RESEARCH ETHICS

A qualitative study of institutional review board members' experience reviewing research proposals using emergency exception from informed consent

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Background: Emergency exception to informed consent regulation was introduced to provide a venue to perform research on subjects in emergency situations before obtaining informed consent. For a study to proceed, institutional review boards (IRBs) need to determine if the regulations have been met.
Aim: To determine IRB members' experience reviewing research protocols using emergency exception to informed consent.
Methods: This qualitative research used semistructured telephone interviews of 10 selected IRB members from around the US in the fall of 2003. IRB members were chosen as little is known about their views of exception to consent, and part of their mandate is the protection of human subjects in research. Interview questions focused on the length of review process, ethical and legal considerations, training provided to IRB members on the regulations, and experience using community consultation and notification. Content analysis was performed on the transcripts of interviews. To ensure validity, data analysis was performed by individuals with varying backgrounds: three emergency physicians, an IRB member and a layperson.
Results: Respondents noted that: (1) emergency exception to informed consent studies require lengthy review; (2) community consultation and notification regulations are vague and hard to implement; (3) current regulations, if applied correctly, protect human subjects; (4) legal counsel is an important aspect of reviewing exception to informed-consent protocols; and (5) IRB members have had little or no formal training in these regulations, but are able to access materials needed to review such protocols.
Conclusions: This preliminary study suggests that IRB members find emergency exception to informed consent studies take longer to review than other protocols, and that community consultation and community notification are the most difficult aspect of the regulations with which to comply but that they adequately protect human subjects.

Use of human subjects in research advances current knowledge of treatment of diseases, but this research may pose risks to those who participate. Historical events, such as the Nazi medical experiments, have shaped current regulations governing human subject research. In these experiments, prisoners were subjected to inhumane experiments without their consent, and the physicians who carried out these experiments were ultimately put on trial. During the trial, expert witnesses provided a code of research ethics, now known as the Nuremberg Code, which established guidelines for the ethical conduct of medical research. The Code begins, ''The voluntary consent of the human subject is absolutely essential'', making informed consent the cornerstone of protection of human subjects. The Code further stipulates that human subject research should be based on preliminary animal studies, should be conducted by qualified medical researchers and should avoid mental suffering and exclude death or disabling injury.[1]

Even though the Nuremberg Code was developed in 1949, it was never codified into US law, and research involving subjects without their prior informed consent continued. The Tuskegee syphilis trial is a notable example. Until 1972, this trial withheld treatment of syphilis to African-American men without their knowledge or consent.[2] In 1964, with modifications in 1975 and 1983, the World Health Organization developed the Declaration of Helsinki. These research guidelines also addressed informed consent in research but allowed surrogate consent when the subject was unable to consent. In 1966, the National Institutes of Health (NIH) first established rules requiring review by an independent institutional review board (IRB) before approving federally-funded research.[3]

It was not until 1979 that the US Department of Health, Education and Welfare charged a National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research with articulating the basic ethical principles that should underlie the conduct of human subject research. In 1991, the Office of Science and Technology Policy, Executive Office of the President used the proceedings of this Commission, known as the Belmont Report, to draft and adopt a Federal Policy for the protection of human subjects, known as the Common Rule (45CFR46). The Belmont Report is still the touchstone of human subject research ethics, resting upon the foundation of the guiding ethical principles of justice, respect for autonomy, beneficence and non-maleficence. In all, 16 federal departments and agencies adopted the Common Rule, the regulatory policy governing human subject research funded by those agencies. The US Food and Drug Administration (FDA) agreed with the content of the Common Rule, but did not adopt it, preferring instead to make some selected changes and adopt a similar but separate set of regulatory guidance.

The Common Rule established three main protective measures: review of research by an IRB, informed consent of subjects and institutional assurances of compliance. Vulnerable populations including people with impaired decision making, prisoners, children and pregnant women were addressed

Abbreviations: ARENA, Applied Research Ethics National Association; FDA, Food and Drug Administration; IRB, institutional review board

separately in the Common Rule.[3] However, no provision was made for those subjects who are unable to consent due to their acute medical condition. Because of this, in 1991, the federal government halted all resuscitation research, recognising the ethical challenge of obtaining informed consent in this population. However, they did note that this research is vital because no effective treatments exist for a number of life-threatening conditions. To help answer some of these important acute-care medical questions, in November 1996, the US FDA and the Department of Health and Human Services developed a set of regulations allowing exception from informed consent under certain circumstances, commonly called the Final Rule.

These regulations require that the research subject be in a situation that is acutely life threatening, for which currently available treatments are untested or believed to be unsatisfactory. In addition, the potential subject must be unable to provide informed consent because of the acute clinical condition, without time to contact the legally authorised representative (as defined by the individual state in which the research is being conducted) to obtain prospective consent. Further, the possibility must exist that the subject will directly benefit from participation in the study and there needs to be no known potential harm to the subject. Finally, the regulations require community buy-in for proposed research, in the form of community consultation and public notification. A summary of one institution's steps to getting approval of an emergency exception in informed consent can be found at http://www.ohsu.edu/research/rda/irb/docs/procedures/padstudy.pdf.

In May 2005, the Society of Academic Emergency Medicine convened a consensus conference to evaluate the state of the Final Rule in the US. Several themes developed during this daylong conference of 80 participants. One theme was the need for resuscitation researchers to participate in IRB reviews when determining clinical equipoise. Another theme related to the definition of the community. Many of the participants were concerned that the community in need of consultation and public notification is difficult to define. The majority of the participants agreed that working through these issues is extremely important, as many of our current resuscitation treatments are probably inadequate.[4–10]

The US is not the only country addressing this complex ethical issue. In Europe, resuscitation research had been conducted based on the concept of implied consent, assuming that a subject would want a treatment that had potential for benefit and needed to be studied for the greater good. In fact, there was a significant increase in the number of cardiac arrest trials in Europe as compared to the US after 1993 when the US temporarily suspended resuscitation research performed without consent and Europe continued to allow it.[11] This may be changing as the European Union has adopted new guidelines to govern medical research. One of the requirements will be to obtain informed consent from the legal representative before including a subject not capable of providing informed consent for himself or herself in a clinical trial. This could significantly change how resuscitation research is performed in Europe.[12]

Ultimately, the final decision to approve any given research protocol in the US is dependent upon the individual institution's IRB. Little is known about the experience IRB members have had reviewing such protocols since the implementation of the Final Rule. Some studies have evaluated subject's perception of exception to consent research but to our knowledge, there are no studies addressing the unique opinion of those asked to review these protocols.[13] We sought to determine IRB members' experience applying the emergency exception to informed consent protocols. We hypothesised that emergency exception to informed consent protocols require lengthy review, are ethically challenging for IRB members and create barriers to resuscitation research.

METHODS

Study design

This study was approved by the IRB of Oregon Health & Science University, Portland, Oregon, USA. We conducted a qualitative study using semistructured telephone interviews to examine IRB members' perceptions regarding exception from informed consent in resuscitation research. Qualitative methods are well suited to examine complex phenomena and to understand multiple viewpoints,[14] and these methods have been used increasingly in healthcare research, including emergency medicine.[15–17]

Study setting and population

The population of interest for this study included members of IRBs at institutions conducting research in the US, represented by the membership in Applied Research Ethics National Association (ARENA), the sole professional society for IRB members in the US. Respondents were purposely selected to represent different regions of the country, IRBs at both academic and non-academic centres, IRB members, IRB chairs and both genders, in order to include the full range of IRB members' perspectives and experiences.[18]

Study protocol

Using the ARENA membership list, we selected at random 20 IRB members from each of the six geographical regions: northeast, midatlantic, south, midwest, southwest/mountain and west. Invitations to participate in the study were sent by electronic mail to these 120 individuals. Of the 40 who responded, we selected 10 who represented the diverse backgrounds and experiences of IRB membership, and were willing to do a phone interview. The survey instrument was developed by the authors, including our institution's IRB chair (GC), to explore what we expected would be difficult aspects of the regulations, including the length of the review process, training, ethical and legal considerations, and experience using community notification and consultation. The instrument was pilot tested with the help of one of the authors (GC). Data collection was accomplished through semistructured telephone interviews conducted by a single investigator (KBM) and transcribed verbatim. Open-ended questions and a semistructured format allowed for subject and interviewer to adequately explore subject perceptions, experiences and beliefs. Data collection was conducted in two rounds to enhance internal validity through iterative data collection and analysis.

Content analysis was performed by a multidisciplinary team through systematic examination and re-examination of interview transcripts to identify themes and patterns in the subject responses.[14 18] Analysis was conducted by readers of varying backgrounds to enhance internal validity. The interviews were reviewed by two emergency physicians, an emergency physician/resuscitation researcher, an IRB member and a layperson. Data collection and analysis was conducted in an iterative fashion. Eight interviews were completed and their transcripts analysed to develop an initial set of themes, then two further interviews were conducted to identify any additional themes. The process stopped when saturation was achieved and no further themes emerged.

RESULTS

We interviewed 10 IRB members from around the US; 7 men and 3 women (identified as respondents R1–R10). These IRB members represented IRBs in both academic and non-academic departments and from the southern, Midwest, northeast and

western regions of the country. We purposely surveyed both IRB members, and IRB chairs, as well as individuals with and without medical degrees. Five major ideas emerged[1]: the length of review process,[2] the clarity of the Final Rule,[3] training in application of the Final Rule,[4] protection afforded to research subjects and[5] legal ramifications.

The first finding was that emergency exception to informed consent studies take IRBs longer to review than other studies. All of the respondents agreed with this and commented in some fashion. Specific comments included:

> Yes, they do take longer to review than usual. (R3)
> It was primarily because of setting up the community review process and that just seemed like a handful. (R6)

Secondly, our survey was designed to determine what part of the regulations are the most challenging and probably the most time consuming for the IRBs. The community consultation and notification aspect of the regulations emerged as the issue most concerning to our survey respondents. The second common opinion was that the community consultation and notification requirement of the regulations is vague and hard to implement. Reflecting this, respondents commented:

> [Researchers] have all decided it is easier to change their plan than to [have to undergo community notification and consultation]. (R10)
> It just seemed like the regulations themselves are kind of vague[…] We're thinking of better ways of notifying the community as we go along. (R6)

We had one IRB member report that their IRB was uncomfortable informing the community because of how the institution might be viewed:

> Historically we have been skittish, I guess, about the community perception of our hospital as a major research institution. (R7)

The third area of the study was the amount of training IRB members have had in interpreting the Final Rule and applying it to their protocols. Most respondents reported that the IRB members have had no formal training, but are able to access materials needed to review these protocols. Members had the following to say:

> No specific training[…]when we have one of these come up[…] we print the[…]guidelines and distribute it to the board. (R1)
> They have to go to at least one national or regional meeting per year[…] I will tell you that we did not have any specific training for emergency use protocols. (R4)

Consistently, these IRB members told us that although they had no formal training in reviewing exemption from consent studies, they believed that they were able to access instructive materials as needed. The majority denied needing more training and thought that the current system of looking up information ad hoc is effective.

The fourth area of agreement related to the protection of human subjects. The IRB members we interviewed believe that the current regulations, if applied correctly, do protect human subjects. IRB members felt comfortable with human subjects' protection if the regulations were followed adequately. To further elucidate this point,

> I think the pendulum is probably more toward protection human subjects than making it easier for researchers. (R7)
> [F]rom everything I can see there are adequate protections, but to tell you the honest truth, I don't think we've done enough of this to know. (R1)

Fifth and finally, during our interviews, the legal aspects of the review process were noted by our interviewees. This was an area that was not originally addressed in our survey, but interviewees noted and began to spontaneously mention. We found that respondents believe that legal counsel is an important aspect of reviewing emergency exception to informed consent protocols.

> We also had an attorney…speak to each of the IRBs about her take on all this[…] All that [legal review] said we were able to feel comfortable that state law did not preclude the research from proceeding. (R9)
> [When] we reviewed one of these,[…]it required extensive review and we actually had subcommittees to meet with the investigators and to pull in the lawyers. We have lawyers on the IRB but we had extra meetings [with them…E]ven lawyers that were not normally members of the IRB were called in as consultants. (R8)

DISCUSSION

How do we advance our understanding of resuscitation medicine while honouring the rights of human subjects? A recent study suggests that the number of studies on cardiac arrests undertaken in the US has declined in the past decade, and the regulatory requirements of the Final Rule may be one of the reasons.[19] Paediatric researchers report that since the implementation of the Final Rule, no randomised controlled trials using it have been performed on children.[20 21] On the other hand, several studies on adults have already successfully been carried out under the emergency exception to informed consent regulations.[22–28] Although the current rules are used more and more often to perform resuscitation research, protection of human subjects still remains the responsibility of every researcher and a primary purpose of the IRB. The experiences and beliefs of IRB members is one of the ways to increase understanding of the effectiveness of these rules.

Since implementation of the Final Rule in 1996, reports have described the experience of researchers invoking the regulations.[22 23 25 27] There has also been work done determining public attitudes toward research without consent.[13 29] However, until our study, feedback from the IRBs reviewing these protocols has been missing. We know that IRBs are being asked to review emergency exception to informed consent protocols. In a recent survey, 80% of 122 university IRBs surveyed had reviewed such a protocol.[30] Our study describes the experience of IRBs in attempting to protect subjects when consent is not possible, using qualitative research techniques to determine the attitudes and experiences of the very people being asked to review such studies. The qualitative approach allowed us to have an open dialogue with IRB members and therefore, learn more about what issues they are facing when reviewing these protocols.

Because subjects are unable to provide informed consent, the Final Rule mandates community consultation and community notification as safeguards, yet does not delineate how these are to take place. Together, IRBs and researchers are struggling to develop the best methods of using these safeguards. In our discussions, we heard that this is one of the most challenging aspects of the regulations.

Community notification requires that researchers inform the community that a study will be occurring in a one-way communication. Notification can take many forms, such as newspaper, radio, television advertisements, fliers and other one-way communications. In our previous work, we found that the public would most likely rely on the media for distribution of information,[13] though this is an expensive means of communicating with the public and does not allow for a two-way communication between researchers and the public. In addition, it may not be effective. In our previous work, we also found that only 5% our study population knew of ongoing studies in their community involving emergency exception to informed consent.[13]

Community consultation is designed to allow members of the public to provide comment on the study advising the IRB of concerns. As we found with our IRB members, many researchers have found it difficult to engage the community in this activity. Recently, Shah and Sugarman[31] reviewed the community consultation and notification process of four studies using emergency exception to informed consent. They found that community consultation was not directed at general and <15 participants would typically show up at meetings. To date, it is unclear which strategies are effective for complying with the community notification and community consultation requirements, making it difficult for IRBs to guide researchers. Dix *et al*[32] have recommend standardising the process of community consultation and notification to make the process more streamlined. This would seem to help the IRB members with the vagueness of the regulations.

Another proposed solution to the difficulty in reviewing emergency exception to informed consent protocols is to have a national IRB that reviews all protocols that seek an emergency exception to informed consent.[33] Such a national IRB would have the advantage of being specifically educated and experienced in reviewing these protocols. It has been noted that education on research ethics is haphazard at best.[34] Although this may be true, our respondents believed that they were able to access the information if they needed it, even though they had little formal training. A dedicated IRB might provide more consistent training but this was not a major concern for our respondents. A national IRB could have a mandated resuscitation researcher member, to ensure that the special circumstances involved in resuscitation research are addressed. The major drawback of this approach is that it might not be able to take the unique characteristics of each community into consideration. Certain populations, such as African-Americans, may need special considerations given negative, past experiences with medical research.[35] Therefore, each community may have different needs when reviewing emergency exception to informed consent protocols.

We also found that IRBs have legal concerns about these protocols. Several respondents noted the importance of having legal counsel available when reviewing these protocols. This may partially be explained by the fact that the regulations are relatively new and untested. To our knowledge, there have been no legal cases challenging the use of these regulations to perform studies. However, at least one respondent was concerned about public perception of an institution performing research without consent. One study being performed in the US using exception to informed consent, The PolyHeme Trial has received negative publicity and at least one Senator has raised concerns about that study and the US FDA's oversight of it.

Despite these concerns, one thing is clear in talking with IRB members from around the country. Although they may be struggling with some of the particular aspects of the regulations, they do not believe that the Final Rule violates human subjects' rights. Overall, they believe that the Final Rule meets its goal of protecting subjects.

LIMITATIONS

The nature of qualitative research lends itself to some strengths and some limitations. The qualitative interviews provide rich detail and allow exploration of ideas, which were not originally expected by the researchers. For example, we did not realise until after our initial reviews that legal issues and public perception would be a major concern for our respondents and may be one of the reasons that reviewing these protocols is difficult.

By contrast, we were only able to interview IRB members who responded to our email and were willing to participate in a phone interview. Specifically, it is possible that IRB members, who were more familiar with the rules were more willing to participate in an interview to minimise this by having multiple reviewers of the data with varying backgrounds. Our sample size is small but we had saturation of our data, implying that further interviews would have produced similar results. Of course, the views of the IRB members cannot be extrapolated to resuscitation researchers or society as a whole.

The primary question asked about the Final Rule is whether or not it adequately protects subjects while allowing important resuscitation research to occur. This study elicited the views of IRB members on this question and found that IRB members believe that subjects are indeed protected. As it is the task of the IRB to protect subjects, they probably have a bias toward reporting that they indeed do so.

CONCLUSIONS

From this study, we are able to conclude that IRB members found that emergency exception to informed-consent protocols take longer to review than other protocols and that the most difficult part of the review process is implementing and assuring appropriate community consultation and community notifications. Most IRB members have had no formal training, but are able to access reference materials as needed. Legal counsel also proved to be important for IRB members when reviewing emergency exception to informed-consent protocols. IRB members view the regulations as providing sufficient protection of human subjects if followed correctly. It is not clear from this study what the cost is, to researchers and the community at large, to conduct an emergency exception to informed consent study. We believe, based on our findings, that the community notification and community consultation requirements of the emergency exception to informed consent regulations should be clarified in order for IRBs to facilitate resuscitation research.

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