a study that was terminated after 4 persons were enrolled.⁷

Current efforts at our institution and around the county have demonstrated that initiation of interventional studies as part of the Resuscitation Outcomes Consortium (ROC) are delayed 4 to 7 months by the process of community consultation. For the current ROC trial we have used multiple means of community consultation including a random access dialing phone survey, pre-existing meetings, specific meetings convened on this topic and a website. We are in the process of evaluating all these methods of community consultation, but are struck by the ineffectiveness of community meetings convened specifically on the research topic. Our participation rate has been very low despite multiple media efforts to encourage attendance. This is consistent with what the public tells us. Our survey of emergency department patients and visitors found that few would be interested in attending public meetings; most laypersons prefer mass media and other means of notification and feedback when perceived as relevant.²³

Based on our preliminary experiences, we believe that the convening of meetings to discuss a proposed study is not feasible and is a waste of resources. Community consultation can be done via a combination of other methods. Random digit dialing allows a general overview of a random sample of the public. This can and should be supplemented by presentation and discussion at already scheduled forums and public meetings targeting communities or citizen groups that may be most likely to be enrolled or might have particular concerns about a study. Thus, for example, one might target citizen groups with specific concerns about blood products when proposing a study that would use such a product. An open website also can be used to elicit opinion and comment.

Both the investigators at OHSU and the IRBs in this community find questions about the adequacy of the community consultation a vexing one. While supporting the concept, questions remain about how much consultation is enough consultation and the best response to negative comments. Certainly the goals should include reaching out to members of the community most likely to be impacted by the study in question and approaching diverse communities. In any consultative process one expects a vocal minority to be opposed to any study despite efforts to address community concerns. Questions remain about when that opposition raises to the level that should halt a study, when it should lead to modifications and when it is time to move forward with the study. IRBs and researchers would appreciate guidance in this area.

Summary

The FDA Rule surrounding exception to consent in emergency research needs to strike a balance assuring protection of human subjects and while allowing important research to move forward. The Rule has been in place since 1996 and there is now a body of experience with the Rule and limited empirical research on attitudes and experience with the Rule. This experience shows that community consultation may be a valuable method of protecting subjects, but its implementation has been difficult. IRBs continue to have questions about Rule application and interpretation. In general, the lay public has not shown an interest in attending public meetings and researchers express frustration about how to conduct the process in a timely and cost-effective manner, while protecting

subjects. Novel approaches to community consultation should be encouraged and guidelines that establish criteria for acceptance of the community consultation should be established.

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