

Research Without Consent: Current Status, 2003

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In November 1996, regulations developed by the US Food and Drug Administration (FDA) and the Department of Health and Human Services (HHS) went into effect to allow certain emergency and resuscitation human subjects research to proceed without prospective informed consent. These new regulations brought harmonization to the requirements of the 2 federal agencies charged with research oversight and ended a moratorium that had essentially shut down resuscitation research for almost 4 years. However, the FDA's emergency exception from informed consent and the HHS's waiver of informed consent have been used infrequently. Many perceived obstacles to implementation of the regulations have been described, including the additional regulatory burden for investigators and institutional review boards, the extra expense and time required to adequately fulfill the regulatory requirements, and the reluctance of institutional review boards to allow these studies to move forward because of concerns about potential legal ramifications. Regardless of the arguments advanced, these regulations are essentially the only current regulatory options that have been provided for research without consent. This article presents a brief history of the development of the FDA's Final Rule, a summary of its requirements and its use so far, and suggestions for its implementation. Some strategies to allow the resuscitation research community to suggest fine tuning of the regulations are suggested in hopes that research requiring an exception from informed consent is allowed to proceed in a manner acceptable to regulators, is stringent in patient protection, and yet is sensitive to the practical aspects of performing resuscitation research.

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INTRODUCTION

In November 1996, new regulations developed by the Food and Drug Administration (FDA) and the Department of Health and Human Services (HHS)¹ went into effect to allow certain human subjects emergency and resuscitation research to proceed without prospective informed consent. The FDA regulations, known as the Final Rule, provided an exception to the requirement for informed consent and were the result of a multidisciplinary effort spearheaded by the specialty of emergency medicine in conjunction with the federal regulatory agencies.² The HHS regulations, which allow waiver of informed consent, were developed simultaneously and parallel to the FDA's Final Rule. These new regulations brought harmonization to the requirements of the 2 federal agencies charged with research oversight and ended a moratorium that had essentially shut down acute resuscitation research for almost 4 years.

The regulations for Exception from Informed Consent (the FDA's Final Rule) and for Waiver of Informed Consent (the HHS regulations) can be applied in narrowly prescribed circumstances and under very specific surveillance. Included in them are patient safeguards that have never before been required in the oversight of research. Increased reporting and communication by study sponsors and investigators with the regulatory agencies are necessary before, during, and after emergency study protocols are developed and implemented. Institutional review boards are now obligated to provide early, active involvement with investigators and the lay community to assist in developing strategies to meet the requirements of the regulations and to witness and document the adequacy of these efforts. In short, more responsibilities, time, work, and probably money are demanded of all parties involved in resuscitation research to implement these regulations.

The additional requirements of these regulations; the limited knowledge of most investigators, institutional review boards, and sponsors about their details; and the initial lack of specific regulatory guidance on adequate fulfillment of the requirements have resulted in confusion and misunderstanding about the rationale for the

new regulations and their appropriate application. As a result, much hesitancy and frustration has surrounded their use. Despite the current availability of an exception from the requirement for prospective informed consent for emergency research and the impatience of the resuscitation research community to restart resuscitation research after a hiatus of several years, the Final Rule has been used infrequently since it was released. Some investigators believe the Final Rule is too cumbersome to be practical for application to emergency research.^{3,4} Others suggest that institutional review boards are hesitant to allow the exception to informed consent because they are afraid of added liability and other legal consequences.⁵ Regardless of the argument advanced, the FDA's Final Rule and the HHS's Waiver of Informed Consent are the only current regulatory options that have been provided for research without consent.

Many researchers have called for revisions to reduce the additional burden imposed by these regulations.⁴⁻⁶ Although such revisions are possible in the future, they are unlikely to occur soon. As evidenced by the lengthy process required for the development of the Final Rule,^{2,7} any changes to the regulations will likely take a significant amount of time. If resuscitation research is to proceed without interruption, it is important for investigators and institutional review boards to understand the Final Rule. It is also important for those who are interested in suggesting changes in these regulations or in developing a different set of recommendations for regulatory consideration to know the process by which these current regulations were successfully developed.

This article presents a brief history of the development of the FDA's Final Rule, a summary of its requirements, a summary of its use so far, and suggestions for implementation. Some strategies to allow the resuscitation research community to suggest fine tuning of the regulations are suggested in hopes that research requiring an exception from informed consent is allowed to proceed in a manner acceptable to regulators, stringent in patient protection, yet sensitive to the practical aspects of performing resuscitation research.

THE DEVELOPMENT OF THE FINAL RULE

In August 1993, the Office of Protection from Research Risks (OPRR; now called the Office for Human Research Protection [OHRP]) notified institutional review boards and research institutions that all human subjects research approved by institutional review boards and all studies funded by the National Institutes of Health (NIH) required prospective informed consent from the patient or from a legally authorized representative.⁸ Previously described consenting mechanisms, such as deferred consent, implied consent, or 2-tiered consent, were not acceptable, despite their longstanding use in resuscitation research.⁹⁻¹¹ Institutional review boards were instructed to stop all studies currently using these alternative consenting mechanisms and not to approve further studies without prospective informed consent.

Several issues that had recently come to public and regulatory attention contributed to the decision. In 1992, a series of experiments conducted in the 1940s and 1950s by the Department of Energy were described in the lay press. These experiments had exposed patients to ionized radiation without their knowledge.¹² The report prompted public and political outrage, and President Clinton issued a directive to all federal agencies and to the OPRR to examine the existing research regulations regarding informed consent.¹³ In April 1993, the FDA shut down a study of active compression-decompression cardiopulmonary resuscitation (CPR), citing the use of deferred consent and concerns about the study's design as the primary reasons for their decision.¹⁴ This study had been enrolling patients for more than a year before it was closed. The FDA also denied a waiver of informed consent for an out-of-hospital study of a vest CPR device (the Cardiologic Study)¹⁵; the device had been used in several inpatient studies over the preceding decade using deferred consent.

Although these events all contributed to the OPRR directive, the specific issue that most likely triggered the widespread research shutdown was an inquiry and a challenge advanced to the FDA by the institutional review board of the University of Nebraska after their

favorable review in April 1993 of an interventional head injury trial, the Polyethylene Glycol Superoxide Dismutase (PEG-SOD) Clinical Trial.¹⁶ The study proposed to use deferred consent in the event that a surrogate could not be found to speak on behalf of a potential study subject. A very similar study using deferred consent had begun a year before at several other institutions after each institutional review board's approval, and the FDA was aware of this.^{11,17} The Nebraska institutional review board went through a detailed analysis of the protocol and deemed that informed consent would not be possible in these severely head-injured patients. They also believed that the possibility of identifying and contacting the subjects' legally authorized representatives within the estimated therapeutic window of the study agent was negligible. The institutional review board believed the protocol qualified for an exception from informed consent because it satisfied the conditions of the existing FDA regulations¹⁸ for exception for emergency treatment and also the conditions of existing HHS regulations¹⁹ for waiver of informed consent. These regulations had been written in 1981 (and revised in 1991); during the course of their deliberations, the Nebraska institutional review board challenged these regulations as too restrictive when considering emergency research in the 1990s.¹⁷ The institutional review board informed the investigators that the study could proceed.

In July 1993, the FDA informed the Nebraska institutional review board that it was investigating the legality of the protocol if it did not include prospective consent.¹⁷ In the meantime, the FDA mandated that enrollment be limited to patients who could give consent or for whom surrogates could be found. From the study's perspective, this severely limited enrollment and was projected to greatly prolong the course of the study of a potentially beneficial treatment of a devastating injury. The study sponsor therefore began high-level discussions with the FDA to revisit this decision. The OPRR also took part in these discussions. The subsequent communications from both the FDA and the OPRR are most remarkable for their resistance to the concept of deferred consent. The FDA indicated that the term does

not appear in their federal research regulations but did acknowledge that it had been used in FDA-approved protocols before.¹⁷ The OPRR also indicated that deferred consent failed to comply with existing HHS regulations and, in fact, that no alternative consenting mechanisms were permissible. In September 1993, the FDA ruled that the study could proceed with an exception from informed consent if certain criteria were met; the OPRR took no additional action at that time.¹⁷

The issue became even more volatile in March 1994, when the US House Subcommittee on the Regulation of Small Business and Technology, chaired by then-congressman Ron Wyden, released a document entitled “Human Guinea Pig Research in Emergency Rooms: How Some Drug and Device Manufacturers Use Patients Who Can’t Say No.”

This document was based on an audit of FDA files of several research studies that had allegedly violated approved FDA protocols and described patients who claimed they had been abused by clinician researchers who ignored the federal research regulations.²⁰ Both the PEG-SOD Clinical Trial and the Cardiologic CPR–Vest Study were listed among those studies that had inappropriately enrolled patients without their consent. The document was written by Wyden’s health staff in preparation for a public hearing on unethical research practices that Wyden was convening. The hearing would include testimony from researchers and institutional review board chairs who had been accused of unethical research conduct and patients who had allegedly been subjected to research abuse. The hearing was scheduled to occur in May 1994.

Wyden’s document was brought to the attention of the Society for Academic Emergency Medicine (SAEM) Research committee by a Washington lawyer who had originally been hired by Cardiologic Systems to assist in negotiating through the FDA’s regulations to allow field testing of the CPR vest and to prepare a presentation to the FDA on their proposed trial. When Wyden’s document named Cardiologic Systems as a perpetrator of unethical research, the lawyer began to prepare a defense against Wyden’s criticism of resuscitation research. He believed that a statement by a professional academic

society on the importance of resuscitation research and the inadequacy of existing informed consent regulations for emergency research might deflate some of the accusations Wyden was expected to make against researchers. The statement could also serve to inform the public of the need to revisit the existing regulations in terms of the rapidly evolving research environment of 1994.²¹

Representatives from the SAEM research committee met with Wyden’s chief of staff to discuss the March document and the existing regulations for research. The motivation behind the Wyden subcommittee meeting was also discussed in great detail. After considering the input from SAEM, Wyden’s staff invited SAEM to submit a statement to the public record of the subcommittee hearing.²² In addition, it was agreed that the hearing might be more productive if its focus changed from criticism of specific researchers to investigation of discrepancies and inconsistencies within the federal regulations that could lead to misunderstandings and misapplications when these regulations were applied to resuscitation research.

Gary Ellis, the director of the OPRR (who had written the August 1993 OPRR directive), and Mary Pendergast, the deputy director of the FDA, also presented public testimony at Wyden’s subcommittee hearing. Both acknowledged the problems with the regulations concerning informed consent in resuscitation research and pledged to convene a public forum to solicit formal input from the research community.^{23,24} The forum was set for January 1995.

SAEM decided that a consensus statement from the resuscitation research community regarding the need for regulations that would allow waiver of informed consent would make a strong argument at the FDA-OPRR public forum. To reach such consensus, the Coalition of Acute Resuscitation and Critical Care Researchers was founded, with the goal of advancing recommendations on how future regulations might address the problem of informed consent in resuscitation research.⁷ The Coalition was also designed to provide a leadership organization to serve as a liaison with the regulatory agencies. The politics and composition

of the Coalition were very carefully considered as it was developed. It was important that it be inclusive of the resuscitation research community but had to consist of open-minded representatives who were committed to patient rights, cognizant of patient vulnerability, free of conflicts of interest, and committed to advancing resuscitation science to save lives. The Coalition initially consisted of representatives from 12 professional organizations. A Coalition Consensus Conference was convened with representatives of the member organizations in October 1994. Regulators, congressional representatives, and patient advocates were also in attendance as observers at the consensus conference. A series of recommendations were produced to provide guidance for the regulators as the issue was further considered.⁷ These recommendations were formally presented at the FDA-NIH-sponsored Public Forum on Informed Consent in Clinical Research Conducted in Emergency Circumstances in January 1995. The Coalition also engaged in a high-profile letter-writing and telephoning campaign, a citizens' petition, an active congressional and senate lobbying effort, frequent meetings with legislative staff, a comprehensive legal analysis of the current regulatory position, and drafting of a senate bill, successfully soliciting a senator to present it on the floor, if all else failed. It was in weekly contact with key FDA and NIH-OPRR representatives who had been specifically assigned to interact with the Coalition. The Coalition recommendations were eventually endorsed by 26 professional organizations before their publication in April 1995.²⁵ The activities of the Coalition managed to keep the issue at the forefront, and their recommendations served as the basis for the FDA's Final Rule.²⁶

At the January 1995 Public Forum, the director of the OPRR suggested that, until new regulations regarding informed consent could be developed, researchers engaging in studies that were currently on hold should apply for a secretarial override of the existing informed consent regulations. The HHS regulations included a provision that would permit a waiver of informed consent for a specific research study if the protocol met certain criteria and if the waiver was deemed appropriate

by the Secretary of Health.^{23,27,28} Because the secretarial waiver was determined on a case-by-case basis and covered only those studies that did not fall under FDA regulations (ie, do not use pharmaceuticals, biologic agents, or devices), most of the studies that were on hold after the 1993 OPRR directive did not qualify for this option. However, one study that was currently on hold because of the OPRR directive did: a clinical trial designed to examine the effectiveness of hypothermia on outcome after severe head injury (the Hypothermia Study).²⁹ Pilot studies had attempted to obtain consent from patient surrogates but the requirement for proxy prospective informed consent drastically skewed the study population by excluding many minority patients whose family and friends did not have telephones and therefore could not be notified that their loved one had been seriously head injured.³⁰ The investigators were aware of the sensitive nature of enrolling minority patients into a research study without consent but also realized that unless this was done, the study would suffer from significant selection bias, with resulting scientific skepticism of its anticipated results. The investigators applied for and were granted a secretarial override from HHS Secretary Donna Shalala in July 1995.^{28,30} The Secretary mandated that the Hypothermia Study incorporate community consultation as a patient safeguard before it could proceed. The need for community consultation became part of the FDA Final Rule and the HHS Waiver regulations. In addition, the HHS Waiver regulations changed the concept of a secretarial waiver of informed consent, granted on a case-by-case basis, to a secretarial waiver for a narrowly defined class of emergency research.

In July 1995, the FDA developed a Proposed Rule³¹ that was cosigned by FDA Commissioner Kessler and HHS Secretary Donna Shalala. The Proposed Rule was sent to the Office of Management and Budget (OMB), which is responsible for budgetary assessments of all new regulations and for determining whether proposed regulations are consistent with the mission of the current administration. The Proposed Rule was considered by the OMB for 2 months and was then opened for public comment. Ninety comments were received in the 45-

day comment period. Sixteen comments were in frank opposition to the concept of waiving consent in any human subject research; the rest were supportive of the Proposed Rule but asked for additional clarification and, in particular, asked for advice on how to implement its requirements. The FDA reviewed every comment received (see Preamble of the Final Rule)¹ and considered each as it revised the Proposed Rule into the Final Rule. A public comment period and responses to public comments are not required for regulatory changes proposed by the HHS.

The revision of the FDA's Proposed Rule took 9 months. The Final Rule was published in October 1996.¹ Both the FDA's Final Rule for Exception from Informed Consent³² and the HHS regulations for Waiver of Informed Consent for Emergency Research³³ went into effect in November 1996, 39 months after the OPRR moratorium on research without consent was launched.

KEY CONCEPTS: THE FINAL RULE

The Final Rule provides a very narrow exception to the requirement to obtain and document prospective informed consent for research involvement from the patient or a legally authorized representative. The requirements for the FDA's exception to informed consent are briefly listed in Figure 1 and have been described in detail.³⁴⁻³⁶ Exception from informed consent is not indicated when there is sufficient time to obtain consent from the legally authorized representative, when most subjects who would be eligible for enrollment have a legally authorized representative readily available, and when the study population can be readily identified and prospective informed consent obtained before a predictable life-threatening emergency.

The FDA's Final Rule does not allow waiver of informed consent under any circumstances; it allows an exception from informed consent for life-threatening conditions³⁷ and for emergency research.³² This distinction is important because it has been the basis of FDA denials of protocols that apply for exception from informed consent. The FDA's Final Rule requires that an

informed consent process be developed should at least one potential patient or legally authorized representative be available to provide prospective informed consent for study enrollment. When prospective consent cannot be obtained in an approved protocol, an exception is made from the existing informed consent process. The HHS regulations, applicable to those studies not falling under FDA authority, require the same additional patient safeguards that are required by the Final Rule but waive the informed consent requirement.³⁸ The HHS waiver extends the secretarial override (applied to the Hypothermia Study, see above) from a case-by-case application to resuscitation and emergency research activities that involve subjects who cannot provide prospective informed consent.¹

Figure 1.

Exception from informed consent requirements for emergency research.³²

1. The research involves human subjects who cannot give informed consent because of their emerging life-threatening medical condition.
2. The condition requires immediate intervention.
3. Available treatments are unproven or unsatisfactory; further research is needed to determine the best therapy.
4. Clinical equipoise exists between the treatment's understudy and standard treatment.
5. The research might provide direct benefit to each subject.
6. The research cannot move forward without the exception to informed consent because the subject cannot consent as a result of his or her medical condition AND intervention must start before consent from a legally authorized representative is feasible AND there is no reasonable way to identify likely research subjects prospectively.
7. The study plan includes a defined therapeutic window.
8. The principle investigator commits to try to contact, within the therapeutic window, the legally authorized representative and family members who might object to the study.
9. The investigator has provided an informed consent procedure to use if and when feasible, information to provide to family members who might object to study participation, and procedures to inform, when appropriate, of the details of the study after the subject's inclusion and disclosure of the subject's inclusion in the event of the subject's death.
10. The additional patient safeguards that exist are in effect beyond those additionally required.
11. State laws allow research with an exception from informed consent (state laws supercede federal research regulations).
12. The sponsor has received written permission from the FDA to proceed with the research.

The Final Rule does not restrict the type of study designs that can be used in protocols using exception from informed consent, as long as the study design is considered the best to answer the study question. Placebo trials are acceptable, as long as the other criteria for applying the exception exists. In this context, the FDA assumes that placebo does not equate with no care but rather that placebo administration is in addition to the standard of care. However, studies designed to test the current standard of care are allowed. In these studies, a group of patients who do not receive the standard of care (the placebo group) would be compared with those receiving the standard of care (the experimental group). Investigators and sponsors intending to determine the effectiveness of the current standard by withholding it must clearly justify why this study is important relative to the existing knowledge that has led to the current care standards.

The Final Rule assumes that clinical equipoise exists between 2 potential therapies.¹ This means that the likelihood of benefit to a patient from one investigational agent is at least as good as the currently accepted care involving a second therapeutic agent, with no additional risk. The research study is aimed at resolving the scientific question of which of the 2 is a better treatment. If scientific equipoise between 2 treatments does not exist, one of the 2 has been shown to be superior to the other either in terms of the benefit it provides or has a reduced risk profile.³⁹ In this circumstance, the exception from informed consent is not applicable. In addition, in these circumstances, the need to do the proposed research at all must be carefully considered.

Written FDA approval is required before a study using exception from informed consent can be initiated. This might be granted either after the study has undergone institutional review board review and has already fulfilled regulatory requirements, including community consultation and public notification, or, preferably, when the commitment and plan for fulfilling the regulatory requirements are submitted to the FDA. Another required regulatory step is submission of a unique investigational new drug or investigational device exemption application. In the case of studies

using already approved drugs, devices, or biologics, it is not necessary to repeat information contained in an existing investigational new drug or investigational device exemption; this additional application, which the FDA states will be reviewed within 30 days of its receipt, should emphasize how the study protocol has been developed to comply with the requirements of the Final Rule.^{1,40}

Because the Final Rule can only be applied to research that involves critically ill or injured subjects, who are by definition a vulnerable patient population, the Final Rule requires additional patient protections that are not required for other studies. It is these additional patient safeguards and the lack of specific FDA guidance on how to fulfill them that have caused the most confusion about the implementation of the Final Rule.

LESSONS LEARNED: USING THE FINAL RULE

In June 2002, the Federal docket listed 4 applications for investigational new drugs—investigational device exemptions that had publicly disclosed information under the FDA's emergency research exception from informed consent regulation; discussions with chief officers of the FDA centers suggest that more, possibly as many as 20, have been submitted but have not yet been listed on the public docket.²⁶ Some studies submitted to the FDA under this Rule have not been allowed to proceed. The most common reason for failure to obtain FDA approval is that the study itself does not fulfill the requirements to qualify for exception from informed consent. In other words, prospective informed consent could be obtained from subjects or legally authorized representatives before study enrollment. Several disapproved studies have failed to develop the required informed consent procedures and documents or have not defined an independent data and safety monitoring committee. Some fail to include a description of the procedures that will be used to inform the legally authorized representative of study participation in the event of the death of the study subject. Some disapproved studies have minimal or no plans for community consultation, public notification,

or both, and some have failed to define the therapeutic window of the investigational agent.

SUGGESTIONS FOR IMPLEMENTING THE FINAL RULE

In response to these problems with submitted protocols, the FDA developed a guidance document that provides some answers to questions on implementation of the Final Rule.⁴⁰ Many other suggestions for implementation have been described.^{34-36,41}

Specific comments about the interpretation and implementation of key concepts are included here.

Community Consultation

Community consultation is included in the regulations as a patient safeguard. Although not necessarily the most common reason for failure to obtain FDA approval, community consultation is often the most difficult requirement for investigators and institutional review boards to understand and perform. Community consultation is meant to provide an exchange of information among the study investigators, the institutional review board, and the community. Two communities must be involved, the community of potential study subjects and the community where the research will be performed, if these are not the same communities. The appropriate methods of community consultation will depend on the study and the community itself; the institutional review board and the investigator should plan community consultation together. Some specific details to consider include how to define the community, how to best reach them, how to engage them in the process, the numbers of attendants that can be considered to be an adequate representation of the community, and how often consultation should occur.⁷ None of these issues are prescribed in the Final Rule or in the FDA guidance document; instead, the effort should be directed by the nature of the protocol itself and the local community's attitudes and values. Development of an acceptable plan for community consultation will require that the investigator approach the institutional review board early in the protocol-planning process, and it requires

the institutional review board to do more than simply approve the protocol. There is an obvious increase in the institutional review board and investigator workload and regulatory burden to fulfill the regulations; well-planned and appropriate community consultation before the fact will ease the process. Some successful methods of performing community consultation are listed in [Figure 2](#). Even though the best means of community consultation are variable depending on the community and the study, the information that needs to be conveyed is defined.^{1,40} These are also listed in [Figure 2](#). Although the definition of what constitutes adequate community consultation is not provided by the FDA, it is clear from them that certain interactions are less effective. The FDA suggests approaching community gate-keeping groups to help determine what the most effective means of communication are in their community and where effective interactions can most efficiently be done.²⁶

Figure 2.

Community consultation.

Required Content

The investigators must reveal:

- The nature and purpose of the study
- The meaning of informed consent
- That informed consent will not be obtained
- The risks and benefits of the research
- Answers to community questions about the research

The community must be asked:

- How can those not wishing to be enrolled be prospectively identified?
- How does this study interface with local cultural beliefs?

Suggestions for fulfilling the regulations:

- Identify and use existing community networks to actively engage the community
- Ask community gate-keeping groups for assistance
- Standing civic meetings
- School, club, church meetings
- Set up special open community meetings around the topic of the research
- Include a public health message
- Discuss prevalence/prognosis of disease under study
- Incorporate local health related information
- Identify and consult with specific representatives or leaders of the communities
- Invite members of the community to serve as institutional review board consultants
- Develop a representative community advisory panel to provide consultation

Community consultation is not community consent. Although the institutional review board must attend to the community's concerns, the community does not have veto power over the institutional review board's decisions regarding the study protocol. During community consultation, an institutional review board representative is required to document the discussions about controversial issues in the study protocol and the objections brought up by the community. Before making a decision regarding the protocol, the institutional review board must decide whether community consultation has indeed been adequate: this depends on their assessment of whether meaningful feedback was provided from the community to the investigators. After adequate community consultation, the institutional review board has several options: (1) the study can be approved despite community concerns, (2) a change in the study might be required before institutional review board approval if the community concerns are considered to be valid, (3) the institutional review board might determine that the study is not appropriate for the community, and (4) the institutional review board might request more community consultation before it makes a decision to approve or disallow the study.⁴⁰

The costs of community consultation are usually covered by the sponsors of multicentered clinical trials and can be substantial.⁵ In addition, community consultation can add extra time to protocol development. With small studies or single-institution studies, the investigators and their institutional review boards usually bear the cost and time investments themselves.

Public Notification

Public notification is a requirement of the regulations that is sometimes confused with community consultation. Unlike community consultation, public notification is not designed for 2-way communication; instead, it is simply meant for dissemination of information. It must occur at least once before the study is begun and target the same communities as community consultation. The study investigators are responsible for public notification; institutional review boards are required to ensure it has been properly done. Study sponsors are

responsible for providing the FDA with evidence that adequate public notification has occurred.

Some suggestions for public notification and the information that is to be disseminated are listed in Figure 3. After the study is over, the public must be provided with general information about the study, including the demographic characteristics of the enrolled subjects and the results, regardless of whether they are positive or negative. The timing of poststudy public notification is not defined, except that it should be done in a "timely fashion" after the study has been completed at all sites.⁴⁰ Poststudy public notification includes dissemination of the results to other researchers to avoid unnecessary duplication of the work.

Independent Data Monitoring

The Final Rule requires the establishment of an independent data and safety monitoring committee to periodically review the progress of a clinical trial. The data and safety monitoring committee is usually established by the study sponsor and is comprised of experts on study design, the medical subject being studied, and

Figure 3.
Public notification.

Prestudy Public Notification: Required Content

The investigators must reveal:

- The nature and purpose of the study
- Summary of how the study will be conducted
- That informed consent will not be obtained
- The risks and benefits of the research
- How attempts to contact legally authorized representatives will be made
- How those not wishing to be enrolled can communicate this (ie, medic bracelets)

Poststudy Public Notification: Required Content

- Demographic characteristics of those enrolled
- Results

Suggestions for Public Notification

- Press releases
- Advertisements
- Media notification
- Public service announcements
- Announcements at community meetings
- Community newsletters
- Mailings
- E-mail/Web site distributions
- Television health reports

statisticians and biomedical ethicists who have no vested interest in the results of the research. The data and safety monitoring committee should also have a member representing the lay community from which potential study subjects will come. The data and safety monitoring committee conducts periodic assessments of the balance between the study's benefits and risks as the study is performed. On the basis of this analysis, the data and safety monitoring committee can recommend that a trial be continued, modified, or stopped.^{1,40,42} A recent book has been published summarizing the responsibilities of the data and safety monitoring committee.⁴³

The method and timing of these periodic reviews are determined by the study design before the trial begins. Specific criteria for possible data and safety monitoring committee recommendation are also generally established before hand.⁴⁴ Because of the complexity of most clinical trials and the specialized expertise needed for ongoing data assessments, the institutional review board is probably not qualified to serve as the data and safety monitoring committee. The institutional review board can suggest the composition of the data and safety monitoring committee and, in some circumstances, can assist in its development.

Many safeguards for the protection of patients enrolled in clinical trials existed before the Final Rule, including institutional review board assessments of protocols, FDA and government audits and site visits to research institutions, specific federal regulations, and various other oversight mechanisms. To date, little information or data support their effectiveness in protecting patients from research harm.¹³ The effectiveness of community consultation and public notification as patient safeguards, as required by the Final Rule, has also been questioned.^{4,45,46} However, the workings of the data and safety monitoring committee involved in the assessment of the first multicentered clinical trial proceeding under the Final Rule objectively demonstrate an effective mechanism for patient protection.⁴² This data and safety monitoring committee terminated the study before its anticipated enrollment because of an imbalance in the safety profile between the treatment

and the placebo. The study involved the use of diaspirin cross-linked hemoglobin as a blood substitute in critically injured patients with hypovolemic hypotension from trauma (the Baxter Study), who were unable to provide meaningful prospective informed consent.⁴⁷ The detection of a potential problem occurred before the first interim analysis (scheduled to occur after 10% enrollment) and after enrollment of only 74 of the anticipated 850 patients. When an asymmetric distribution of fatal serious adverse events was noted ($P=.006$), the data and safety monitoring committee voted to unmask itself to the treatment assignments and discovered that the apparent excess in deaths occurred among patients receiving the experimental agent. The trial was placed on hold, and extensive additional data analysis occurred, taking into account premorbid differences, different institutional management styles, differences in supportive care received, different mechanisms of injury, potential misapplication and misinterpretation of injury severity scoring systems, and other possible confounders that could explain the difference between the 2 groups. No explanation of the differences in mortality between the 2 groups could be found after this in-depth analysis; however, the data and safety monitoring committee was reluctant to conclude that the treatment was the cause of the discrepancy because other unknown factors might not have been considered in their analysis. Its recommendation to terminate the study was therefore based on a calculation of predictive power, which indicated that the chances of finding a statistically significant difference in favor of the treatment would be 1 in 2,200.⁴² The study sponsor agreed with this decision, and the Baxter study was formally terminated about 11 months after it was started, after a final enrollment of 112 patients.⁴⁸ A few months later, a European trial of the same product was also placed on hold because of patient safety concerns,⁴⁹ and 3 months later, Baxter ended all formal testing of the product.⁵⁰ Although establishment of the data and safety monitoring committee was an additional regulatory burden for the sponsors, investigators, and institutional review boards, it provided the patient protection it was designed to provide. By terminating the study early, the

data and safety monitoring committee and the study sponsor reduced the risk of the research for future potential study subjects.

Commitment to Notify

Despite the likelihood that there will be no possible means of obtaining prospective informed consent from all subjects in a specific clinical trial requesting an exception from informed consent, all protocols must contain a commitment to do so when it is feasible, as well as a description of how this will occur and be documented. An informed consent process and document must therefore be developed and approved by the institutional review board, even if it is unlikely that it will be used. For instance, in the Baxter study, prospective informed consent was obtained for 6 of 112 patients enrolled.⁵¹ The Cook County Hospital institutional review board has proposed a consent process for studies that qualify for the exception from informed consent.⁵² A decision tree is applied to determine whether an individual patient is eligible for study enrollment with an exception from informed consent. The plan also includes a number of formatted steps to help meet the regulatory requirements of the Final Rule, such as a screen to determine patient competence, a document to provide consent by a legally authorized representative, a screening tool to allow a noninvestigator clinician to certify that the patient cannot provide prospective consent, and a contact plan for the subject's family members and legally authorized representatives.

The period of notification for study enrollment and attempts to obtain informed consent from the patient or the legally authorized representative must be within the therapeutic time frame of the investigational agent, if one exists. However, it is not necessary that these attempts extend throughout the entire therapeutic window.⁴⁰ The institutional review board is responsible for determining what will constitute an acceptable attempt, keeping in mind that for most agents, the earlier they are applied, the better the chances of improving patient outcome. Family members identified before patient enrollment but who are not the patient's legally autho-

rized representative cannot provide informed consent for patient enrollment but are able to object to enrollment.¹ In this circumstance, the patient cannot be enrolled.

Attempts at identifying and notifying the legally authorized representative must continue, even after a patient has received the intervention. If the patient recovers, they must also be included in the notification of study enrollment. The method and appropriateness of these attempts require institutional review board oversight and documentation by the investigators. If requested by the legally authorized representative or the patient, the patient must be withdrawn from the study, and the investigator must ensure that the patient suffers no penalty for this decision. Postenrollment attempts at notification are required to occur "at the earliest feasible opportunity,"⁴⁰ but the FDA has not defined the actual timing. These attempts are required even if the patient has died "if it is feasible to do so," as determined by the investigator and the institutional review board.¹ The "feasibility" of these contacts must be realistically assessed to avoid selection bias in study enrollment. For example, Hsieh et al⁵³ recently evaluated the availability of family members of patients in cardiac arrest who might be eligible for enrollment into a research protocol. They also determined the time between physician and family contact and the willingness of family members (presumably legally authorized representatives) to provide surrogate prospective informed consent. Very few legally authorized representatives were present or could be contacted within the therapeutic time window; the demographic characteristics of the patients for whom legally authorized representatives were present were different from those with no immediately available legally authorized representative. In addition, family members (presumed legally authorized representatives) who were present were often too distraught to provide meaningful consent for study enrollment. Clifton et al³⁰ found that minorities were underrepresented in the Hypothermia Study before the secretarial override allowed a waiver of informed consent; after the waiver was granted, the discrepancy resolved.

The Therapeutic Window

The therapeutic window of the test agent is defined as “the time period, based on scientific evidence, during which the administration of the study agent might reasonably produce a demonstrable clinical effect.”⁴⁰ Because the actual therapeutic window cannot be known until after the completion of the study, the regulations require that the clinician investigator provide an estimate of the therapeutic window on the basis of existing preclinical data. In certain circumstances, the therapeutic window is very short or nonexistent (ie, cardiac arrest studies looking at immediate interventions). Regardless of its length, the therapeutic window and the basis for its estimation must be presented in the protocol.

REFINING THE REGULATIONS

Investigators from various disciplines have called for changes in the Final Rule, suggesting that it is cumbersome and impractical, imposes an excessive regulatory burden, and is not relevant to current resuscitation research.⁴⁻⁶ Some have pointed out special research circumstances or populations for which the existing regulations do not seem amenable, such as emergency medical services research or emergency pediatric research. There is evidence that even when well done, the goals of some requirements of the regulations are not being met. For instance, community consultation does not always reach the communities to the extent suspected or expected. McClure et al⁴⁵ surveyed adults in 2 urban trauma center emergency departments (EDs) in which the same national study using exception from informed consent was being performed. Both sites had undertaken extensive community consultation and public notification before initiating the study. Less than 5% of the adults in these EDs were aware that the study had been occurring in their community for more than a year. Although the Final Rule provides an avenue for research that previously did not exist, it will likely be revised as experience indicates its weaknesses. It is unlikely that such revision will be initiated by the regulatory agencies themselves; it will be up to the research community to launch this effort.

How can such an initiative begin, and what will best be heard by the regulators who will have the final authority to initiate proposed changes to the existing regulations? The approach used to develop the Final Rule, as described previously, although carefully strategized, was essentially charting an unknown course. It required perseverance and great patience. Many lessons were learned that might be useful to others interested in refining the Final Rule.

The development of the Coalition of Acute Resuscitation Researchers that crossed specialties was regarded by the regulators as an excellent means to provide a reasoned, unified voice for the research community.²⁶ The FDA has recommended that future efforts aimed at refining the regulations also use the coalition model of consensus development.^{2,7}

The current regulations should be evaluated to identify specific impediments to their interpretation and application in general, and in particular for specific patient populations, such as out-of-hospital or pediatric patients. When possible, the assessment of problems within the regulations should be supported by data. The ultimate goal is to justify why a specific regulatory requirement needs revision and to propose an acceptable alternative means of providing the same high level of patient protection.

Specific examples on how the current regulatory requirements have been successfully fulfilled might also be welcomed by investigators, institutional review boards, and sponsors and should be included in publications describing studies using exception from informed consent. This would likely reduce the time and cost of implementing the regulations for other studies. For instance, the approval of the multicentered Cardiac Systems study by one study site's institutional review board required 4 months because of ethical and legal concerns, especially regarding community consultation; \$5,600 were spent at this site solely to cover the costs of community consultation and public notification.⁵ Lessons learned from the costly and lengthy experience of this research group would be helpful for other investigators.

A strong and thoughtful institutional review board, with an adequate knowledge base, is essential to allow

these studies to move forward. Unfortunately, institutional review boards vary in their effectiveness, their education, their interpretations of protocols,^{54,55} and their experience with acute resuscitation researchers. The Nebraska institutional review board involved in the evaluation of the PEG-SOD study in 1993 presented a critical analysis of the project and the existing regulations that supported their decision to allow the research to proceed, despite the concerns of the FDA and OPRR.¹⁷ Their decisionmaking process could serve as a model for other institutional review boards that might be required to judge the eligibility of a study for exception from informed consent. Some investigators have called for a national advisory panel (ie, a national institutional review board) to eliminate the variability of decisionmaking among institutional review boards and to evaluate studies that cannot be performed if prospective informed consent is required.⁶ However, a national institutional review board cannot truly identify local research concerns, the local reputation of the researchers, and the community characteristics that might make this research acceptable at a certain site and objectionable at another. A national institutional review board may not be appropriate for the review of small, single-institution studies.⁵⁵ Perhaps a better strategy for resuscitation researchers is to ensure fair representation of resuscitation researchers to local institutional review boards and to assist in the education of institutional review boards that have not had experience with protocols asking for exception from informed consent. This is best done by having a resuscitation researcher serve on the local institutional review board.

It is notable that the data and safety monitoring committee involved in the Baxter study was composed of experts from many disciplines, including biomedical ethicists and representatives from the nonscientific community.⁴² The Baxter data and safety monitoring committee was chaired by an emergency physician with sound knowledge of the regulatory requirements of the Final Rule, as well as an understanding of the clinical aspects of the research itself. Because of its careful, analytic, and professional manner, its recommendation to terminate an expensive study was well received and

immediately acted on by a responsible sponsor. To do so, however, intimate knowledge of the project and the investigators involved was required. With this detailed understanding, the data and safety monitoring committee has a unique position to provide additional oversight to sponsors, such as determining the effectiveness of community consultation across study sites. It seems logical to expand the role of this group to include additional oversight of the project beyond what can be provided by the local institutional review board. Future revisions of the regulations might consider other responsibilities for the data and safety monitoring committee.

Finally, and perhaps most importantly, those who advocate rewriting the regulations must carefully assess whether the regulations in and of themselves are the real barrier to resuscitation research. Over the past several years, certain themes regarding research without consent have emerged during national debates, discussions, and presentations. A general lack of understanding of the regulations seems to exist among institutional review boards and investigators. Some investigators are not aware of the regulations themselves⁵⁶ or of the guidance document the FDA has posted, which provides some (but not all) answers to key questions that seem to arise repeatedly. Institutional review boards are often accused by investigators of being too concerned with potential litigation to allow these studies in their community or being inadequately educated regarding the current regulations.^{4,6} Some institutional review boards have ethical objections to research without consent under all circumstances. Sponsors are accused of pressuring the scientific advisory panels and investigators to move forward with their research, probably so products can be marketed quickly. Emergency researchers rarely are included as consultants on scientific advisory boards for industry-sponsored resuscitation research projects.⁵⁷ Inadequate funding from sponsors to ensure that proper community consultation and public notification has also been cited as a barrier to fulfilling the regulations. If any of these issues are in fact a barrier to the performance of a study in a particular community, this issue must be addressed first

rather than calling for rewriting the regulations; even if the regulations were to be rewritten, these same issues might remain to again present an obstacle to resuscitation research.

As emergency medicine researchers, we must remember that the ability to do research is a privilege and not a right. We must be willing to accept accountability in public for our actions because people can be hurt in research. The Final Rule was not written to make research without consent easy to do; it was written to protect patients who might become research subjects. Any concerns, frustrations, setbacks, or impatience we have must keep the primary ethical concept of patient safety at the forefront as we work with, through, and in spite of the Final Rule.

The FDA's Final Rule on Exception From Informed Consent for Emergency Research (21 CFR §50.23) was based on the recommendations advanced by the Coalition of Acute Resuscitation and Critical Care Researchers, which was a creation of the specialty of emergency medicine. A number of key individuals were involved from the start and, to the best of my knowledge, have never been formally acknowledged. These individuals include Jeff Runge, MD, Chris Doherty, JD, Sue Fish, PharmD, Roger Lewis, MD, PhD, and Bonnie Lee, Associate Director for Human Subjects Protection Policy, FDA. Without the active (and mostly voluntary) involvement of these dedicated individuals, we would undoubtedly still be struggling to do resuscitation research. They deserve our sincere appreciation regardless of our current feelings regarding the Rule, and I personally thank them on behalf of the emergency resuscitation research community. I also thank Bonnie Lee and Roger Lewis for their helpful comments on parts of this manuscript.

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REFERENCES

1. Department of Health and Human Services. Protection of human subjects: informed consent and waiver of consent requirements in certain emergency research: final rules. (codified at 21 CFR §50, et.al, 45 CFR §46) *Federal Register* (Oct 2, 1996);61(192): 51500-33.
2. Biros MH, Runge JW, Lewis RJ, et al. Emergency medicine and the development of the FDA's final rule on informed consent and waiver of informed consent in emergency research circumstances. *Acad Emerg Med*. 1998;5:359-368.
3. Lurie K, Benditt D. Regulated to death: the matter of informed consent for human experimentation in emergency research. *Pacing Clin Electrophysiol*. 1995;18:1443-1447.
4. Sayre MR, White LJ, Brown LH, et al. The national EMS research agenda executive summary. *Ann Emerg Med*. 2002;40:636-642.
5. Kremers MS, Whitsnant DR, Lowder LS, et al. Initial experience using the food and drug administration guidelines for emergency research without consent. *Ann Emerg Med*. 1999;33:224-229.
6. Passamani ER, Weisfeldt ML. Special aspects of research conduct in the emergency setting: waiver of informed consent. *J Am Coll Cardiol*. 2000;35:862-880.
7. Biros MH. Development of the multiorganizational document regarding emergency research consent. *Acad Emerg Med*. 1996;3:101-105.
8. Ellis GB. "Dear colleague" letter: human subject protection. *OPRR Rep*. Aug. 12, 1993; No. 93-3.
9. Abramson NS, Meisel A, Safar P. Deferred consent: a new approach for resuscitation research on comatose patients. *JAMA*. 1986;255:2466-2471.
10. Ellensberg SS. Informed consent: protection or obstacle? *Control Clin Trials*. 1997;18:628-636.
11. Prentice ED, Antonson DL, Leibrock LG, et al. IRB review of a phase II randomized clinical trial involving incompetent patients suffering from severe head trauma. *IRB Rev Hum Subject Res*. 1993;15:1-7.
12. Advisory Committee on Human Radiation Experiments. Research ethics and the medical profession. *JAMA*. 1996;276:403-409.
13. United States General Accounting Office Report to the Ranking Minority Member, Committee on Governmental Affairs, US Senate. Scientific research: continued vigilance critical to protecting human subjects. Washington, DC: General Accounting Office; 1996.
14. Lurie KG, Schultz JS, Callahan ML, et al. Evaluation of active compression-decompression CPR in victims of out of hospital cardiac arrest. *JAMA*. 1994;271:1405-1411.
15. *Hearings before the Subcommittee on Regulation, Business Opportunities, and Technology of the Committee on Small Business of the U.S. House of Representatives*, 103rd Cong, 2nd Sess (1994) (testimony of Jeffrey Koepsell, President and CEO, Cardiol-logic Systems, Inc.).
16. Muizelaar JP, Marmarou A, Young HF, et al. Improving the outcome if severe head trauma with the oxygen radical scavenger polyethylene glycol-conjugated superoxide dismutase: a phase II clinical trial. *J Neurosurg*. 1993;78:375-382.
17. Prentice ED, Antonson DL, Leibrock LG, et al. An update on the PEG-SOD Study involving incompetent subjects: FDA permits an exception to informed consent. *IRB*. 1994;16:16-19.
18. 21 CFR §50.23(a).
19. 45 CFR §46.116(d).
20. Staff memo to Ron Wyden, Chairman of the Subcommittee on Regulation, Business Opportunities, and Technology of the 103rd Congress. Human guinea pigs in the hospital emergency room—how some drug and device manufacturers use patients who can't say no. March 11, 1994.
21. Doherty C. Informed consent update. Presented at: Society for Academic Emergency Medicine annual meeting, May 1996, Denver, CO.
22. Biros MH, Lewis RJ, Runge J. SAEM Testimony on issues consent in acute resuscitation research. *SAEM Newsletter*. 1994;5:2-3.
23. *Hearings before the Subcommittee on Regulation, Business Opportunities, and Technology of the Committee on Small Business of the US House of Representatives*, 103rd Cong, 2nd Sess (1994) (testimony of Gary Ellis, PhD, Director, Office for Protection from Research Risks, National Institutes of Health).
24. *Hearings before the Subcommittee on Regulation, Business Opportunities, and Technology of the Committee on Small Business of the US House of Representatives*, 103rd Cong, 2nd Sess (1994) (testimony of Mary Pendergast, Deputy Commissioner and Senior Advisor to the Commissioner, Food and Drug Administration).
25. Biros MH, Lewis RJ, Olson CM, et al. Informed consent in emergency research. Consensus statement from the Coalition of Acute Resuscitation and Critical Care Researchers. *JAMA*. 1995;273:1283-1287.
26. Lee B. Presentation to the National Association of EMS Physicians conference, "Setting the research agenda." June 2002, Washington, DC.
27. 45 CFR §46. 101i.
28. Menasche A. FDA revises informed consent regulations for emergency research. *IRB*. 1995;17:19-22.
29. Clifton GL, Miller ER, Choi S, et al. Lack of effect of induction of hypothermia after acute brain injury. *N Engl J Med*. 2001;344:556-563.

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30. Clifton GL, Knudson P, McDonald M. Waiver of consent in studies of acute brain injury. *J Neurotrauma*. 2002;19:1121-1126.
 31. US Food and Drug Administration Protection of Human Subjects. Informed consent: proposed rule. *Federal Register* (Sept 21, 1995);60:1830:49086-103.
 32. 21 CFR §50.24.
 33. 45 CFR §46.101.
 34. Biros MH, Fish SS, Lewis RJ. Implementing the FDA's Final rule for waiver of informed consent in certain emergency research circumstances. *Acad Emerg Med*. 1999;6:1272-1282.
 35. Davis AM. Exception from informed consent for emergency research: drawing in existing skills and experience. *IRB*. 1998;20:1-7.
 36. Santora TA, Cowell V, Trooskin SZ. Working through the public disclosure process mandated by use of 21 CFR §50.24 (exception from informed consent): guidelines for success. *J Trauma*. 1998;45:907-913.
 37. 21 CFR §50.23.
 38. 46 CFR §101.
 39. McRae AD, Weijer C. Lessons from everyday lives: a moral justification for acute care research. *Crit Care Med*. 2002;30:1146-1151.
 40. Food and Drug Administration. Guidance for institutional review boards, clinical investigators and sponsors: exception from informed consent requirements for emergency research-draft guidance. Washington, DC: Food and Drug Administration; 2000.
 41. Baren J, Ancietti JP, Ledesma S, et al. An approach to community consultation prior to initiating an emergency research study incorporating a waiver of informed consent. *Acad Emerg Med*. 1999;6:1210-1215.
 42. Lewis RJ, Berry DA, Cryer H, et al. Monitoring a clinical trial conducted under the Food and Drug Administration regulations allowing a waiver of prospective informed consent: the diaspirin cross linked hemoglobin traumatic hemorrhagic shock efficacy trial. *Ann Emerg Med*. 2001;38:397-404.
 43. Ellenberg SS, Fleming TR, DeMets DL. *Data Monitoring Committees in Clinical trials. A Practical Perspective*. West Sussex, United Kingdom: Wiley; 2002.
 44. Lewis RJ. An introduction to the use of interim data analysis in clinical trials. *Ann Emerg Med*. 1993;22:1463-1469.
 45. McLure KB, Delorio NM, Gunnels MD, et al. Attitudes of ED patients and visitors regarding emergency exception from informed consent in resuscitation research, community consultation, and public notification. *Acad Emerg Med*. 2003;10:352-359.
 46. Shah AN, Sugarman J. Protecting human subjects under the waiver of informed consent for emergency research: experiences with efforts to inform the community. *Ann Emerg Med*. 2003;41:72-78.
 47. Sloan EP, Koenigsberg M, Gens D, et al. Diaspirin cross-linked hemoglobin (DCLHb) in the treatment of severe traumatic hemorrhagic shock. *JAMA*. 1999;282:1857-1864.
 48. Baxter International Web Site. Baxter ends US trauma study of Hemassist (DCLHb) [press release]. Available at: <http://www.baxter.com/utilities/news/releases/1998/03-31hemassist.html>. Accessed June 26, 2000.
 49. Baxter International Web Site. Baxter suspends European trial for its hemoglobin therapeutic [press release]. Available at: <http://www.baxter.com/utilities/news/releases/1998/06-02hemassist.html>. Accessed June 26, 2000.
 50. Baxter International Web Site. Baxter to focus on next-generation oxygen-carrying therapeutics [press release]. Available at: <http://www.baxter.com/utilities/news/releases/1998/09-16hemassist.html>. Accessed June 26, 2000.
 51. Sloane EP, Koenigsberg M, Houghton J, et al. The informed consent process and the use of the exception from informed consent in the clinical trial of diaspirin cross-linked hemoglobin (DCLHb) in severe hemorrhagic shock. *Acad Emerg Med*. 1999;6:1203-1209.
 52. Sloane EP, Nagy K, Barrett J. A proposed consent process in studies that use an exception to informed consent. *Acad Emerg Med*. 1999;12:1283-1291.
 53. Hsieh M, Dailey MW, Callaway CW. Surrogate consent by family members for out of hospital cardiac arrest research. *Acad Emerg Med*. 2001;8:851-853.
 54. Hirshon JM, Krugman SD, Witting MD, et al. Variability in institutional review board assessment of minimal risk research. *Acad Emerg Med*. 2002;9:49-52.
 55. Silverman H, Hull SC, Sugarman J. Variability among institutional review boards' decisions within the context of a multicenter trial. *Crit Care Med*. 2001;29:235-241.
 56. Kowey P, Ornato J. resuscitation research and emergency waiver of informed consent. *Resuscitation*. 2000;47:307-310.
 57. Newgard E, Kim S, Camargo CA. Emergency medicine leadership on industry-sponsored clinical trials. *Acad Emerg Med*. 2003;10:169-174.