Regulatory Challenges for the Resuscitation Outcomes Consortium

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Resuscitation research is challenging but vital because few effective therapies exist for a number of life-threatening conditions. Cardiovascular disease has been a leading cause of death and morbidity in the United States. Although estimates vary, the American Heart Association estimates >150,000 out-of-hospital cardiac arrests each year in the United States,1 with little improvement in survival (≈5%) despite medical advances.2 Traumatic injury, resulting in severe hemorrhagic shock or traumatic brain injury, is the leading cause of death in persons 1 to 44 years of age and is a leading cause of morbidity.3 For treatments to be effective in these life-threatening situations, they must be administered immediately, usually at the site of the event.4 Consequently, researchers and regulatory agencies find that typical standards for informed consent cannot be applied in the emergency setting.

In 2004, the National Heart, Lung and Blood Institute organized the Resuscitation Outcomes Consortium (ROC) to conduct simultaneous prehospital studies of novel therapies for trauma and cardiac arrest. The consortium consists of 11 regional centers in the United States and Canada and a data coordinating center.

It was anticipated that these trials would require extra effort from a regulatory perspective because of the need to administer treatments during a relatively brief therapeutic window, making the standard practice of obtaining informed consent from the subjects before enrollment impossible. Because of the nature of the medical conditions being studied, the potential subjects would not be competent to consent. In addition, surrogate decision makers are not commonly available at the scene, and when they are, the emotional nature of the situation makes obtaining consent infeasible.5,6 These challenges are compounded in a trial involving multiple emergency medical services (EMS) systems and hospitals within each regional center. Finally, such trials may be logistically challenging because of the need to comply with multiple regulatory issues, including federal wide assurances (FWAs), institutional review boards (IRBs)/research ethics boards (REBs), and the Food and Drug Administration (FDA).

The first implemented ROC trial involves testing hypertonic fluid resuscitation in victims of life-threatening hemorrhagic shock or traumatic brain injury who are ≥15 years of age. The double-blind, randomized intervention, completed before hospital arrival, consists of the infusion of 250 mL normal saline (0.9%), hypertonic saline (7.5%), or hypertonic saline-dextran.

Before patients were enrolled in this trial, the regulatory issues above had to be satisfied. A survey was completed by each center regarding this process. The primary objective of this article is to describe the experience of the ROC centers with regulatory affairs in preparation for this trial and, on the basis of lessons learned, recommend future approaches.

The FWA

The FWA is a formal agreement of compliance between the Office for Human Research Protections, the federal body in the United States now charged with safeguarding human subject research, and an agency, hospital, or institution conducting or participating in human subject research. This assurance describes the procedures and principles under which the research will be conducted to protect the rights and welfare of human subjects. The challenges for the ROC were the sheer number of FWAs required and the fact that some entities had not participated in research previously and did not already have FWAs.

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ROC Approach

For the 11 ROC centers, 98 unique FWAs (1 to 13 per center) were required (Table 1), 56 for trauma centers and 56 for EMS agencies. Some hospital FWAs covered EMS agencies; some FWAs covered multiple EMS agencies. Five of the 11 ROC regional centers reported no major difficulties obtaining FWAs. Six centers reported major difficulties, including determining the IRB of record for EMS agencies (especially county EMS agencies), providing coverage for first responders, and establishing human subject administrators in hospitals without existing FWAs. Difficulties encountered with IRBs included a lack of familiarity with EMS, assuming responsibility for an agency outside their normal jurisdiction, and legal concerns. Furthermore, investigators had difficulty convincing administrators to take responsibility for the protection of human subjects in hospitals without existing FWAs. Providing adequate FWA coverage required restructuring the medical directorship of 2 EMS agencies and extensive education by the data coordinating center on the FWA application process.

Commentary

The responsibility of an FWA may have been daunting for an agency that had not previously conducted research. These difficulties were somewhat unexpected and contributed significantly to the time and resources needed to complete study preparation. More experience with multicenter, multihospital, and multi-EMS agency trials like ROC, along with increased communication between experienced centers and new centers, may help alleviate concerns for IRBs and administrators. Early engagement of the local medical community on all levels, from the EMS through receiving hospitals, is critical to timely acquisition of the FWA.

Informed Consent

Although prospective, informed consent is fundamental to the protection of human research subjects, there are circumstances when it is not possible. The Declaration of Helsinki allows legally authorized representatives (LARs) to consent for research when subjects are unable. Adopted in 1991, the Common Rule governing human subjects research funded by US federal agencies provided 3 main protective measures: review of research by an IRB, informed consent of subjects, and institutional assurances of compliance. For research involving greater than minimal risk, there was no provision for consent for potential subjects unable to consent because of their acute medical conditions with no LAR available or for situations too time sensitive to allow an informed consent discussion with the LAR.

After the Common Rule was adopted, the Office for the Protection From Research Risks (the federal agency that was, at that time, charged with enforcing the Common Rule) halted all resuscitation research in the United States in situations when there was no means of obtaining informed consent. In 1996, the US FDA and the Department of Health and Human Services developed the Final Rule to allow research to be...
performed without informed consent under limited circumstances (21 CFR 50.24). These federal regulations require that (1) the research subject is in a situation that is acutely life threatening, (2) currently available treatments are untested or believed to be unsatisfactory, (3) the potential subject must be unable to consent because of the acute clinical condition, (4) there must not be time within the proposed therapeutic window to contact the LAR to obtain prospective consent, and (5) the possibility must exist that the subject will directly benefit from participation in the study. The regulations mandated the following protective measures. First, community consultation, a 2-way process involving the investigators and community representatives, is designed to provide the IRB with community attitudes and cultural beliefs regarding the research. Second, public disclosure is a 1-way process that informs the potential study population about the study. Options for members of the community to opt out of a study with some type of identification such as a bracelet, although not federally mandated, may be required by the local IRB. Third is subject notification, whereby either the subject or the LAR is informed of the participation in the research and afforded the opportunity to discontinue further participation or to consent for further treatment or follow-up if required. Finally, a Data Safety and Monitoring Board monitors the study for subject safety. Implementation of the Final Rule is open to interpretation by local IRBs, leading to significant variability in requirements.

In Canada, similar regulations were developed for REBs as the TriCouncil Policy Statement (TCPS): Ethical Conduct for Research Involving Humans. The conduct of research in emergency situations with the exception from informed consent is guided by Article 2.8 of the TCPS, which includes criteria similar to those in the Final Rule (Table I of the online Data Supplement). Community consultation and public disclosure, however, are not required.

A recent survey of US medical school IRBs found that a significant number of IRBs have reviewed at least 1 study of exception from informed consent and that the more funding a site receives from the National Institutes of Health, the more likely it was to have reviewed such a study. However, some researchers have suggested that the Final Rule hinders important research. A recent study found a decrease in US cardiac arrest trials in the past decade. Pediatric researchers report that since implementation of the Final Rule, no randomized controlled trials using it have been completed on children, although some are in progress. In contrast, several Canadian researchers have successfully completed cardiac trials using their policy for exception from informed consent.

ROC Approach to IRBs/REBs

Recognizing the unique challenges for the consortium, the ROC established a Regulatory Committee to take a proactive approach to assisting local IRBs with the protocol review process. Before the first protocols were developed, the local principal investigators introduced their IRB leadership to the ROC mission. An introductory document was developed for distribution. A conference call with the ROC, National Institutes of Health, and local IRB leadership introduced the local IRBs to the ROC and established dialogue between the IRBs and ROC, as well as among local IRBs. The IRBs had an opportunity to share previous experiences with exception from consent trials.

Ten of the 11 regional centers reported previous experience implementing studies involving exception from informed consent for emergency research. Six IRBs had reviewed <5 such trials (1 had reviewed 0), and 4 had reviewed 5 to 10; 1 site did not track this information.

The 11 regional centers and the data coordinating center obtained approval from a total of 58 IRBs (range, 1 to 12 per center). The IRB of the principal investigator’s institution was classified as the primary IRB; the IRBs at other institutions were considered secondary. Before IRB submission, almost all centers had discussions with key local individuals to facilitate approval (online supplemental Table I), including a variety of university or medical center, EMS, and community leaders. One center used its public relations department to notify elected officials about the study to try to avoid the impact of changing administrations. The presubmission process took up to 18 months (median, 6 months) (Table 2). The US IRBs granted provisional approval pending completion of community consultation and public disclosure after a median of 2 months (range, 1 to 7 months). After provisional approval, the time to final IRB approval was 4 months (range, 3.5 to 13 months).

Six of the 11 regional centers addressed major issues with their primary IRB/REBs and 5 of 11 with their secondary IRB/REBs. These included requirements for increasing the number of community consultation meetings, the need for focus groups targeting minorities, the establishment of processes for subject/family notification, informed consent for continued participation in the trial after enrollment, access to hospital medical records, confidentiality/privacy issues, FWA coverage for hospitals and EMS agencies participating in the trial, and communication among multiple EMS agencies and hospitals. Sites generally were not allowed to begin enrollment until contracts and subcontracts had been finalized at secondary EMS agencies and hospitals.

Three regional centers reported that the IRB/REB process for ROC was “significantly harder” than usual; 1, a little harder than usual; 6, neither harder nor easier than usual; and 1, a little easier than usual. The IRB/REBs at the centers that reported no increased difficulty with IRB/REB approval for this study had previously reviewed at least 4 studies with the exception from informed consent, suggesting that such studies may become easier for IRB/REBs to review once they have more experience.

A unique aspect of the ROC study was the inclusion at some sites of individuals 15 to 17 years of age in a trial using exception from informed consent. For most studies, the consent process in the pediatric population requires informed consent from parents and assent of the minors. Because experience with using the rules for exception from consent with minors is very limited, some IRBs required inclusion of additional focus groups targeting children.

Commentary

Uncertainty in how to properly interpret and implement the Final Rule, the TCPS, and variable policies of IRBs/REBs
may be limiting resuscitation research because detailed interpretations have not been specifically stipulated in the current federal policies and best practices have not been disseminated.22–24 Some IRBs/REBs have developed their own requirements through intuition and experience, which may or may not reflect specific characteristics of the local community. The experience from the recent Public Access Defibrillation (PAD) trial25 demonstrates that the responses from the investigators and the community were generally positive, although the process was labor intensive.

In the ROC trial, the approval process at the center level likely was facilitated by the fact that the protocol underwent extensive multilevel review before it could be implemented. This included review at a national level by the National Heart, Lung and Blood Institute, an independent Protocol Review Committee, the Data Safety and Monitoring Board (national panels of resuscitation research experts), and the FDA. We believe that the groundwork laid by the early introduction of the ROC mission by the local principal investigators and the consortium-wide conference call with the IRB leadership was helpful.

Although all of the ROC sites obtained approval, the challenges encountered significantly increased the amount of work required to prepare for study implementation, making it difficult to estimate the resources that would be necessary. Delays in IRB/REB approval delayed protocol implementation. These delays occurred despite the fact that all but 1 site had prior experience implementing studies using exception from informed consent under emergency circumstances. Budgets and timelines for future studies should take this into account.

**ROC Approach to Community Consultation and Public Disclosure**

Although each ROC center was given latitude, all sites adhered to the following general guidelines: (1) Each center was required to meet local IRB directives for community consultation; (2) details of community consultation activities were documented and provided to the data coordinating center and the FDA; (3) each center used a minimum set of information points for presentation to targeted community groups; and (4) information was translated into common

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PTO indicates parent-teacher organization.
Community Consultation

Each regional center developed specific approaches for community consultation (Table 3). One approach was modeled after the traditional town hall meeting to which community members and IRB members were invited. The meetings involved presentations by the investigators and other study representatives, followed by a public discussion period. A written summary of attendee feedback was forwarded to the IRB. These forums drew very few participants (Table 3).

Other approaches to consultation targeted government groups; community organizations such as rotary clubs, parent-teacher associations, church groups, activity centers, and senior centers; or focus groups comprising persons who might have survived conditions similar to those in the ROC study (Table 3). These meetings tended to have more participants than the town hall type of forums.

Five centers sought an alternative to the public meeting approach by using a random-digit-dialing structured telephone survey of the population residing in the geographic catchment area. Even though community consultation was not required by Canadian regulations, it was requested by the FDA, and all Canadian regional centers performed a phone survey. These surveys were conducted by an independent organization experienced in the performance of such surveys that had no vested interest in the ROC. Questions were approved by the local IRB. Hundreds of surveys were completed. A detailed description of the experience with the telephone survey approach will be reported separately.

One IRB required that the center provide documentation of ongoing community consultation with each annual review, including a list of all the presentations given by the investigators to organizations. To help achieve this requirement, the investigators have added hypertonic saline study updates to their community consultation process for a concurrent cardiac arrest trial. One other site is required to document ongoing public disclosure.

Public Disclosure

Techniques for public disclosure included press releases with newspaper, radio, and television interviews; creation of websites; and paid advertisements (online supplemental Table III). One center sent an e-mail notification of the study to all members of a large university population.

Individual Opt Out

All US IRBs considered a process to allow individuals to opt out of the research before enrollment. An opt-out process, although not mandated by federal regulations, was required by IRBs at 3 regional centers and optionally provided at 5 other centers. Seven centers issued bracelets; 1 center issued a pocket card that would be recognized by EMS personnel. As of November 2007, 1079 (0 to 679 per regional center; median, 15) individuals have requested to opt out in the 11 regional centers covering ~24 million inhabitants (online supplemental Table III).

Commentary

Dickert and Sugarman have proposed that the ethical goals of community consultation include enhanced protection of subjects and communities by identifying risks, enhanced benefits to participants and the community, legitimacy by giving stakeholders opportunities to express their views, and shared responsibility between communities and the investigators. Early experiences with the exception from informed consent for emergency research raised concerns about the inability to refuse study participation, potential racial bias in study design, and ambiguity about how community consultation would affect the study.

Our study shows that the optimal approach to community consultation is evolving. Open public meetings sponsored by investigators are poorly attended, yield little effective consultation, yet consume study resources. In addition, it is not clear how well the attendees represent the broader community. Targeting specific community groups, if the groups are chosen appropriately vis-à-vis potential candidates for the intervention, may be more effective.

To the best of our knowledge, this ROC trial represents the first reported use of telephone surveys for community consultation for a multicenter trial. The telephone survey reaches a larger segment of the population for consultation, may be more representative of the population at risk, and may be better able to characterize responses by demographic characteristics. Additionally, it can be performed impartially. Although expensive (costs range from $10,000 to $20,000 per study per center), the survey could be completed and results available within a month of commissioning. The major limitation of such surveys as they were conducted is that they did not allow dialogue with the investigators. Further study of this approach is needed.

The public disclosure component of the Final Rule also deserves further discussion. The basic question of how much public awareness of the study is acceptable has not been addressed. Current approaches to community consultation and public disclosure may reach only a small segment of the population. In a recent trauma trial, only 8% of a convenience sample of potentially eligible subjects were aware of the study. During the PAD trial, only 5% of respondents at 1 site were aware of any studies using exception to consent occurring in their communities. More recently, a random-digit-dialing phone survey of the effectiveness of public disclosure found a 10% awareness level of an ongoing trial; understanding of the nature of the trial was poor. It has been clear that the current approaches do not necessarily inform potential subjects before enrollment, and it seems impractical to even consider this feasible. One consideration for increasing community penetration would be to consult marketing...
organizations. Although transparency about this sort of research is critical, policies regarding public disclosure should be sensitive to the limitations of feasible methods for such disclosures.

The process of obtaining IRB approval, including community consultation and public disclosure plan approval, might be facilitated by a national IRB that would set a standard for studies conducted under the exception from informed consent for research in the emergency setting. Because local IRBs would likely want to consider local factors in developing an optimal approach for their communities, a national IRB would create an additional layer of review. Unfortunately, many IRBs at the local level lack sufficient experience and expertise in research involving exception from informed consent. A recent survey of IRB chairpersons found that 25 of 52 had reviewed such a study, whereas 42 of 52 felt prepared to do so. Even if an institution had previous experience with exception from informed consent, many IRB members may not feel adequately trained to review these protocols.

A realistic alternative would be the development of regional, centralized IRBs. At a minimum, a community could agree on which local/regional IRB would be designated the primary IRB for approval and execution of community consultation and public disclosure plans, as well as local oversight and monitoring. Another alternative solution may be the creation of specialized community IRBs. These local IRBs would have special interest and expertise in trials in the emergency setting. For communities still gaining experience with these trials, the specialty IRB could draw from the expertise of a mentoring IRB. The IRBs might include respected community leaders, including politicians, clergy, and scientists. Local IRBs would provide input and retain responsibility for final approval of protocols but would delegate responsibility for establishing uniform policies and procedures for the local approval and conduct of trials requiring an exception from the requirement for informed consent to the regional or specialized IRB.

The FDA is interested in offering appropriate guidance and has recently hosted a public forum to discuss new guidance on the interpretation of the Final Rule. Ongoing dialogue between the FDA and resuscitation researchers is critical for the development of rational guidelines that protect subjects yet facilitate research. To determine whether community consultation is truly achieving its intended goals, more research is needed.

Notification of Subjects and LARs
The subject notification and consent process is a key requirement common to both the FDA’s Final Rule and the Canadian TCPS. The FDA’s Final Rule specifies that all clinical trial protocols must contain a plan to obtain and document consent for continued participation. Similarly, the TCPS requires notification of subjects or LARs. The Final Rule further stipulates that postenrollment attempts at notification must occur at the earliest feasible opportunity, left to the discretion of the individual IRBs. Attempts to notify LARs are required at US sites if feasible, as determined by the IRB and investigator, even if the subject has died. The Canadian TCPS does not explicitly require such notification.

ROC Approach
One center required that the notification occur by the next business day; another required notification within 48 hours of hospital admission. Some centers specifically indicated that any notification would depend on the availability of family and condition of the subject. Recognizing that some subjects enrolled in the study will have less critical injuries and may be discharged before subject or LAR notification is feasible, some centers specifically stated that, in this situation, a letter would be mailed informing and seeking consent from the subject or LAR for further participation in the study. One center further stated that a follow-up telephone call would be made to such subjects if no reply had been received.

For expired subjects, 6 centers responded that a letter would be sent in the mail to notify the family of the deceased family member’s enrollment in the study. The only center providing a time frame for notification of admitted subjects also stipulated that the letter of notification would be mailed to the family within 1 week of the subject’s death. Two centers responded that notification by mail would be sent as soon as feasible. The remaining centers gave no specific time frame in which the notification letter would be sent.

Additional consent for review of in-hospital medical records for subjects agreeing to continued participation was not required at 9 centers but was required at 1 center. One regional center had variable hospital-dependent requirements, although most of its hospitals do not require consent.

Commentary
If the subject or LAR refuses continued participation or if the subject dies, the ability of the investigator to obtain relevant study data from medical records varies from site to site. This potential lack of postintervention data can prevent the determination of the cause of an adverse event. Concern has been raised that variable access to medical records may bias sampling with respect to age, sex, functional status, ethnicity, or diagnoses (ie, sensitive diagnoses such as mental health, infectious disease, or trauma may be underrepresented). Although voluntary and informed consent from subjects or LARs is a fundamental requirement for research involving humans and their personal data, there may be specific circumstances under which an IRB or REB may grant a waiver or partial waiver of consent requirement for medical record review. In the United States, the requirements of the Health Insurance Portability and Accountability Act must be met. Both federal and individual state laws and regulations may impose additional restrictions on the use of protected health information for research. In Canada, confidentiality/privacy legislation is regulated locally through the provinces and territories, as well as the TCPS and CIHR Best Practices for Protecting Privacy in Health Research.

For future studies, we recommend that IRBs/REBs allow examination of appropriate medical records of subjects enrolled in clinical trials under the exception from informed consent at least up to the time that a subject or LAR declines further participation in the study. For most research in the
emergency setting, any exposure to physical risk based on experimental intervention will have already occurred. The risk of this exposure is justified because the intervention has the potential to benefit the individual subject and future patients. The best way to justify the risk is to assure that the information gathered regarding the intervention will be included in the study and that any adverse events were detected and documented.

Conclusions

The logistics of implementing large, multicenter trials using exception from the requirement to obtain informed consent under emergency circumstances present challenges, but they can be properly addressed with perseverance.

A number of obstacles need to be overcome to prevent stagnation in clinical resuscitation research. One of the major steps forward would be the development of novel models of IRB approval. Although establishment of a single, national IRB seems unlikely, establishing either special local/regional IRBs or a regional agreement for a primary IRB seems feasible and advantageous. Improving and coordinating communication between investigators and IRBs, as well as between IRBs, is vital in conducting prehospital research.

As resuscitation researchers and communities gain more experience with studies under the Final Rule, sharing the lessons learned and novel approaches with each other and federal agencies will be critical. One advantage of a consortium approach to resuscitation research, as represented by the ROC, is how the development and implementation of common research protocols promote communication and exchange of experiences between clinical sites. Such communication and cooperation will enable researchers to improve care of patient-subjects with immediately life-threatening cardiac and traumatic events with scientifically valid and ethically acceptable clinical trials.

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Disclosures

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