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ANALYZING THE LAWS, REGULATIONS, AND POLICIES AFFECTING FDA-REGULATED PRODUCTS: FDA's Emergency Research Rule: An Inch Given, a Yard Taken

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SUMMARY:

... In response to growing concerns that informed consent regulations were making high-quality acute care research difficult or impossible to carry out, the Food and Drug Administration (FDA) amended its regulations to allow a waiver of informed consent for emergency research. ... If a subject is enrolled in a study without informed consent, at the earliest feasible opportunity, the subject, or if the subject remains incapacitated, an LAR or family member is to be informed of the subject's inclusion in the clinical investigation. ... If there is insufficient time to obtain informed consent, but there is sufficient time to convey some basic risk and benefit information about the clinical investigation, then that information should be conveyed to the subject, the subject's LAR or the subject's family member. ... In addition, whenever an emergency research study is not approved by an IRB, it is required to notify the investigator and sponsor, who, in turn, is to disclose this information to FDA as well as the investigators and IRBs of the nonapproved study and any substantially equivalent studies. ... (v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. ...

TEXT:

[*217] I. INTRODUCTION

In response to growing concerns that informed consent regulations were making high-quality acute care research difficult or impossible to carry out, the Food and Drug Administration (FDA) amended its regulations to allow a waiver of informed consent for emergency research. n1 The regulation, which went into effect on November 1, 1996, is referred to as "The Emergency Research Rule" and includes *section 50.24 of Title 21, Code of Federal Regulations (CFR) (21 C.F.R. § 50.24)* and conforming amendments in parts 50, 56, 312, 314, 601, 812 and 814. Also in 1996, the Department of Health and Human Services (HHS) announced its Secretarial emergency research consent waiver in order to harmonize HHS regulations with FDA regulations. n2

FDA intended to strike a balance between the need for scientifically sound emergency research and the need to protect the vulnerable subjects who participate in these studies. n3 To address this issue, FDA limited the exception from informed consent to only those research activities involving human subjects in life-threatening situations who are unable to give informed consent and do not have a legally authorized representative n4 (LAR) to provide consent. Available treatments must be unproven or unsatisfactory. The research must be necessary and hold out the prospect of direct benefit to the subject. FDA also increased the subject's protections by requiring that the researchers disclose key information about the research and engage in discussions with community members. In addition, FDA increased the responsibilities of sponsors, clinical investigators and Investigational Review Boards (IRBs). FDA also increased its own workload by requiring that a separate Investigational New Drug (IND) Application or Investigational Device Exemption (IDE) be submitted for each protocol, a formal letter of authorization be sent by FDA to the sponsor prior to start of emergency research studies, and IRB-approved public disclosure documents be submitted to the IND/IDE file and FDA's docket. n5

[*218] As the Emergency Research Rule enters its second decade, FDA has continued its commitment to facilitate emergency research requiring exception of informed consent, while still protecting the public health. n6 In July 2006, a draft guidance on exception from informed consent requirements was issued, n7 and in October 2006, FDA convened a public hearing, at which time FDA asked specific questions regarding aspects of emergency research and additional human subject protections. n8 The purpose of these activities was for FDA to determine whether the current framework is adequate for the ethical conduct of emergency research, or whether modifications would be appropriate.

Over the last few years, there has been a substantial increase in the use of the Emergency Research Rule, and most of this increase is related to studies supported by the National Institutes of Health (NIH). Currently, NIH is funding three large research networks and one large clinical trial center to conduct emergency research studies with waiver of consent. n9 More than 36,000 non-consenting patients with life-threatening conditions are scheduled to be enrolled in ongoing emergency research studies--primarily in the NIH-sponsored studies--with an unspecified additional number of patients to be enrolled in studies currently in planning stages. With the increasing frequency of research studies with waiver of informed consent, it is important that individuals with an interest in legal, regulatory, clinical and ethical aspects of FDA-regulated research become familiar with the Emergency Research Rule.

In this article, the Emergency Research Rule will be reviewed as well as applicable regulations in the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule. n10 The article also will review completed and ongoing emergency research studies, evaluate the outcome of key assumptions made by FDA when the regulation was enacted in 1996, and provide recommendations for addressing shortcomings in the implementation of the regulation.

II. THE EMERGENCY RESEARCH RULE

Emergency research refers to "planned studies involving patients who are in an imminently life-threatening situation that requires immediate intervention, who cannot give consent, and for whom there is either no proven or no satisfactory treatment." n11 The Emergency Research Rule describes specific conditions that must be met and extra protections that must be in place before an IRB can waive the

[*219] consent requirement for emergency research (see Table 1). When these requirements are met, certain individuals in emergency situations can have access to potentially life-saving therapies, leading to improvement of emergency therapies that currently have poor clinical outcome. Key provisions of the Emergency Research Rule are discussed in the following sections.

A. Each Protocol Requires a Separate IND/IDE Application

FDA requires submission of a separate IND or IDE for each study protocol. n12 This requirement was included in the regulation to ensure that an emergency research study does not inadvertently proceed without FDA review. Even if there is an active IND or IDE for the product being studied, each protocol with waiver of consent must be submitted in a separate IND or IDE; that is, amendments to an existing IND or IDE are not acceptable for a protocol with waiver of consent. n13 Similarly, an IND or IDE is required for an approved product being studied under a protocol with waiver of consent. n14 Before an emergency research study can begin, FDA must provide written authorization, which is to be provided to the sponsor at least 30 days after FDA receives the IND or IDE. n15

B. Subjects Are in a Life-Threatening Situation

Subjects in emergency research studies with waiver of informed consent must be in a life-threatening situation, n16 and the intervention to treat the life-threatening disease or condition must need to be administered before consent from an LAR is feasible. n17 There is no requirement in the Emergency Research Rule for the patient's condition to be *immediately* life-threatening or to *immediately* result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before consent from an LAR is feasible. On the other hand, the informed consent waiver provision does not apply to persons who are not in an emergent situation, e.g., a research intervention to be administered to individuals who have been in a coma for a long period of time and whose condition is such that there is sufficient time for consent to be obtained from an LAR of the subject.

C. Obtaining Informed Consent is Not Feasible

The most fundamental requirement for exception from the informed consent regulations is that it is not feasible to obtain informed consent from the subject or an LAR. A licensed physician who is not otherwise participating in the clinical investigation must concur with the IRB determination that informed consent is not feasible. n18 The licensed physician may either be a member of the IRB or a consultant to the IRB.

[*220] Usually it would not be feasible to obtain informed consent when the following two conditions are met: 1) subjects are unable to give informed consent as a result of their medical condition, and 2) the intervention under investigation must be administered before it is feasible to obtain consent from subjects' LAR. n19 On the other hand, if there is a reasonable way to identify prospectively the individuals likely to become eligible for the clinical investigation, the IRB may determine that it is not appropriate to waive the requirement of informed consent. n20 If this situation were to occur, then only those subjects with the condition who gave prior consent could be enrolled in the investigation. Those individuals who either did not make a decision or who refused would be excluded from participation in the investigation.

D. Available Treatments Are Unproven or Unsatisfactory

The Emergency Research Rule requires that the IRB determine whether available treatments are unproven or unsatisfactory. n21 The concept of "unproven" is relatively straightforward because an unproven treatment is defined by the limited data available. It may be more challenging for the IRB to determine whether available treatments are unsatisfactory. Effective therapies may be unsatisfactory if they are associated with unacceptable effectiveness, significant adverse effects or high costs. If an IRB does not have the expertise to evaluate a therapy in an emergency research protocol, the IRB is allowed to invite individuals with competence in special areas to assist in the review of complex issues that require expertise beyond or in addition to that within the IRB. n22

E. The Research Study Is Necessary

The Emergency Research Rule has a higher standard for approval of studies with waiver of consent than for studies with consenting subjects. The emergency research study must be necessary to determine the safety and effectiveness of the intervention, and the study must be designed so that valid scientific data are collected. n23 Recognized study designs (e.g., dose-response concurrent control, no-treatment concurrent control, active treatment concurrent control and historical control) including placebo-controlled trials can be used in emergency research studies. With respect to use of placebos, FDA clarified its intent in the preamble to the final rule:

In virtually all cases, when a placebo is used, standard care, if any, would be given to all subjects, with subjects randomized to receive, in addition, the test treatment or a placebo...[a]n exception to this would be the situation in which the test is to determine whether standard treatment is in fact useful. In that case, there must be a group that does not receive it. n24

The other consideration for approving an emergency research study with exception from informed consent is whether the investigation could be practically carried

[*221] out without the waiver. n25 If scientifically sound research can be practicably carried out using only consenting subjects (directly or with consent by an LAR), then it must be carried out without involving nonconsenting subjects. Two examples are provided to explain "practicable": 1) when recruitment of consenting subjects does not bias the science and the science is no less rigorous as a result of restricting it to consenting subjects, and 2) when the research is not unduly delayed by restricting it to consenting subjects. n26

F. Participation Provides the Prospect of Direct Benefit

The IRB also must find and document that participation in the research holds out the prospect of direct benefit to subjects because 1) the subjects are in a life-threatening situation that necessitates intervention; 2) appropriate animal and other preclinical studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and 3) risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects and what is known about the risks and benefits of standard therapy and the proposed intervention. n27

FDA is very clear that the intervention must hold out the possibility of benefit to the subject and has stated:

This extra assurance is necessary because it must be possible to state honestly that the intervention is for the patient's benefit, at least at the level of being promising, and is not a project only for pure science, future generations or the community, although it will, of course, benefit those too. n28

Sponsors are specifically required to provide animal and other data demonstrating to the satisfaction of the IRB that the investigational product holds the promise of benefit to the research subjects, without provision for an investigational product that has a long-established efficacy and safety profile to be excepted from this requirement. n29

G. Investigators Attempt to Contact LAR within Therapeutic Window

1. Definition of Therapeutic Window

The protocol must define the duration of the therapeutic window, which is the time period, based on available scientific evidence, during which the investigational product must be administered to have its potential clinical effect. n30 The therapeutic window often has not been completely defined at the time of IRB review of a research study. In fact, the therapeutic window cannot be fully known until the relationship between time of treatment and treatment outcome has been formally studied. Nevertheless, the sponsor must use available data (e.g., pathophysiologic

[*222] data, animal data, etc.) to identify, to the extent possible, the duration of the therapeutic window. n31

2. Attempt to Contact LAR/Family During Therapeutic Window

The investigator must attempt to contact an LAR for each subject who cannot provide informed consent within the therapeutic window and, if feasible, n32 to obtain consent from the LAR for the subject's participation in the research study. n33 Because state and local laws vary with respect to who can qualify as an LAR, the protocol cannot delineate specific persons authorized to serve as LARs in the investigation. Instead, the protocol should contain the procedures for determining acceptable LARs for the study centers. IRBs have the option of consulting with legal counsel when deciding who can serve as an LAR for subjects in emergency research studies.

A key protection in the Emergency Research Rule is the requirement that a family member n34 be provided with an opportunity to object to an individual's participation in an emergency research study, if feasible, within the therapeutic window if consent cannot be obtained from the subject or an LAR. Only one family member needs to be consulted and agree or object to the patient's participation in the research. If family members disagree, the researcher and family members need to work out the disagreement. n35 FDA specifically included family members under the Emergency Research Rule because by permitting a family member (even one who is not an LAR) to object to an individual's inclusion in the investigation, a further protection is provided to that individual. n36

The sponsor should not exhaust the therapeutic window with attempts to contact an LAR or family member. Rather, the attempt to contact these persons should be balanced against the effects of delaying administration of the intervention. FDA noted that if the window of time is narrow, it will be difficult or impossible to identify an LAR or family member, especially for potential subjects whose identities are unknown. n37

3. Plan and Procedures for Contacting LAR/Family Members

The sponsor must provide for IRB review of the proposed plan and procedures that will be used when attempting to contact an LAR or family member. The plan also is to include the period of time that will be allocated for making these attempts, if any, before the intervention may be administered. n38

[*223] The investigator is required to summarize efforts made to contact the LAR and/or family members for each subject who cannot provide informed consent. n39 This summary is to be provided to the IRB at the time of continuing review, which will occur at least annually or more frequently if requested by the IRB. n40 This requirement is intended to provide additional protections to the subject by requiring scheduled IRB reviews of the manner in which each investigator carries out the procedures that were previously provided to the IRB.

H. Notifications Following the Intervention

As described in the following sections, the investigator is to notify the subject, LAR or family member that the subject was enrolled in the study without consent.

1. Subject's Participation in Research Study

If a subject is enrolled in a study without informed consent, at the earliest feasible opportunity, the subject, or if the subject remains incapacitated, an LAR or family member is to be informed of the subject's inclusion in the clinical investigation. n41 In addition, they are to be advised of the details of the investigation and other information contained in the informed consent document. n42

2. Right to Discontinue from Research Study

After a nonconsenting subject has been enrolled in an emergency research study, the subject or, if the subject remains incapacitated, an LAR or family member is to be informed that the subject may be discontinued from the study at any time without penalty or loss of benefits to which the subject is otherwise entitled. n43 If a subject, LAR or family member decides to discontinue the subject from the study, the investigator no longer can perform protocol-specific procedures or evaluations. The investigator also no longer can review the subject's medical record for data to be used in efficacy evaluations. On the other hand, safety reporting of adverse events and other investigator responsibilities under IND or IDE regulations would continue. n44

3. Change in Subject's Condition

If an LAR or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If the subject dies before an LAR or family member can be contacted, information about the clinical investigation still is to be provided to an LAR or family member, if feasible. n45 In consideration of the emotional condition of the family members

[*224] who have just learned of the subject's death, the regulation does not contain a time limit for providing this information to the family. n46

I. Informed Consent Procedures and Documents

1. Consent Prior to the Intervention

A standard informed consent form--including policies on compensation and medical treatment if injury were to occur, expenses that a subject could incur by participating in the study, and the person to contact to obtain further information about the study--is to be reviewed and approved by the IRB, and this consent form is to be given to subjects and LARs when feasible. n47 If there is insufficient time to obtain informed consent, but there is sufficient time to convey some basic risk and benefit information about the clinical investigation, then that information should be conveyed to the subject, the subject's LAR or the subject's family member. n48 If any one of these persons objects to a potential subject's inclusion in the investigation based upon the information conveyed to them, then that subject should be excluded from participation in the clinical investigation. If only partial information from the standard informed consent form was conveyed, then complete information is to be provided at the earliest feasible opportunity.

2. Consent for Continuing Participation

The Emergency Research Rule does not require written informed consent for continued participation in research studies with waiver of consent. Rather, the agency has left it up to the IRB to determine whether to require a consent form for continuing participation. n49 FDA noted that consent to continue participating in an investigation is not genuine consent because administration of the intervention already has occurred, and the subject or LAR cannot, meaningfully, be said to have consented to its use. n50 FDA also noted that a document signed after entry into an investigation, would not constitute consent for what had already occurred; it could, however, serve to document that the subject consented to continued participation in the investigation. n51

Information contained in the informed consent form is to be given to subjects, LARs or family members whenever an informed consent form was not signed by a subject or an LAR prior to the intervention. n52 This information will be useful to subjects, LARs and family members when deciding whether to continue or discontinue the subject's participation in an emergency research study. Also, as previously discussed, even if the IRB does not require written consent for continued participation in a research study, the Emergency Research Rule requires that subjects, LARs and family members are to be informed of the subject's participation in the emergency research study and provided with an opportunity to discontinue the subject from the study.

[*225] *J. Special Protections*

FDA recognizes that subjects enrolled in emergency research are a vulnerable population and has provided additional protections for these subjects. Special protections include consultation with representatives of the communities where the research will take place, public disclosure of information before the start of the study and following its completion, and establishment of an independent Data Monitoring Committee (DMC). In addition, whenever an emergency research study is not approved by an IRB, it is required to notify the investigator and sponsor, who, in turn, is to disclose this information to FDA as well as the investigators and IRBs of the nonapproved study and any substantially equivalent studies. These special protections are further discussed in the sections below.

1. *Community Consultation*

Community consultation is a new and often difficult requirement for many sponsors, clinical investigators and IRBs involved in emergency research. FDA requires that consultation is to be carried out in two communities: 1) the community in which the clinical investigation will be conducted (i.e., city or region where the research will take place); and 2) the community from which the subjects will be drawn (i.e., group of patients who have a particular medical condition or those persons in a multistate region served by a regional trauma center).ⁿ⁵³ FDA regards community consultation as a very important protection for subjects participating in research studies and considers it as one of the ways to prevent unethical research from occurring.ⁿ⁵⁴ The goal of community consultation is for the clinical investigator, sponsor and/or IRB to meet with representatives of the community to discuss the study, including its risks and benefits.ⁿ⁵⁵ Consequently, community consultation is intended to be an interactive process requiring dialog between the study team and the community. The number one issue to discuss during community consultation is the waiver of informed consent for most (or all) research subjects.ⁿ⁵⁶ The IRB is to use the information from community consultation in its deliberations concerning the research. The IRB is responsible for listening and considering the community's support, concerns, etc., and then ultimately deciding whether the investigation should be modified, approved or disapproved.ⁿ⁵⁷ The community is expected to provide input to the IRB on its support for or its concerns about the research activity.ⁿ⁵⁸ While the sponsor may provide a plan for community consultation, it is the responsibility of the IRB to ensure the adequacy of the community consultation.ⁿ⁵⁹

FDA has issued a draft guidance on how to accomplish community consultation.ⁿ⁶⁰ Some suggestions for IRBs to consider include having a public meeting in the community to discuss the protocol; establishing a separate panel of members of the

[*226] community from which the subjects will be drawn; using representatives from the community as consultants to the IRB; enhancing the membership of the IRB by adding members who are not affiliated with the institution and are representative of the community; or developing other mechanisms to ensure community involvement and input into the IRB's decision-making process. There can be significant costs associated with community consultation. FDA has indicated that the sponsor normally would incur the costs associated with community consultation. n61

2. Public Disclosure

FDA requires public disclosure of important study information before the study takes place and after it has been completed. n62 Unlike community consultation, public disclosure is a one-way transfer of information. Prior to the initiation of the clinical investigation, FDA requires that the communities where the investigation will take place are to be advised of plans for the investigation and its risks and expected benefits. n63 Disclosures include information from the informed consent document, the investigator's brochure, and the study protocol (e.g., plans for the study, nature and purpose of the study, risks and expected benefits from participating in the study, and the fact that informed consent will not be obtained from most study subjects). Disclosure should also include suggestions as to how individuals who do not want to participate in the research can communicate this (e.g., by use of medical identification bracelets or necklaces). n64

An important difference between routine clinical research studies and emergency research studies is associated with information that sponsors consider to be confidential. In routine clinical studies, study documents are confidential to the sponsor; in emergency research studies, study documents, including the protocol, informed consent and investigators brochure are not confidential, which is explained by FDA as follows:

While it is true that much information relating to clinical investigations is normally treated as confidential by sponsors, the agency believes that when a sponsor chooses to invoke the exception from informed consent contained in this rule that it is essential that reasonable disclosure occur to the community. n65

The agency believes that the benefit to a sponsor of invoking the Emergency Research Rule will outweigh concerns that a sponsor will have about disclosing information about the investigation. Because this disclosure is made only when the exception from informed consent is invoked, it will not create any precedent for companies not invoking the exception. The agency notes that sponsors release research information to investigators and IRB's (for example, through the protocol and investigators brochure) and to potential subjects in the research through the informed consent process and informed consent form; this regulation states that the same information should be released to the community so it can be informed as it considers the research.

After the study has been completed, information regarding the study is to be disclosed to the community and researchers. n66 The information disclosed should

[*227] provide sufficient detail to allow a clear understanding of the study design and its results, including the demographic characteristics of the research population. n67 The IRB has responsibility for determining the sufficiency of the information to be disclosed. FDA anticipates that study results will be published (or reported in the lay press) within a reasonable period of time following completion of the investigation. n68 For a multisite investigation, this ordinarily will require waiting until the data from all sites have been analyzed by the sponsor. n69 In addition, after the results have been published, comprehensive summary data are to be provided to researchers on request. n70 Subsequently, the IRB will be responsible for determining appropriate mechanisms for providing this information to the community from which research subjects were drawn.

The conforming amendments specify additional responsibilities by the IRB and sponsor with respect to publicly disclosed information. The IRB is to provide a copy of information that has been publicly disclosed to the sponsor of the research. n71 The sponsor in turn is required to monitor the progress of all studies invoking the Emergency Research Rule to determine when the public disclosures occur and to promptly submit copies of the information that has been publicly disclosed to the IND or IDE file and also to the FDA docket. n72 As with community consultation, there can be significant costs associated with public disclosure, and FDA has indicated that the sponsor normally would incur these costs. n73

3. Data Monitoring Committee

The sponsor is to set up a DMC as an advisory body to exercise oversight of the clinical investigation. n74 The committee is to be "independent," that is, composed solely of individuals who have no financial interest in the outcome of the study, and who have not been involved in the design or conduct of the study. n75 Members of the DMC usually will include clinicians specializing in the relevant medical fields, biostatisticians and bioethicists. The DMC is responsible for making sure that continuing the investigation in its current format remains appropriate, on both safety and scientific grounds. n76 Study data are to be provided to the DMC on a predetermined schedule, and based on its ongoing review of study data, the DMC may recommend to the sponsor that the clinical investigation be modified or stopped. If a sponsor agrees with a DMC's recommendation to stop the investigation or to institute a major modification of the trial, the sponsor is required to notify FDA, all participating investigators and IRBs in a written IND or IDE safety report within

[*228] 15 calendar days (IND) or 10 working days (IDE) after the sponsor's initial receipt of the information. n77 FDA has issued a guidance on the agency's current thinking on the roles, responsibilities and operating procedures of DMCs. n78

K. IRB and Sponsor Responsibilities When Study Is Not Approved

If an IRB does not approve a clinical investigation either because it does not meet the criteria in the Emergency Research Rule or because of ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. n79 Note that this regulation requires the IRB to have direct communication with the sponsor. The agency considers it appropriate for the IRB to communicate directly with the sponsor and for the sponsor to communicate directly with the IRB when this improves efficiency and/or safety. n80 When a sponsor receives written notification from the IRB that a clinical investigation has not been approved, the sponsor must promptly disclose this information in writing to FDA as well as all investigators and IRBs associated with the nonapproved study and any substantially equivalent studies. n81

L. Special Responsibilities of IRBs

The Emergency Research Rule includes numerous safeguards to protect the health and welfare of nonconsenting subjects. Implementation of these safeguards requires special duties and responsibilities on the part of IRBs and are summarized in Table 2. To handle these additional responsibilities, IRBs often will require additional resources, e.g., extra review time, financial support, personnel and, in some cases, expert consultants in relevant preclinical and medical fields. The FDA rationale for providing IRBs with the additional responsibilities was based on the assumption that most emergency research studies would be performed in institutions that have an IRB, and such IRBs already would have considerable responsibility and authority in reviewing all studies performed in the institution. n82

M. Applicable Federal, State and Local Laws Not Preempted

The Emergency Research Rule is not intended to preempt any applicable Federal, State or local laws and regulations that may apply to emergency research. n83 Institutions wishing to participate in emergency research studies may wish to consult their attorneys regarding any state and local restrictions that preclude such research. It also is important that IRBs become familiar with their specific state and local laws prior to approving protocols containing a waiver of informed consent.

[*229] III. COMPLIANCE WITH HIPAA PRIVACY RULE

The HIPAA Privacy Rule n84 was issued to assure that health information that can identify an individual is protected. This rule balances safeguards to protect individuals' privacy interest against researchers' need to access individuals' health information to conduct important, and potentially lifesaving studies. Essentially all hospitals, trauma centers, healthcare providers and other such institutions providing medical care in the course of emergency research studies are considered to be "covered entities" n85 and are subject to Privacy Rule regulations. The Privacy Rule establishes a category of individually identifiable health information n86 known as protected health information (PHI), which includes most of the information in a research subject's medical record. Subjects in emergency research study have rights under the Privacy Rule that are not applicable to consenting subjects, and it is important that investigators, sponsors and IRBs understand their responsibilities under the Privacy Rule.

1. Waiver of Authorization to Use or Disclose PHI

All human clinical research is impacted by the Privacy Rule to the extent that researchers obtain, create, use, and/or disclose PHI in the course of their research. In non-emergency research studies, compliance with the Privacy Rule usually is accomplished by having subjects voluntarily sign an authorization that allows their PHI to be used for research purposes. n87 In emergency research, it is not feasible to obtain a signed authorization from nonconsenting subjects. The Privacy Rule allows the use or disclosure of PHI without an individual's authorization if a waiver of authorization is obtained from either an IRB or a new type of review body, a

[*230] Privacy Board. n88 The following three criteria must be met for the IRB/Privacy Board to grant a waiver of authorization: n89

1. The use or disclosure of PHI involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:

- An adequate plan to protect the identifiers from improper use and disclosure;
- An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of research, unless a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
- Adequate written assurances that the PHI will not be reused or disclosed except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of PHI would be permitted by the Privacy Rule.

2. The research could not practicably be conducted without the waiver or alteration.

3. The research could not practicably be conducted without access to and use of the PHI.

The IRB/Privacy Board that approves a waiver of authorization has the responsibility to document each of the following: n90

- . Identity of the approving IRB/Privacy Board;
- . Date on which the waiver was approved;
- . Statement that the IRB/Privacy Board has determined that all of the specified criteria for a waiver of authorization were met;
- . Brief description of the PHI for which use or access has been determined by the IRB/Privacy Board to be necessary in connection with the specific research activity;
- . Statement that the waiver was reviewed and approved under either normal or expedited review procedures; and
- . Signature of the IRB/Privacy Board chair or the chair's designee.

2. Right to Receive Accounting of Disclosures of PHI

Under the Privacy Rule, individuals have the right to receive an accounting of their PHI that was used or disclosed. n91 In routine clinical studies this right is excepted because research subjects have knowingly and voluntarily provided permission for use and disclosure of their PHI by signing a valid authorization. However, emergency research studies are conducted with a waiver of authorization, and the

[*231] right to receive an accounting of PHI disclosures is retained by research subjects. HHS emphasized the importance of this right to research subjects in the preamble to the final modification to the Privacy Rule:

The Department disagrees with commenters' proposal to exempt all research disclosures made pursuant to a waiver of authorization from the accounting requirement. Individuals have a right to know what information about them has been disclosed without their authorization, and for what purpose(s). n92

Under the Privacy Rule's Accounting of Disclosures of PHI, all subjects enrolled in emergency research studies with a waiver of authorization (in addition to a waiver of informed consent) must be provided with the following information for each PHI disclosure: n93

- . Date of the disclosure;
- . Name of the entity or person who received the PHI and, if known, the address of such entity or person;
- . Brief description of the PHI disclosed; and
- . Brief statement of the purpose of the disclosure.

Abbreviated procedures for accounting for multiple disclosures of PHI to the same person or entity for a single research purpose are allowed. n94 For the first disclosure, all of the prior information is to be provided; for subsequent disclosures, only the frequency, periodicity, or number of disclosures and the date of the final disclosure are required. When the covered entity has made PHI disclosures for a particular research purpose for 50 or more individuals, the accounting may be further abbreviated. n95

3. Notice of Privacy Practices for PHI

All subjects enrolled in emergency research studies with waiver of authorization are to be provided with a Notice of Privacy Practices for PHI. n96 The notice must be written in plain language and contain:

- . Description of the uses and disclosures of PHI;
- . Statement of the individual's rights, including among others, the right to receive an accounting of disclosures of PHI;
- . Statement that a complaint may be filed if individuals believe that their privacy rights have been violated and the procedures for making such a complaint;
- . Contact information including the name, title and telephone number of a person or office to contact for further information; and
- . Effective date of the notice.

[*232] Although most hospitals and health providers routinely provide patients with the institution's Notice of Privacy Practices, this document does not satisfy the notification requirements for subjects in emergency research studies because it would not include information regarding PHI disclosures associated with the subject's participation in an emergency research study.

4. *Privacy Rights Not Enforced*

The Office for Civil Rights (OCR) has responsibility for implementing and enforcing the Privacy Rule, and OCR may conduct compliance reviews to determine whether covered entities are complying with the Privacy Rule. n97 In addition, OCR has authority to receive and investigate complaints against covered entities related to the Privacy Rule. n98

Consequently, unlike many other clinical research regulations, neither the Office for Human Research Protections (OHRP) nor FDA enforces the Privacy Rule. This means that the Division of Compliance Oversight within OHRP that reviews institutional compliance with the federal regulations governing the protection of human subjects in HHS-sponsored research will not assess compliance with the Privacy Rule during its compliance oversight evaluations, and FDA will not assess compliance with the requirements of the Privacy Rule during inspections to determine compliance with their respective regulations. In addition, IRBs are not required to oversee investigators' compliance with the Privacy Rule. *Consequently, there appears to be a large loophole with respect to oversight of the Privacy Rule in emergency research studies.* If subjects are not provided with a Notice of Privacy Practices for PHI, they will not be aware of their rights, specifically the right to accounting of disclosures of PHI, and will not have information regarding the process for filing complaints with OCR. On the other hand, there is no way for OCR to know that a covered hospital or other institution or health provider is participating in an emergency research study, and compliance reviews of such covered entities will not be scheduled. Most seriously, institutions and health providers that are covered under the Privacy Rule and are conducting emergency research in violation of the provisions for notification of PHI disclosures are at risk for ongoing civil money penalties and criminal sanctions.

IV. USE OF THE EMERGENCY RESEARCH RULE

FDA intended for the Emergency Research Rule to be used "infrequently." n99 During the first 10 years following its adoption, a total of 56 submissions requesting waiver of informed consent for emergency research were received by CDRH, CDER and CBER, and 21 of these submissions resulted in studies that have been completed, are ongoing or intend to enroll patients in the near future. n100 During the first 10 years, emergency research studies were rare and relatively small, affirming FDA's expectation that the Emergency Research Rule would be used infrequently.

[*233] Currently, emergency research is undergoing a sea change, and several large, federally funded, multicenter emergency research studies involving thousands of patients are ongoing or planned. The translational emphasis of NIH has led to the development of at least three research networks to test new therapies and procedures in critically ill and injured patients. n101 Resuscitation Outcomes Consortium (ROC) is funded by several agencies and led by the National Heart, Lung and Blood Institute (NHLBI); Neurological Emergencies Treatment Trials (NETT) is funded by the National Institute of Neurological Diseases and Stroke (NINDS); and Pediatric Emergency Care Applied Research Network (PECARN) is funded by the Health Resources Services Administration (HRSA)/Maternal and Child Health Bureau (MCHB) and the National Institute of Child Health and Human Development (NICHD). All of these organizations intend to conduct studies that cannot be completed without exception from consent for emergency research.

ROC n102 is the most advanced of the three emergency research networks in terms of ongoing and proposed studies. ROC was created to conduct clinical research in the areas of cardiopulmonary resuscitation and traumatic injury. ROC consists of 10 regional clinical centers in the U.S. and Canada and a data and coordinating center at the University of Washington. ROC research programs include three ongoing clinical trials and eight other potential clinical trials that are listed on the ROC website with an unspecified number of subjects. Currently there are three active ROC clinical studies listed on the clinicalTrials.gov website, n103 with a combined enrollment of approximately 20,000 subjects.

NETT was created to conduct large "simple" trials to reduce the burden of very acute injuries and illnesses affecting the brain, spinal cord and peripheral nervous system. n104 The NETT network consists of 17 regional hubs, each with several community hospitals, a statistical and data management center and a clinical coordinating center located at the University of Michigan. NETT has one ongoing study that is being conducted with standard informed consent in subjects with acute ischemic stroke. Three other studies evaluating treatments for status epilepticus, Bell's palsy and traumatic brain injury are being planned.

PECARN conducts "high-priority, multi-institutional research" in pediatric emergency care. n105 The PECARN network consists of a data coordinating center, four research node centers, and over 20 hospital emergency department affiliates. Currently there are no active PECARN studies listed on the ClinicalTrials.gov website, however, a feasibility study of therapeutic hypothermia after cardiac arrest in children is in preparation for a future randomized controlled trial. PECARN

[*234] has varied research programs and completed clinical studies that are listed on the organization's website.

In addition to the three emergency research networks, NHLBI is funding one very large clinical trial with waiver of consent. The IMMEDIATE (Immediate Metabolic Myocardial Enhancement During Initial Assessment and Treatment in Emergency Care) Trial is evaluating whether giving an intravenous solution of readily available medications (glucose, insulin and potassium), referred to as "GIK," is helpful to patients at the first signs of a heart attack. n106 The IMMEDIATE Trial coordinating center is based at the Center for Cardiovascular Health Services Research at the Institute for Clinical Research and Health Policy Studies at Tufts-New England Medical Center in Boston. Currently there are three regional coordinating centers: in Massachusetts (two local centers), Texas (four local centers) and Wisconsin (five local centers).

A. Completed and Ongoing Studies

Sponsors of emergency research studies are required to submit public disclosure documents to FDA Docket 1995S-0158, n107 and ongoing and completed studies described in this article were compiled from posts to this Docket. Clinical study details were obtained primarily from information on the ClinicalTrials.gov website n108 with some additional information from published articles. Eight completed studies and seven ongoing studies were identified and are summarized in the next section. *If projected enrollment goals are met, over 36,000 nonconsenting patients with life-threatening conditions will be enrolled in the ongoing emergency research studies, with the addition of an unknown number of patients in upcoming planned studies.*

1. Completed Study: Positive Results

Public Access Defibrillation: The University of Washington PAD Clinical Trial Center sponsored the Public Access Defibrillation (PAD) study n109 (funded by NHLBI and several defibrillator manufacturers n110). This randomized, community-based, controlled, multicenter study involved community units (e.g., shopping malls and apartment complexes) assigned either to a CPR-AED group or to a CPR group. In the CPR-AED group, lay volunteers from units assigned to this group were trained to recognize a cardiac arrest, call 911 and perform cardiopulmonary resuscitation (CPR) plus use of automated external defibrillators (AEDs). In the CPR alone group, lay volunteers from units assigned to this group were trained to recognize a cardiac arrest, call 911 and perform CPR alone. The primary outcome measure was survival to hospital discharge. More than 19,000 volunteer responders from 993 community units in 24 U.S. and Canadian regions participated in the

[*235] study. Results indicated that there were 526 "presumed" cardiac arrests, and this number was subsequently reduced by 55% to 235 "definite" cardiac arrests in a post hoc blinded review. There were more survivors of definite cardiac arrest to hospital discharge in the CPR-AED group (30 survivors among 128 arrests) than there were in the CPR alone group (15 survivors among 107 arrests; $P=0.03$). Of all completed emergency research studies, the PAD trial was the only one to report a statistically significant positive outcome.

2. Completed Study: Negative Results

Diaspirin Cross-Linked Hemoglobin: This was the first clinical trial to be conducted under the Emergency Research Rule. Baxter Healthcare Corporation sponsored this randomized, double-blind, placebo-controlled multicenter study comparing standard care plus diaspirin crosslinked hemoglobin (DCLHb) with standard care plus saline placebo in the initial resuscitation of subjects experiencing severe traumatic hemorrhagic shock. n111 Interim data were analyzed according to treatment received, and the observed 28-day mortality was 8 of 46 (17 percent) in the saline solution group and 24 of 52 (46 percent) in the DCLHb group ($p=.003$). The DMC recommended suspension of subject enrollment, and the trial was terminated after only 112 patients were enrolled (98 treated) of the planned 850 subjects.

3. Completed Studies: No Significant Differences

Magnesium and Diazepam after Cardiac Arrest: The University of Washington sponsored this double-blind, placebo-controlled, randomized clinical trial to determine if magnesium, diazepam, or both, when given immediately following resuscitation from out-of-hospital cardiac arrest, would increase the proportion of patients awakening, defined as following commands or having comprehensible speech. n112 A total of 300 patients were enrolled in this study, and results indicated that neither magnesium nor diazepam significantly improved neurologic outcome from cardiac arrest. No adverse effects were identified.

Humanized monoclonal antibody Hu23F2G: ICOS Corporation sponsored this randomized, double-blind, multicenter, placebo-controlled study that evaluated standard of care plus Hu23F2G compared with standard of care plus placebo for treatment of subjects with traumatic injury in hemorrhagic shock. n113 A total of 150 subjects in 11 trauma centers were enrolled in the study. Results indicated that there was no difference in efficacy or safety results of subjects that received standard of care plus Hu23F2G versus standard of care plus placebo, although there was a suggestion that a higher dose might be beneficial. An analysis of consenting subjects indicated that 14 percent of subjects were able to sign their own consent, 53 percent of subjects were enrolled with assent of a family member, and 33 percent of subjects were enrolled with waiver of consent.

[*236] ResQ-Valve (Impedance Threshold Device): CPRx LLC sponsored this randomized, double-blind, single-center, placebo-controlled study comparing standard CPR plus the ResQ-Valve impedance threshold device with CPR plus a sham valve. n114 A total of 230 patients were enrolled in the study, and although more patients survived to intensive care unit admission if the CPR included the ResQ-Valve rather than the sham valve (25 percent vs. 17 percent), the result was not statistically significant ($p = 0.13$). Adverse events and complication rates were similar for the two groups.

Vasopressin Plus Epinephrine During CPR: The University of Pittsburgh sponsored this randomized, double-blind, placebo-controlled single-center study in subjects with nontraumatic cardiac arrest comparing standard of care (i.e., CPR with epinephrine) plus vasopressin with standard of care plus saline control. n115 A total of 325 patients were enrolled in the study, and no differences between the groups were reported for either rate of return of spontaneous circulation or survival duration for subjects admitted to the hospital.

Hypertonic Resuscitation for Blunt Trauma: The University of Washington sponsored this randomized, double-blind, single-center, placebo-controlled study (funding by NHLBI) that evaluated the occurrence of adult respiratory distress syndrome (ARDS) and other clinical outcomes in patients in hypovolemic shock following blunt traumatic injury who received either hypertonic saline with dextran resuscitation or standard care, i.e., lactated ringer's solution (placebo) resuscitation. n116 A total of 209 patients enrolled in the study and no difference was found in the development of ARDS or impact on mortality between the two groups.

PolyHeme (Polymerized Human Hemoglobin): Northfield Laboratories sponsored a randomized, open-label, placebo-controlled multicenter study of PolyHeme, which is a human hemoglobin-based temporary oxygen-carrying red blood cell substitute for the treatment of life-threatening blood loss when an oxygen-carrying fluid is required and red blood cells are not available. n117 The PolyHeme study had two phases: one phase was conducted at a pre-hospital setting at the scene of an accident or injury and the other was conducted at an in-hospital setting. During the pre-hospital phase, subjects were enrolled under the Emergency Research Rule and randomized to receive either saline (standard treatment) or PolyHeme. During the in-hospital phase, subjects who had been randomized to receive saline continued to receive saline, but these subjects were also given blood as needed, while those in the PolyHeme group continued to receive up to six units of PolyHeme for up to 12 hours (no blood). n118 Eligible subjects not wishing to participate in emergency research studies were enrolled in the PolyHeme study unless they were wearing a plastic blue wristband provided by Northfield Laboratories at the time the study EMS providers arrived at the scene of the accident or injury.

[*237] Enrollment of 722 subjects was completed in July 2006, and in December of that year Northfield Laboratories reported top-line study results, indicating that the primary endpoint in the modified intent-to-treat population was not statistically significant and that there were slightly more deaths (approximately 3 percent, not statistically significant) in patients treated with PolyHeme than with saline control. n119 More promising results were reported in the per protocol analysis. Northfield Laboratories reported in its 2007 annual report that it intends to submit a Biologic License Application (BLA) during the first half of 2008. n120

The PolyHeme study resulted in heightened public awareness and scrutiny of FDA's Emergency Research Rule. Numerous news reports, scientific publications and internet posts have addressed the PolyHeme study. For example, respected members of the emergency research scientific community warned IRBs that the PolyHeme study failed to meet ethical and regulatory standards, n121 and U.S. Senator Chuck Grassley sent an emotionally charged letter to Andrew C. von Eschenbach, then FDA Acting Commissioner, regarding the opt-out bracelets in the PolyHeme study as well as FDA's oversight of emergency research studies:

The idea that FDA would put the burden on the public to opt out of this mass experiment is outrageous. Why should Americans have to wear a bracelet at all times to protect themselves from a government-sanctioned medical experiment if they happen to get into a car accident? I understand the value of a viable blood substitute, but I'm really disturbed by what I'm hearing about FDA's role here and I want to find out what's going on. n122

Grassley followed the von Eschenbach letter with one to Michael Levitt, HHS Secretary, expressing serious concerns about the protections afforded to inhabitants of the 32 communities and 18 states and where the studies were being conducted, and he disclosed an internal breakdown between FDA and Office for Human Research Protections (OHRP) as indicated by the following:

OHRP officials told my Committee staff that after FDA asserted exclusive jurisdiction over the PolyHeme Study, OHRP expressed its urgent concerns to FDA officials over the course of a year and a half. These urgent concerns were raised to the Acting FDA Commissioner and to the Assistant Secretary level within HHS. According to the Director of OHRP and his staff, this was the first and only time OHRP had to formally elevate its urgent concerns to the level of FDA Commissioner. These same officials stated that OHRP would not have approved the PolyHeme Study because its design and implementation remains unethical. n123

The unresolved issues between OHRP and FDA became moot when Northfield Laboratories halted enrollment of the PolyHeme studies a few months after the Grassley letters were sent.

[*238] 4. *Ongoing Emergency Research Studies*

Seven ongoing studies were identified from FDA Docket 1995S-0158t n124 and information about these studies was obtained from the ClinicalTrials.gov website. n125 A summary of these studies follows:

. IMMEDIATE Trial: Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care Trial. n126

Responsible Party (Primary Funding): Tufts New England Medical Center (NINDS).

Purpose: Determine the effects of early administration of glucose, insulin and potassium in reducing mortality in acute coronary syndromes.

Design: Treatment, Randomized, Double Blind Placebo Control, Parallel Assignment, Efficacy Study.

Interventions: Glucose, insulin and potassium and dextrose 5 percent placebo.

Opt-out mechanism: Unknown.

Waiver of Consent Disclosed: No.

No. of Study Centers: 8 study centers in Massachusetts, Texas and Wisconsin.

Estimated Enrollment (Time Period): 15,450 subjects (11/2006-3/2012).

. ROC Pre-hospital Resuscitation Using an Impedance Valve & Early vs. Delayed Analysis (PRIMED Study) n127

Responsible Party (Primary Funding): ROC Clinical Trial Center-University of Washington (NHLBI).

Purpose: Look at two different treatments during a cardiac arrest that occurs outside of the hospital and whether either or both treatments will increase the number of people who live to hospital discharge.

Design: Treatment, Randomized, Double Blind, Active Control, Factorial Assignment, Efficacy Study.

Interventions: Impedance threshold device (ITD) and sham ITD.

Waiver of Consent Disclosed: No.

Opt-out mechanism: Bracelet requested from ROC worn when EMS providers arrive.

No. of Study Centers: 10 in United States and Canada.

Estimated Enrollment (Time Period): 14,154 subjects (5/2007-9/2009).

. Phase 3 Study of Hypertonic Resuscitation Following Traumatic Injury with Hypovolemic Shock n128

[*239] *Responsible Party (Primary Funding):* ROC Clinical Trial Center-University of Washington (NHLBI).

Purpose: To determine if hypertonic saline with and without dextran can improve overall survival in victims of trauma with shock.

Design: Treatment, Randomized, Double Blind, Placebo Control, Parallel Assignment, Safety/Efficacy Study.

Interventions: 7.5 percent hypertonic saline/6 percent Dextran-70, 7.5 percent hypertonic saline, and 0.9 percent normal saline.

Waiver of Consent Disclosed: No.

Opt-out mechanism: Bracelet requested from ROC worn when EMS providers arrive.

No. of Study Centers: 10 in United States and Canada.

Estimated Enrollment (Time Period): 3, 726 (5/2006-4/2010).

. Phase 3 Study of Hypertonic Resuscitation Following Traumatic Brain Injury n129

Responsible Party (Primary Funding): ROC Clinical Trial Center-University of Washington (NHLBI).

Purpose: To determine if hypertonic saline with and without dextran can improve neurologic outcomes in victims of severe traumatic brain injury.

Design: Treatment, Randomized, Double Blind, Placebo Control, Parallel Assignment, Safety/Efficacy Study.

Interventions: 7.5 percent hypertonic saline/6 percent Dextran-70, 7.5 percent hypertonic saline, and 0.9 percent normal saline.

Waiver of Consent Disclosed: No.

Opt-out mechanism: Bracelet requested from ROC worn when EMS providers arrive.

No. of Study Centers: 10 in United States and Canada.

*Estimated Enrollment (Time Period):*2,122 (5/2006-4/2010).

. Prospective, Randomized, Double-Blind, Multi-Center Trial of Low Dose Vasopressin Versus Placebo in Traumatic Shock Resuscitation n130

Responsible Party (Primary Funding): University of Texas Health Science Center at San Antonio (Same).

Purpose: To test the hypothesis that resuscitation regimens which minimize the total volume of resuscitation fluid, while restoring organ perfusion, will lead to lower morbidity and mortality in critically ill patients following trauma.

Design: Treatment, Randomized, Double-Blind, Placebo Control, Single Group Assignment, Efficacy Study.

Interventions: Vasopressin and placebo.

Waiver of Consent Disclosed: No.

Opt-out mechanism: Unknown.

No. of Study Centers: 1 in Texas.

*Estimated Enrollment (Time Period):*333 (2/2007-unspecified).

[*240] . Effects of Erythropoietin on Cerebral Vascular Dysfunction and Anemia in Traumatic Brain Injury n131

Responsible Party (Primary Funding): Baylor College of Medicine (NINDS).

Purpose: To determine the effect of early administration of recombinant human erythropoietin on long-term neurological outcome after severe traumatic brain injury.

Design: Treatment, Randomized, Double Blind (Subject, Investigator), Placebo. Control, Factorial Assignment, Efficacy Study.

Interventions: Recombinant human erythropoietin (rhEpo) and placebo.

Waiver of Consent Disclosed: No.

Opt-out mechanism: Unknown.

No. of Study Centers: 2 in Texas.

*Estimated Enrollment (Time Period):*200 (4/2006-2/2011).

. Treatment of Ventricular Tachyarrhythmias Refractory To Shock With Beta Blockers: The SHOCK and BLOCK Trial n132

Responsible Party (Primary Funding): William Beaumont Hospitals (Medtronic/Vitatron).

Purpose: To evaluate the effectiveness of metoprolol, a "beta blocker," in treating patients in the hospital with a cardiac arrest.

Design: Treatment, Randomized, Double-Blind, Active Control, Parallel Assignment, Safety/Efficacy Study.

Interventions: Standard of care plus metoprolol or standard of care with epinephrine.

Waiver of Consent Disclosed: No.

Opt-out mechanism: Unknown.

No. of Study Centers: 1 in Michigan.

*Estimated Enrollment (Time Period):*100 (1//2007-11/2009).

NIH is sponsoring five of the seven ongoing emergency research studies. None of these studies disclose on the ClinicalTrials.gov website that the studies are being conducted with waiver of consent. Also, none of the studies list under exclusion criteria that subjects will be excluded if a subject, LAR or family member objects to the subject's participation. In addition, there are no exclusion criteria associated with locating an opt-out mechanism (e.g., opt-out bracelet, signed card in subject's wallet, etc.) indicating that a subject does not wish to participate in an emergency research study.

V. EVALUATING FDA'S 1996 ASSUMPTIONS ABOUT EMERGENCY RESEARCH

A. Most Studies Will Have Commercial Sponsors

A key assumption in the 1996 preamble to the Emergency Research Rule was that emergency research studies would have commercial sponsors who would be

[*241] submitting marketing applications (e.g., new drug application (NDA), biologics license application (BLA), or premarket approval application (PMA)) to FDA. n133 This is an important assumption because commercial sponsors generally have experience managing FDA-regulated clinical studies and have an infrastructure for complying with IND/IDE regulations. Also, FDA intended to use the reporting and record keeping requirements associated with these regulatory activities to assess how well the Emergency Research Rule was working. n134

A review of ongoing emergency research studies shows that all of the ongoing emergency research studies are sponsored by academic or healthcare organizations. Such noncommercial sponsors often have little experience with IND/IDE sponsor responsibilities. n135 This is because many federally funded studies are conducted either to evaluate procedures (e.g., different surgical techniques) that are not FDA regulated or to evaluate marketed products in studies that often are exempt from IND/IDE regulations. Also, when noncommercial sponsors do participate in studies evaluating FDA-regulated products, the IND/IDE often is held by a commercial sponsor, and the role of academic institution or healthcare organization is to perform the clinical research.

Based on a review of the websites of ROC, n136 NETT, n137 PECARN n138 and IMMEDIATE Trial n139 as well as their listings on ClinicalTrials.gov and documents obtained under the Freedom of Information Act (FOIA) for the ROC studies, it appears that these sponsors are not complying with IND/IDE sponsor regulations. For example, sponsors are required to monitor research studies to assure adequate protection of the rights and safety of human subjects as well as the quality and integrity of the data collected in the study, n140 and only NETT has standard operating procedures for limited monitoring of regional hubs without on-site monitoring of local hospitals. n141 There may be a mistaken assumption that satisfying the requirement for a DMC to exercise oversight of the clinical investigation is the only monitoring responsibility of sponsors of emergency research studies.

B. Valid Scientific Evidence Will Be Collected

The Emergency Research Rule requires that valid scientific evidence will be collected from these studies. n142 There is a very high standard for the quality of scientific information obtained from studies conducted by commercial sponsors to obtain FDA approval to market a product, or expand a product's labeling. These sponsors are required to submit to FDA detailed study reports, integrated summaries of safety and effectiveness, raw data and specified case report forms. n143

[*242] Also, many processes are in place to ensure the quality of the data is high, such as the use of validated databases and analysis software. The quality of the data is further ensured by FDA's external oversight activities including auditing clinical investigators, sponsors and product manufacturers. However, if a study is conducted by academic institutions and healthcare organizations for publication in a peer-reviewed journal and distribution to the scientific community, FDA generally will not perform external audits, receive detailed study reports or confirm the quality of the data by independent analyses. In situations where nonconsenting subjects are being enrolled into emergency research studies without commercial sponsors, it is especially important that FDA carefully review study designs in protocols in the initial IND/IDE submission to ensure that nonconsenting subjects are not enrolled into studies with study designs that cannot achieve the requirement that valid scientific evidence be collected. n144

It is also important that FDA review protocol procedures for collecting safety data. For example, in the protocol for the ROC PRIMED study, the section describing procedures for collecting unexpected adverse device events states that "[t]he death or neurological impairment of an individual patient is not considered an adverse event in this study." n145 The review of safety procedures by FDA is especially important with noncommercial sponsors who may not be familiar with IND/IDE requirements for collecting and reporting adverse events.

C. Notification that Subject Can Discontinue Participation

One of the most important of the special protections afforded by the Emergency Research Rule is that if a nonconsenting subject is enrolled in an emergency research study, *at the earliest feasible opportunity* the subject, LAR and family members are to be informed that the subject is in the study and provided with an opportunity to discontinue the subject's participation in the study. n146 The ROC PRIMED protocol does not include any references to notifications of family members. Rather, it only references notifications to the subject and the subject's representative, and no provisions are made to allow a family member to object to the subject's initial or continuing participation in the study.

The ROC PRIMED protocol also disregards Emergency Research Rule notification rights of subjects and LARs concerning discontinuation of subjects participating in the ROC PRIMED study:

[*243] The local ROC investigator will provide information about the emergency research study to the patient or their representative at the earliest feasible opportunity after administration of the intervention. Since in many cases this will be while the patient is still hospitalized, *this will not include a request for consent for further participation/intervention*, [emphasis added] but will provide the patient/representative contact names/numbers for purposes of obtaining further information if desired. n147

The protocol justifies this policy in a Request for Waiver of Written Consent that is "seeking to review the clinical record without documented consent under minimal risk criteria." This request explains that "[i]f consent is required for this review but not granted then these data are missing during analysis." n148

It is unknown whether other ongoing emergency researchers have taken a similar position with respect to Emergency Research Rule notification rights. The ROC PRIMED protocol is important to carefully review because this study plans to enroll 14,154 subjects, a large percentage of the total number of subjects who will be enrolled into emergency research studies.

D. Community Consultation Will Be Successfully Implemented

FDA held a public hearing in 2006 to discuss the emergency research process with invited speakers from the emergency research community and other interested parties. n149 In general, the emergency research community indicated that it was supportive of the requirements in the Emergency Research Rule and appreciative of FDA's efforts to restore clinical investigations involving subjects unable to provide informed consent. Concerns expressed at the 2006 Public Hearing and in follow-up comments to FDA's docket suggested that the methods used to achieve community consultation have reached only a small fraction of the community and that those who do attend public meetings may not be representative of the at-risk community being studied. n150 In addition to meetings not being well attended, the community has been hard to reach through television and newspaper articles due to the volume of competing messages and also because emergency research is not something most people want to think about. n151 Consequently, community consultation was found to be a "cumbersome and futile exercise" that was not providing the intended patient safeguards. n152

Clearly, many emergency research investigators have spent considerable time, money and resources on unsuccessful community consultation activities. One obvious observation is that investigators and IRB members usually are not trained in media and communications. Based on review of samples of a press release and letter to community leaders used to comply with the community consultation

[*244] requirement, n153 it is possible that the low attendance at community consultation functions may have been associated with the similarity of these materials to clinical trial recruiting advertisements that come in the mail and are heard on television and radio. Also, some of the documents either do not disclose that the study involves waiver of informed consent or this critical fact is buried in the body of the document. Consequently, there does not appear to be any motivation for persons to attend community consultation meetings. One other important consideration in the low success rate of community consultation is that investigators and IRB members usually do not have media and communications training, and few have involved professional health communication firms to ensure that information regarding research with waiver of consent is provided to the community in a productive and efficient manner. Currently, many cities and corporate firms have community responsibility programs and study-related communication services in many areas can be obtained at no cost or at a reasonable fee. n154

In general, researchers who made presentations during the 2006 public hearing were dissatisfied with the community consultation requirement because of the significant time and costs associated with community consultation. A key concern of several researchers n155 is that there has been very little research on the process of community consultation, and it has not been shown that subjects are being protected by community consultation. Objective outcome measures that can find best practices as well as evaluate the adequacy and appropriateness of community consultation need to be identified and validated. Others expressed dissatisfaction with delays in IRB approval, lack of community response to attempts at community consultation, low retention of information presented, etc. Because community consultation provides an important protection to emergency research subjects, it is important that FDA work with sponsors, investigators and IRBs to develop effective and efficient community consultation programs reach a large percentage of the target communities.

E. Appropriate Public Disclosures Will Be Made

Public disclosure of study-related information is required prior to study initiation and after completion of the study. While community consultation challenges primarily deal with finding methods to meet face-to-face with the community, public disclosure issues involve determining what information should be disclosed. FDA has provided guidance on methods for public disclosure of study information. n156 However, there are no regulations or guidance regarding the extent of public disclosure required to satisfy the requirement.

[*245] 1. *Disclosure of Research Documents*

One of the major controversies surrounding the public disclosure requirement is whether key study documents (e.g., informed consent, protocol and investigators brochure, etc.) should be disclosed. While some investigators argue that transparency demands that such materials be available either on request or be posted on internet websites and FDA's docket, n157 others argue against making the materials available to the public. n158 There are concerns that the information in the documents may not actually reach the public as intended or that intellectual property will be compromised, creating a significant barrier to research. FDA's position is that research information such as protocol, investigators brochure and information should be released to the community. n159

2. *Disclosure that Informed Consent is Waived*

As previously mentioned for community consultation, study notifications often do not disclose that the study is being conducted with waiver of informed consent or bury this information within disclosed documents. Disclosure that a study is being conducted without including notification of waiver of informed consent not only reduces the value of the disclosure, but is also misleading. None of the ongoing emergency research studies posted on the ClinicalTrials.gov website disclose that the study involves waiver of consent.

3. *Disclosure Accuracy*

All of the materials on FDA Docket No. 199-0158 have first been reviewed by IRBs and submitted to FDA prior to being posted on the docket. Review of some documents posted on the docket suggests that not all public disclosure documents are being examined by IRBs and FDA. Some posts were found to contain disclosures that indicate patients enrolled in emergency research studies are being provided with inaccurate information about research studies with waiver of consent. n160 Also

[*246] many of the documents either do not mention that the study is being conducted with waiver of consent or this information is buried within the text.

4. Public Disclosures after Study Completion

There have been relatively few completed emergency research studies, however, there is evidence that post-study disclosures are working well. For example, the PolyHeme study was completed in July 2007, results were presented at the American College of Surgeons 93rd Annual Clinical Congress in October, n161 and study results were distributed to communities in the form of a press release in November. n162 With the recently enacted Food and Drug Administration Amendments Act of 2007 (FDAAA 2007), drug and device trials such as those being conducted under emergency research are required to be posted on the ClinicalTrials.gov website. n163

F. Emergency Research Studies Will Include Opt Out Procedures

The Emergency Research Rule does not require that studies provide a mechanism for subjects to opt out if they do not wish to participate in the research. However, the preamble to the Final Research Rule provided several ways for individuals to express objections to participating in the research. n164 The Draft Guidance also states that "[t]he clinical investigation should provide that first responders examine, as time permits, easily accessible sources of information, such as an individual's medical identification bracelets or necklaces, for evidence that may be related to that individual's willingness to participate in research." n165

The wristband as an opt-out mechanism has been the target of much controversy. In the recently completed PolyHeme study, patients could opt-out by ordering and wearing a light blue wristband imprinted with a statement indicating the person declined the PolyHeme Study. As previously mentioned, Senator Charles Grassley expressed his indignation with the opt-out wristbands in letters sent to senior FDA officials. n166 The ongoing ROC studies have designated bracelets as the opt-out device for all three of the active studies. n167 However, a review of exclusion criteria on the ClinicalTrials.gov website does not list a subject wearing a bracelet as an exclusion criterion, and the case report forms that EMS providers complete do not include any items to check or complete to indicate that a subject wearing a

[*247] bracelet would not be enrolled. n168 It is not known what, if any, opt-out mechanisms are being considered for other ongoing emergency research studies.

There are two main issues with implementing opt-out mechanisms. First, opt-out mechanisms can be effective only if community members are aware that opt-out mechanisms are available if they do not wish to be enrolled in a study with waived informed consent. Second, EMS providers must be trained to check for the opt-out mechanism described in the protocol. Although the first priority of EMS providers is to provide medical care, EMS providers participating in clinical trials do not follow routine procedures for emergency care, but rather they follow set study procedures for administering the assigned study treatment and completing study records. Procedures for quickly checking one specific location (e.g., wrist, wallet, etc.) for an opt-out device could be included in the EMS providers training. Both of the two issues regarding the opt-out mechanism can be addressed in a straightforward manner: the first by having the opt-out cards widely available, and the second by EMS provider training.

G. IRBs Can Handle the Additional Responsibilities

FDA made it clear in the preamble to the 1996 regulation that it intended for an institutional IRB to review all studies performed in the institution. The agency prohibited delegation of review responsibility for emergency research studies to another IRB unless the institution and its IRB agreed in writing to the delegation of review responsibility. n169 Given that FDA conferred IRBs with much of the responsibility for protecting the health and safety of nonconsenting subjects participating in emergency research studies, it is important to evaluate the performance of IRBs in carrying out these responsibilities.

Recently, uniform concern has been raised about the variability of expertise among IRBs reviewing emergency research activities, especially when an extremely large number of IRBs are reviewing the same multicenter study. There were 101 separate IRBs that reviewed the PAD study n170 and 32 IRBs reviewed the PolyHeme study. n171 Biros noted that there are variable levels of comfort and experience among IRBs regarding exception from informed consent and asked whether it was "reasonable to expect that all IRBs will achieve a working knowledge of this complex and infrequently used rule?" n172 Weisfeldt reported that he has found that few IRBs are equipped with experts to make the required judgments required for emergency research studies, especially with respect to cardiac arrest in out-of-hospital settings and severe traumatic injury in which the majority of these patients will die. n173

Many emergency research investigators have suggested that some type of central IRB or National Advisory Panel should be convened to review emergency research studies. A breakout group from the 2005 *Academic Emergency Medicine*

[*248] Consensus Conference overwhelmingly endorsed the idea of a national advisor group consisting of resuscitation researchers, physicians and ethicists. n174 Such a group could assess the scientific validity of studies requesting emergency exception from informed consent and provide a medical perspective and then give feedback to the local IRBs and FDA. The breakout group rejected the idea of a national IRB due to concerns regarding whether it could adequately take local cultural variability into account. Along these same lines, Schmidt found that most IRB chairs do not support a centralized IRB, and only 6 percent endorsed the idea of a national IRB for emergency research studies. n175 Weisfeldt proposed the formation of a national consensus advisory panel that could be constituted as an advisory to FDA, NIH, and local IRB or government agencies for emergency research studies and review could be mandatory or voluntary. n176 IRB chairs, on the other hand, reported a different perspective on their qualification to review emergency research studies. Schmidt n177 reported results from a survey of the chairs of the IRBs at all U.S. allopathic medical schools and found that most of the IRB chairs (68 percent) felt adequately trained to review emergency research studies.

Silbergleit has proposed that a central IRB (CIRB) for emergency research set up along the lines of the CIRB that the National Cancer Institute (NCI) set up in 2001 to conduct oncology studies n178 could satisfy the concerns of investigators, sponsors, IRBs and FDA. n179 As Silbergleit points out, given that NIH has recently funded ROC, NETT and PECARN--as well as the IMMEDIATE trial--that together intend to enroll tens of thousands of patients in emergency research studies in the near future, it is important that an IRB system be in place to ensure that any IRB reviewing emergency research has the expertise and resources to handle the responsibility and authority vested into IRBs under the Emergency Research Rule.

H. The Rights and Welfare of Subjects Will Be Protected

FDA and IRBs make considerable upfront efforts to ensure that subjects enrolled in emergency research studies will be protected and that the study will provide scientifically useful information. However, there is a serious lapse in oversight of ongoing emergency research studies because 1) most IRBs reviewing emergency research protocols are considered to lack the expertise and resources to carry out the responsibilities in the Emergency Research Rule; 2) FDA generally exercises limited oversight of ongoing studies; and 3) sponsors are primarily academic institutions and healthcare organizations with minimal or no monitoring plans other than establishment of a DMC.

FDA has full authority over research conducted under the Emergency Research Rule. With a few modifications to FDA policies and procedures that already are in place, nonconsenting subjects can have the protections FDA intended when the regulation was adopted. Suggested modifications include:

[*249] . Ensure that all sponsors of emergency research studies--especially noncommercial sponsors--understand the responsibilities of sponsors and investigators under IND/IDE regulations and have policies and procedures in place to ensure good clinical practices are followed prior to issuing IND/IDE authorization letters.

. Require that study protocols or other associated documents being provided to FDA include procedures that will be used in monitoring the study, a summary of training of EMS providers, especially training to identify opt-out devices and to obtain informed consent or opportunity for LAR or family members to object.

. Notify sponsors, investigators and IRBs participating in ongoing studies that failure to inform subjects, LARs and family members *at the earliest feasible opportunity* of a subject's enrollment in an emergency research study and failure to provide an opportunity for these individuals to discontinue a subject from the study are significant violations of federal regulations that can result in considerable sanctions such as disqualification of the investigator, withdrawal of IRB assurance and discontinuation of the investigation, etc.

. Notify OCR that emergency research studies are being conducted to provide OCR with an opportunity to schedule compliance reviews to ensure compliance with the Privacy Rule. (FDA could copy OCR on IND/IDE authorization letters.)

. Increase FDA's presence in ongoing clinical studies by requesting that FDA's Bioresearch Monitoring (BIMO) program conduct on-site clinical investigator inspections. n180 BIMO IRB and sponsor inspections also should be conducted.

. Require that emergency research studies disclose in their ClinicalTrials.gov postings that the study is being conducted under waiver of consent and also describe opt-out procedures.

. Consult with independent medical experts on conditions being evaluated in emergency research studies to ensure that the therapeutic window is reasonable and an appropriate amount of time has been allocated to obtain consent.

. Consult with independent statisticians (i.e., not involved in the study) to ensure that the study design and the data collection and analysis plan will lead to scientifically sound data and conclusions. The design of studies involving thousands of nonconsenting subjects should be carefully scrutinized, and the independent statistician should concur that the primary outcome measure is being effectively evaluated with the minimum number of subjects enrolled to achieve a valid result. Procedures that are not routinely used such as randomization by "clusters" or other nonstandard study designs or analyses should be carefully reviewed.

[*250] . Reevaluate FDA's position on a central IRB based on researchers concerns regarding the capability of local IRBs to carry out their responsibilities under the Emergency Research Rule and consider establishment of a CIRB similar NCI's CIRB.

VI. CONCLUSIONS

The Emergency Research Rule provides a narrow exception to the informed consent regulations and allows researchers to conduct a limited class of research activities with waiver of consent for subjects with life-threatening conditions such as major traumatic injuries, sudden cardiac arrest and stroke. The Emergency Research Rule balances the need for the high quality clinical research to develop better treatments for critically ill patients while continuing to protect the rights and welfare of nonconsenting research subjects. For most of the first 10 years after the emergency research rule was adopted, the rule was rarely used. However, more recently, NIH has sponsored large research networks and a clinical trial center to conduct emergency research studies with waiver of consent. Tens of thousands of patients are planned to be enrolled in these studies.

The Emergency Research Rule is sound and can provide adequate safeguards for the many subjects who are to be enrolled in research studies with waiver of consent over the next few years. Based on experience with the first decade of the Emergency Research Rule, it is suggested that FDA evaluate the capability of local IRBs to carry out their responsibilities and consider establishment of a CIRB for emergency research. Also, as the Emergency Research Rule moves into its second decade, FDA should consider the capabilities of organizations that are sponsoring emergency research studies and ensure that they can comply not only with the Emergency Research Rule but all regulations including Good Clinical Practices and sponsor regulations before an IND/IDE authorization letter is issued. Further, FDA should carefully review study protocols and increase oversight of sponsors, investigators and IRBs via the BIMO program. With tighter implementation of regulations and enhanced oversight, emergency research studies can be conducted with appropriate safeguards for the rights and welfare of ongoing and future nonconsenting research subjects.

[*251] Table 1. Exception from informed consent requirements for emergency research (12 C.F.R. § 50.24)

(a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

(2) Obtaining informed consent is not feasible because:

(i) The subjects will not be able to give their informed consent as a result of their medical condition;

(ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and

(iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:

(i) Subjects are facing a life-threatening situation that necessitates intervention;

(ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and

(iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(4) The clinical investigation could not practicably be carried out without the waiver.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

[*252] (6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is

[*253] to be provided to the subject's legally authorized representative or family member, if feasible.

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with 56.115(b) of this chapter.

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under 312.30 or 812.35 of this chapter.

(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

[61 FR 51528, Oct. 2, 1996]

[*254]

Table 2. Special IRB Responsibilities under FDA's Emergency Research Rule

Item	Responsibilities	CFR Sections
IRB Members/ Consultants	Include a licensed physician who is not participating in the clinical investigation	50.24(a)
Emergency Rule Eligibility Requirements	Find & document that all of the following conditions are met: <ul style="list-style-type: none"> . Subjects are in a life-threatening situation, . Available treatments are unproven or unsatisfactory, . A need exists to determine safety and effectiveness of intervention. . Obtaining informed consent is not feasible . There is the prospect of direct benefit to subjects . Study could not practicably be carried out without the waiver 	50.24(a)(1-4)
Standard informed consent form	Confirm standard informed consent has been prepared for use with consenting subject or LAR	50.24(a)(6)
Therapeutic Window	Determine that the length of the therapeutic window is based on scientific evidence Review procedures and information for notification during therapeutic window as appropriate: <ul style="list-style-type: none"> . LAR -- to obtain consent for subject's participation . Family members -- to provide an opportunity to object to subject's participation 	50.24(a)(5) 50.24(a)(7)(v)
Investigator Commitments	Confirm investigator has committed to: <ul style="list-style-type: none"> . Attempting to contact LAR, during therapeutic window and asking for consent * . Attempting to contact family member during therapeutic window and providing opportunity to object to subject's participation in study * . Summarizing efforts to contact LAR and family members and providing summary to IRB at time of continuing review 	50.24(a)(5) 50.24(a)(7)
Procedures for	Review procedures and	50.24(b)

Table 2. Special IRB Responsibilities under FDA's Emergency Research Rule

Item	Responsibilities	CFR Sections
Notification	<p>information used for required notifications:</p> <ul style="list-style-type: none"> . Subjects or if subject is incapacitated, LAR or family members (depending on availability): <ul style="list-style-type: none"> - Subject's inclusion in the study and details about the study - Subject's right to discontinue at any time without penalty or loss of benefits to which the subject is otherwise entitled . Subject whose condition improves - Notification about the study as soon as feasible, even if an LAR or family member has already been told about it. . Nonconsenting subject who dies before an LAR or family member can be contacted - Information about the clinical investigation is to be provided to the LAR or family member * 	
Community Consultation	<p>Ensure community consultation takes place with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn</p>	50.24(a)7(i)
Public Disclosure to the Community and Researchers	<p>Ensure public disclosure of required information:</p> <ul style="list-style-type: none"> . Disclosure before start of the study includes plans for the investigation and risks and expected benefits . Disclosure at end of the study includes notification about the study and its results 	50.24(a)(7)(ii-iii)
Data Monitoring Committee	<p>Ensure data monitoring committee has been established by the sponsor for continuing oversight of the investigation</p>	50.24(a)(7)(iv)
Procedures if Study is not Approved	<p>Follow required procedures if a study is not approved:</p> <ul style="list-style-type: none"> . Document the IRB's findings . Provide findings in writing to investigator and sponsor 	50.24(a)
Records	<p>Retain IRB determinations and</p>	50.24(c)

Table 2. Special IRB Responsibilities under FDA's Emergency Research Rule

Item	Responsibilities	CFR Sections
	documents for at least 3 years after completion of the study and make records accessible for inspection and copying by FDA	

* if feasible

LAR = legally authorized representative;

FOOTNOTES:

n1 Informed Consent and Waiver of Informed Consent Requirements in Certain Emergency Research, *61 Fed. Reg. 51,497* (Oct. 2, 1996) (codified at *21 C.F.R. § 50.24* (2007), conforming amendments codified at *21 C.F.R. §§ 50.3, 56.109, 312.2, 312.20, 312.23, 312.30, 312.42, 312.54, 312.60, 312.130, 314.430, 601.51, 812.20, 812.35, 812.38, 812.47, 814.9*.)

n2 Waiver of Informed Consent Requirements in Certain Emergency Research, *61 Fed. Reg. 51,531* (Oct. 2, 1996) (codified at *45 C.F.R. §§ 46.116(c)-(d), 46.408* (2007)).

n3 See *61 Fed. Reg. 51,498*.

n4 See *21 C.F.R. § 50.3(1)* (2007). An LAR is an individual or judicial or other body authorized under applicable law to give informed consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. The definition of an LAR is governed by state law and is inconsistently defined in the United States. See Jeffrey N. Gibbs, *State Regulation of Pharmaceutical Clinical Trials*, *59 FOOD DRUG LAW J.* 265 at 271-76 (2004) (discussion of the effect of state laws on emergency research and participation in research studies by adults who lack the capacity to consent).

n5 See *21 C.F.R. §§ 312.20, 312.54, 812.20, 812.47* (2007).

n6 Although some emergency research studies are performed without waiver of consent, for purposes of this article, the term "emergency research" means emergency research with waiver of consent.

n7 Good Clinical Practice Program, Center For Devices and Radiological Health, Center for Biologics Evaluation and Research, Center for Drug Evaluation and Research, Center for Devices and Radiological Health, Office of Regulatory Affairs, Food and Drug Administration.

Draft Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research (2006) [hereinafter *Emergency Research Guidance*], available at <http://www.fda.gov/OHRMS/DOCKETS/98fr/06d-0331-gdl0001.pdf> (last visited Dec. 10, 2007).

n8 FDA, *Public Hearing on Emergency Research and Human Subject Protections Challenges and Solutions, Dockets Management, No 2006D-0331* (Oct. 11, 2006) [hereinafter *Public Hearing*], available at <http://www.fda.gov/ohrms/dockets/DOCKETS/06d0331/06d-0331-tr00001-vol4.rtf> (last visited Oct. 4, 2007).

n9 *See infra* Part IV.

n10 *See infra* Part III.

n11 *See Public Hearing, supra* note 8, (testimony of Jeffrey Shuren, Assistant Commissioner for Policy, Office of the Commissioner, FDA).

n12 21 *C.F.R.* β 50.24(d) (2007).

n13 *Id.* §§ 312.30, 812.35 (2007).

n14 *Id.* §§ 312.2(b)(1), 812.2(c) (2007).

n15 *Id.* β 312.20(c), 812.20(a)(4)(i) (2007).

n16 *See 61 Fed. Reg. 51,509* cmt. 38. *See also 21 C.F.R. β 312.81(a)* (2007). Life-threatening includes diseases or conditions where the likelihood of death is high unless the course of the disease or condition is interrupted.

n17 21 *C.F.R.* β 50.24(a)(2)(ii) (2007).

n18 *Id.* β 50.24(a) (2007).

n19 *Id.* § 50.24(a)(2)(ii).

n20 *Id.* § 50.24(a)(2)(iii).

n21 *Id.* § 50.24(a)(1).

n22 21 *C.F.R.* § 56.107(f) (2007).

n23 *Id.* § 50.24(a)(1) (2007).

n24 *See* 61 *Fed. Reg.* 51,509 cmt. 39.

n25 21 *C.F.R.* § 50.24(a)(4) (2007).

n26 61 *Fed. Reg.* 51,513 cmt. 59.

n27 21 *C.F.R.* § 50.24(a)(3).

n28 61 *Fed. Reg.* 51,505 cmt. 21.

n29 21 *C.F.R.* § 50.24(a)(3)(ii).

n30 *See Emergency Research Guidance, supra* note 7, at 5.

n31 21 *C.F.R.* § 50.24(a)(5) (2007).

n32 *See* 61 *Fed. Reg.* 51,519 cmt. 91. The term "feasible" is used in this section and it also occurs throughout the Emergency Research Rule. Feasible incorporates the idea of "practicability" and recognizes that in some instances it may not be feasible to provide information to the subject (e.g., if the individual does not survive or is mentally incompetent), the subject's legal representative, or family member (e.g., if the identity of the subject is never determined).

n33 *21 C.F.R. β 50.24(a)(5) (2007)*.

n34 *Id. β 50.3(m) (2007)*. A family member is defined as "any one of the following legally competent persons: Spouse; parents; children (including adopted children); brothers, sisters and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship."

n35 *61 Fed. Reg. 51,506 cmt. 25*.

n36 *Id.*

n37 *Id. at 51,507 cmt. 27*.

n38 *21 C.F.R. ββ 50.24(a)(5)-(6) (2007)*.

n39 *Id. β 50.24(a)(7)(v)*.

n40 *Id. β 56.109(f)*.

n41 *See id. β 50.24(b)*.

n42 *Id.*

n43 *Id.*

n44 *21 C.F.R. ββ 312.64, 812.46 (2007)*.

n45 *Id. β 50 24(b) (2007)*.

n46 *See Emergency Research Guidance, supra note 7, at 22*.

n47 *See 21 C.F.R. β 50.25 (2007)* for required and optional elements of an informed consent form.

n48 *61 Fed. Reg. 51,498* cmt. 43.

n49 *Id. at 51,519* cmt. 94.

n50 *Id.*

n51 *Id.*

n52 *Id.*

n53 *21 C.F.R. β 50.24(a)(7)(i) (2007)*.

n54 *61 Fed. Reg. 51,500* cmt. 2.

n55 *61 Fed. Reg. 51,514* cmt. 61.

n56 *See Emergency Research Guidance, supra* note 7, at 14.

n57 *61 Fed. Reg. 51,514*, cmt. 61. Based on community consultation, the IRB may decide, among other things, that it is appropriate to attempt to exclude certain groups from participation in the investigation; or that wider community consultation and discussion is needed.

n58 *61 Fed Reg. 51,515* cmt. 64.

n59 *Id.* cmt. 65.

n60 *See* Protection of Human Subjects; Informed Consent; Proposed Rule, *60 Fed. Reg. 49,086* (Sept. 21, 1995).

n61 *61 Fed. Reg. 51,515* cmt. 66.

n62 *See 21 C.F.R. §§ 50.24(7)(ii)-50.24(7)(iii) (2007).*

n63 *See id.* § 50.24(7)(ii).

n64 *See Emergency Research Guidance, supra* note 7, at 17.

n65 *61 Fed. Reg. 51,515* cmt. 71.

n66 *21 C.F.R. § 50.24(7)(iii) (2007).*

n67 *See Emergency Research Guidance, supra* note 7, at 20.

n68 *61 Fed. Reg. 51,516* cmt. 76.

n69 *See Emergency Research Guidance, supra* note 7, at 19.

n70 *See 61 Fed. Reg. 51,516* cmt. 75. FDA considers it necessary to provide comprehensive summary data from the completed trial to the research community in order to permit other researchers to assess the results of the clinical investigation. Also, there must be a scientific need to conduct clinical investigations involving subjects who are unable to consent; if previous investigations have already provided the scientific answer, this should be shared broadly with the research community. Sufficient information may be contained in a scientific publication of the results of the completed investigation; in other instances, a publication may need to be supplemented by additional information.

n71 *21 C.F.R. § 56.109(g) (2007).*

n72 *Id.* §§ 312.54(a) and 812.47(a)(2007) describe procedures for submitting public disclosure information to FDA's Dockets Management Branch.

n73 *61 Fed. Reg. 51,515* cmt. 66.

n74 *21 C.F.R. β 50.24(7)(iv) (2007)*.

n75 *60 Fed. Reg. 49,096*.

n76 *61 Fed. Reg. 51,517 cmt. 79*.

n77 *21 C.F.R. ββ 312.32, 312.56(d), β 812.150(b)(1)*.

n78 Center for Biologics Evaluation and Research, Center for Drug Evaluation and Research, Center for Devices and Radiological Health, Food and Drug Administration, Guidance for Clinical Trial Sponsors, Establishment and Operation of Clinical Trial Data Monitoring Committees (2006), <http://www.fda.gov/CBER/gdlns/clintrialdmc.pdf> (last visited Oct. 10, 2007).

n79 *21 C.F.R. β 50.24(e) (2007)*.

n80 *61 Fed. Reg. 51,522 cmt. 103*.

n81 *21 C.F.R. ββ 50.24(e), 312 54(b), 812.47(b) (2007)*.

n82 *61 Fed. Reg. 51,504 cmt. 18*.

n83 *61 Fed. Reg. 51,502 cmt. 10*.

n84 Standards for Privacy of Individually Identifiable Health Information (Privacy Rule) establishes a set of national standards for the protection of certain health information. The U.S. Department of Health and Human Services (HHS) issued the Privacy Rule to implement the requirement of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), Pub. L. No. 104-191, *110 Stat. 1936* (codified in scattered sections of 42 U.S.C. and 29 U.S.C.) that was enacted on August 21, 1996. *See* Standards for Privacy of Individually Identifiable Health Information, *65 Fed. Reg. 82461* (Dec. 28, 2000) and final modifications to the Privacy Rule in Standards for Privacy of Individually Identifiable Health Information, *67 Fed. Reg. 53,18* (Aug. 14, 2002) (codified in 45 C.F.R. Parts 160 and 164). *See also* the HHS Office for Civil Rights (OCR) Home Page, <http://www.hhs.gov/ocr/hipaa> and the Office for

Human Research Protections (OHRP) Home Page <http://hhs.gov/ohrp> (last visited Feb. 4, 2008).

n85 *See 45 C.F.R. § 160.103 (2007)*. The Privacy rule regulates "covered entities," that are defined in the HIPAA rules as 1) health plans, 2) health care clearinghouses, and 3) health care providers who electronically transmit any health information in connection with transactions for which HHS has adopted standards. Generally, these transactions concern billing and payment for services or insurance coverage. For example, hospitals, academic medical centers, physicians and other health care providers who electronically transmit claims transaction information directly or through an intermediary to a health plan are covered entities. Covered entities can be institutions, organizations or persons. The term Researchers is used to mean persons engaged in research that are associated with a covered entity.

n86 *See id.* "Individually identifiable information" is information that is a subset of health information, including demographic information collected from an individual, that 1) is created or received by a health care provider, health plan, employer or health care clearinghouse, and 2) also relates to the past, present or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present or future payment for the provision of health care to an individual; and 3) that identifies the individual or there is a reasonable basis to believe the information can be used to identify the individual. Individually identifiable health information includes eighteen common identifiers (e.g., name, address, birth date, telephone number, s, e-mail address, social security number, etc.).

n87 *See id.* § 164.508(c) (describing the core elements and required statements in a valid authorization).

n88 *See id.* § 164.512(i)(1)(i)(B). A privacy board is properly constituted if it 1) has members with varying backgrounds and appropriate professional competency as necessary to review the effect of the research protocol on the individual's privacy rights and related interests; 2) includes at least one member who is not affiliated with the covered entity, not affiliated with any entity conducting or sponsoring the research, and not related to any person who is affiliated with any of such entities; and 3) does not have any member participating in a review of any project in which the member has a conflict of interest.

n89 *Id.* § 164.512(i)(2)(ii).

n90 *Id.* § 164.512(i).

n91 *Id.* § 164.520(b)(iv)(E).

n92 *67 Fed. Reg.* 53,245.

n93 *45 C.F.R. § 164.520 (2007)*.

n94 *Id.* § 164.528(b).

n95 *See id.* An abbreviated accounting of disclosures of PHI is to include the following information: name of protocol, description of protocol or research activity and PHI disclosed, date or period of time during which disclosure occurred or may have occurred and last date of disclosure, name, address, and phone no. of sponsor and recipient (with an offer to assist in contacting the sponsor/researcher), statement that the PHI may or may not have been disclosed for a particular protocol or research activity.

n96 *See id.* § 164.520(a) for a full description of the content of a Privacy Rule Notification.

n97 *See* OCR Home Page, <http://www.hhs.gov/ocr/hipaa/> for more information about OCR's role in compliance and enforcement of the Privacy Rule. This website also contains general information about HIPAA and the Privacy Rule, educational materials, and instructions and forms for filing a Privacy Rule complaint.

n98 *45 C.F.R. § 160.306*.

n99 *61 Fed. Reg.* 51,500 cmt. 2.

n100 *See Public Hearing, supra* note 8, (testimony of Sara Goldkind, Sr. Bioethicist, Office of Critical Path Programs, FDA).

n101 *See* Robert Silbergleit & National Institutes of Health/National Institute of Neurological Diseases and Stroke Neurological Emergencies Treatment Trials Investigators, *Response to Food and Drug Administration Draft Guidance Statement on Research into the Treatment of Life-Threatening Emergency Conditions Using Exception From Informed Consent: Testimony of The Neurological Emergencies Treatment Trials*, 14 ACAD. EMERG. MED. e63 (2007).

n102 See the ROC Home Page <https://roc.uwctc.org> (last visited Dec. 10, 2007). The Study Chair is Myron L. Weisfeldt, MD, Chair of Medicine at Johns Hopkins; the co-chair for cardiac arrest is Joseph Ornato, MD, Head of the Emergency Medicine Department at the Medical College of Virginia; and the co-chair for trauma is COL. John Holcomb, MD Commander U.S. Army Institute of Surgical Research, Ft. Sam, Houston, TX.

n103 See description of ROC ongoing clinical trials, *supra* notes 127-29.

n104 See NETT Home Page, <http://sitemaker.umich.edu/nett/welcome> (last visited Dec. 10, 2007.) The Principal Investigator of the Clinical Coordinating Center is William G. Barsan, M.D.

n105 PECARN Home Page <http://www.pecarn.org/> (last visited Dec. 10, 2007). PECARN is governed by a Steering Committee chaired by Nathan Kuppermann, M.D.

n106 IMMEDIATE Trial Home Page <http://www.immediatetrial.com/> (last visited Dec. 20, 2007).

n107 See FDA, Docket 1995S-0158, <http://www.fda.gov/ohrms/dockets/dockets/95s0158/95s0158.htm> (contains postings received from IND sponsors conducting clinical research). This docket previously was referred to as Docket No. 95S-0158.

n108 See the ClinicalTrials.gov Home Page <http://clinicaltrials.gov/> (information about clinical drug and device trials).

n109 See generally Alfred P. Hallstrom et al., *Public-Access Defibrillation and Survival after Out-of-Hospital Cardiac Arrest*, 351 N. ENGL. J. MED., 637-46 (2004).

n110 The manufacturers of debibrillators who sponsored this study included Medtronic/Physio-Control Corp., Guidant Corp., Cardiac Science/Survivalink, Inc., Phillips Corp./Heartstream Operation, and Laerdal Corp.

n111 See generally Roger J. Lewis 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*, 38 ANN. EMERG. MED. 397-404 (2001).

n112 See generally W. T. Longstreth, Jr., *Randomized Clinical Trial of Magnesium, Diazepam, or Both after Out-of-Hospital Cardiac Arrest*, 59 NEUROLOGY, 506-14 (2002).

n113 See *University of Texas -- Houston Medical School Trauma Study Results* (advertisement), HOUSTON CHRON., Mar. 6, 2000, available at <http://www.fda.gov/ohrms/dockets/dockets/95s0158/95s-0158-sup0023-vol19.pdf> (last visited Dec. 30, 2007).

n114 See Tom P. Aufderheide et.al., *Clinical Evaluation of An Inspiratory Impedance Threshold Device During Standard Cardiopulmonary Resuscitation in Patients with Out-of-Hospital Cardiac Arrest*, 33 CRIT. CARE MED., 734-40 (2005).

n115 See Clifton Callaway et al., *Usefulness of Vasopressin Administered with Epinephrine During Out-of-Hospital Cardiac Arrest*, 98 AM. J. CARDIOL., 1316-21 (2006).

n116 See Harborview Medical Center, *Hypertonic Saline FAQs*, <http://www.uwmedicine.org/Facilities/Harborview/Overview/Research/esdfaq.htm> (last visited Dec. 10, 2007).

n117 See Northfield Labs, *PolyHeme Product Description*, <http://www.northfieldlabs.com/polyheme.html> (last visited Dec. 10, 2007) (containing information about PolyHeme).

n118 See *Clinical Trials, Safety and Efficacy of PolyHeme(R) in Hemorrhagic Shock Following Traumatic Injuries Beginning in the Pre-Hospital Setting*, <http://clinicaltrials.gov/ct2/show/NCT00076648?term=Polyheme&rank=1#locn> (last visited Dec. 10, 2007) (containing details of the PolyHeme study).

n119 See Press Release, Northfield Laboratories, *Northfield Laboratories Reports Preliminary Top-Line Data in Pivotal Phase III Trauma Study* (Dec. 19, 2006), available at <http://phx.corporate-ir.net/phoenix.zhtml?c=91374&p=irol-newsArticle&ID=943580highlight=pdf>.

n120 See NORTHFIELD LABORATORIES, 2007 ANNUAL REPORT (2007), available at http://media.corporate-ir.net/media_files/irol/91/91374/2007_Annual_Report.pdf (last visited Dec. 20, 2007).

n121 See Ken Kipnis Nancy M. King & Robert M. Nelson, *An Open Letter to Institutional Review Boards Considering Northfield Laboratories' Polyheme Trial*. 6 AM J BIOETH., 18-21 (2006).

n122 See Press Release, US Senate Committee on Finance, *Grassley Questions FDA's Sanction of Blood Substitute Study Without Patient Consent* (Feb. 23, 2006) [hereinafter *Grassley Press Release*], available at <http://finance.senate.gov/press/Gpress/2005/prg022306a.pdf> (last visited Nov. 20, 2006).

n123 See Letter from Charles E. Grassley, Iowa, Chairman, U.S. Senate Committee on Finance, to Michael Leavitt, Secretary, U.S. Department of Health & Human Services (Mar. 13, 2006), available at <http://finance.senate.gov/press/Gpress/2005/prg031306.pdf> (last visited Nov. 20, 2007).

n124 See FDA *Community Disclosure of Institutional Review Boards for postings of IRB-approved public disclosures*, Docket 1995S-0158, available at <http://www.fda.gov/ohrms/dockets/dockets/95s0158/mostrecent.htm> (last visited Dec. 15, 2007).

n125 See ClinicalTrials.gov Home Page, <http://clinicaltrials.gov/>. (last visited Dec. 10, 2007).

n126 See ClinicalTrials.gov, IMMEDIATE Trial: Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care Trial <http://clinicaltrials.gov/ct2/show/NCT00091507?term=Immediate&rank=3> (last visited Dec. 10, 2007).

n127 See ClinicalTrials.gov, ROC Prehospital Resuscitation Using an Impedance Valve & Early vs. Delayed Analysis, <http://clinicaltrials.gov/ct2/show/NCT00394706?term=resuscitation+emerson&rank=3> (last visited Dec. 10, 2007)

n128 See ClinicalTrials.gov, Hypertonic Resuscitation Following Traumatic Injury, <http://clinicaltrials.gov/ct2/show/NCT00316017?term=resuscitation+emerson&rank=1> (last visited Dec. 10, 2007).

n129 See ClinicalTrials.gov Hypertonic Resuscitation Following Traumatic Brain Injury
<http://clinicaltrials.gov/ct2/show/NCT00316004?term=resuscitation+emerson&rank=2> (last visited Dec. 10, 2007).

n130 See ClinicalTrials.gov, Low Dose Vasopressin in Traumatic Shock,
<http://clinicaltrials.gov/ct2/show/NCT00420407?term=Cohn++vasopressin&rank=1> (last visited Dec. 10, 2007).

n131 See ClinicalTrials.gov, Effects of Erythropoietin on Cerebral Vascular Dysfunction and Anemia in Traumatic Brain Injury,
<http://clinicaltrials.gov/ct2/show/NCT00313716?term=baylor+vascular+robertson&rank=1>
(last visited Dec. 10, 2007).

n132 See ClinicalTrials.gov, Treatment of Ventricular Tachyarrhythmias Refractory To Shock With Beta Blockers: The SHOCK and BLOCK Trial,
<http://clinicaltrials.gov/ct2/show/NCT00401882?recr=open&cond=%22Shock%22> (last visited Dec. 30, 2007).

n133 See 61 Fed. Reg. 51,503 cmt. 11.

n134 *Id.*

n135 21 C.F.R. §§ 312.64, 812.40 (2007).

n136 See ROC *supra* note 102.

n137 See NETT, *supra* note 104.

n138 See PECARN, *supra* note 105.

n139 See IMMEDIATE Trial, *supra* note 106.

n140 See Sponsor Responsibilities, *supra* note 135. See also FDA, Guideline for the Monitoring of Clinical Investigations (1988),
http://www.fda.gov/ora/compliance_ref/bimo/clinguid.html (last visited Nov. 20, 2007).

n141 See NETT, Standard Operating Procedures, http://nett.umich.edu/nett/nett_standard_operating_procedures (last visited Dec. 10, 2007).

n142 21 C.F.R. β 50.24(a)(1).

n143 See generally 21 C.F.R. pts. 314 and 814 for regulations regarding drug and device marketing applications.

n144 See ROC PRIMED protocol (stamped Apr. 2, 2007 by the University of Washington Human Subjects Division), Challenges, 4. The randomization procedures discussed in this section provide an example of the importance of FDA looking at study designs to ensure that valid scientific data will be collected. Rather than using the standard randomization method, i.e., randomization by individuals, the ROC PRIMED protocol uses a cluster method of randomization, with clusters consisting of "geographic areas or monitor/defibrillators within the EMS agencies." When individual randomization is used, the outcome for an individual patient is assumed to be independent of that for any other, but this assumption is not valid when cluster randomization is used because patients within any one cluster are more likely to respond in a similar manner. See also Graham Nichol & Ella Huszti, *Design and Implementation of Resuscitation Research: Special Challenges and Potential Solutions*, 73 RESUSCITATION 337, 337-46 (2007) (discussing randomization by clusters based on geographic area or EMS provider). The ROC PRIMED protocol was obtained through an FOIA request to the Office of University of Washington Public Records & Open Public Meetings on Dec. 7, 2007.

n145 See ROC PRIMED protocol (stamped Apr. 2, 2007 by the University of Washington Human Subjects Division), 17, obtained through an FOIA request to the Office of University of Washington Public Records & Open Public Meetings on Dec. 7, 2007,

n146 21 C.F.R. β 50.24(b)

n147 ROC PRIMED protocol, *supra* note 145, 54.

n148 ROC PRIMED protocol, *supra* note 145, Appendix 12: Justification for Waiver of Documented Written Consent, 104-105.

n149 See generally *Public Hearing*, *supra* note 8.

n150 See *Public Hearing, supra* note 8 (testimony of Michelle Biros, Society for Academic Emergency Medicine and Coalition of Acute Resuscitation; Charles Cairns, American College of Emergency Physician).

n151 See *Public Hearing, supra* note 8 (testimony of Richard Dutton, Director, Trauma Anesthesiology).

n152 See *Public Hearing, supra* note 8 (testimony of Michelle Biros, Society for Academic Emergency Medicine and Coalition of Acute Resuscitation; Charles Cairns, American College of Emergency Physician).

n153 See Joshua G. Salzman et al., *Implementing Emergency Research Requiring Exception from Informed Consent, Community Consultation, and Public Disclosure*, 50 ANN. EMERG. MED., 448-55 (2007).

n154 *Id.* Salzman et al. conducted an extensive public disclosure program. Multiple methods of public disclosure were used (e.g., newspaper: articles, advertisements, letters to editors; television: public service announcements, public interest stories, news spots; radio: talk shows, Public Service Announcement (PSA); Web: announcements; hard copy materials: brochures, correspondence with community groups; and other meetings, presentations and telephone polls). This group took advantage of free publicity and public service announcements and direct costs for the campaign were approximately \$ 5,000. It was estimated that potentially three million people nationwide and 1.9 million in the metropolitan study area were informed of this study in some form. Thus, Salzman et al. have demonstrated that extensive public disclosure can be achieved at reasonable costs with careful planning.

n155 See Michelle Biros, *Struggling with the Rule: The Exception from Informed Consent in Resuscitation Research*, 14 ACAD. EMERG. MED. 344-45 (2007). See also Lynne D. Richardson et al., *Communicating With Communities About Emergency Research*, 12 ACAD. EMERG. MED. 1064-70 (2005).

n156 See *Emergency Research Guidance, supra* note 7 at 12-13, 19-23.

n157 See Leonard Glantz et al., *Comments on Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors; Exception from Informed Consent Requirements for Emergency Research*, FDA Dockets Management No. 2006D-0331 cmt. EC45 (Oct. 29, 2006), available at <http://www.fda.gov/ohrms/dockets/dockets/06d0331/06D-0331-EC46-Attach-1.pdf> (last visited Nov. 30, 2007); Sigrid Fry-Revere, *Comments on Guidance for In-*

stitutional Review Boards, Clinical Investigators, and Sponsors; Exception from Informed Consent Requirements for Emergency Research, FDA Dockets Management No. 2006D-0331, cmt EC56 (Nov. 20, 2006), *available at* <http://www.fda.gov/ohrms/dockets/dockets/06d0331/06D-0331-EC56.htm> (last visited Oct. 10, 2007).

n158 *See Public Hearing, supra* note 8 (testimony of Michelle Biros, Society for Academic Emergency Medicine and Coalition of Acute Resuscitation; Joseph Ornato, NHLBI, ROC; Paul Pepe, U.S. Metropolitan Emergency Medical Services; and Myron Weisfeldt, Johns Hopkins University School of Medicine).

n159 *61 Fed. Reg. 51,515* cmt. 71.

n160 *See* FDA, Documentation of Community Notification/Consultation for Use of the Emergency Consent Exception in the Study <http://www.fda.gov/ohrms/dockets/dockets/95s0158/95s-0158-rpt002300-toc.html> (follow "Alabama Community Consultation and Public Notification Materials" hyperlink). The first item contains disclosures by the Alabama Resuscitation Center, examples including a press release entitled, "Media Advisory for Wednesday, April 11: UAB Kicks Off Emergency Rescue Research Project" fail to mention that there is waiver of informed consent, *id.* at 10, a PSA states that "most of the patients who meet enrollment criteria will be unable to give proper consent," suggesting that there will be some degree of consent by the patient, *id.* at 9; and a brochure entitled, "*Participate in Research Studies University of Alabama*" that states "[I]f you are asked to participate in a research study, you have the right to...[b]e given the time and opportunity to decide freely whether to consent or not consent to participate in the study," providing false information to potential subjects in emergency research studies. *Id.* at 15.

n161 *See* Press Release, Northfield Laboratories, *Multicenter PolyHeme Trauma Study Presented at the American College of Surgeons 93rd Annual Clinical Congress* (Oct. 10, 2007), *available at* <http://phx.corporate-ir.net/phoenix.zhtml?c=91374&p=irol-newsArticle&ID=1061082&highlight=> (last visited Dec. 13, 2007).

n162 *See* Press Release, University of Texas Health Science Center at San Antonio, S.A. *Trauma Centers Release Blood Substitute Study Results* (Nov. 7, 2007), *available at* <http://www.universityhealthsystem.com/news/DOCS/PR-11-07-07.pdf> (last visited Dec. 13, 2007).

n163 Food and Drug Administration Amendments Act of 2007 (FDAAA 2007), Pub. L. No. 110-85, *121 Stat. 823* (2007).

n164 *61 Fed. Reg. 51,500* cmt. 2.

n165 *See Emergency Research Guidance, supra* note 7 at 4.

n166 *See Grassley Press Release, supra* note 122.

n167 *See* <http://www.uwmedicine.org/Facilities/Harborview/Overview/Research/esdfaq.htm> (last visited Dec. 10, 2007). The use of bracelets for patients to wear who do not wish to participate in the study is discussed. For example, Harborview Medical Center Hypertonic Saline FAQs states that "[i]f you choose to opt-out we will mail you a Medic-Alert type bracelet with the words 'No Study' engraved on it. You will have to wear this bracelet during the time the study is being conducted through 2010. Even if you wear this bracelet there is no guarantee that under emergency circumstances the bracelet will be read by those providing care for you." *See also* <http://www.ohsu.edu/emergency/roc/survey/index.htm>.

n168 EMS provider case report forms for ongoing ROC studies were obtained through an FOIA request to the Office of University of Washington Public Records & Open Public Meetings on Dec. 7, 2007.

n169 *61 Fed. Reg. 51,504* cmt. 4.

n170 *See* Vincent N. Mosesso Jr., *Conducting Research Using the Emergency Exception from Informed Consent: The Public Access Defibrillation (PAD) Trial Experience*, 61 RESUSCITATION 29, 33 (2004).

n171 *See* Press Release, Northfield Laboratories, *Statement of Northfield Laboratories* (Mar 1, 2006), available at <http://phx.corporate-ir.net/phoenix.zhtml?c=91374&p=irol-newsArticle&ID=824752&highlight=> (last visited Dec. 15, 2007).

n172 *Biros, supra* note 155 at 344.

n173 *See* Myron L. Weisfeldt, *Food and Drug Administration Public Hearing on the Conduct of Emergency Clinical Research: Testimony of Dr. Weisfeldt*, 14 ACAD. EMERG. MED. e69 (2006).

n174 See Nicole N. Delorio & Katie B. McClure, *Does the Emergency Exception from Informed Consent Process Protect Research Subjects?*, 12 ACAD. EMERG. MED. 1056, 1058 (2005).

n175 See Terri A. Schmidt, *Food and Drug Administration Public Hearing on the Conduct of Emergency Clinical Research: Testimony of Dr. Schmidt*, 14 ACAD. EMERG. MED. e59, e60 (2007).

n176 See Weisfeldt, *supra* note 173 at e69.

n177 See Schmidt, *supra* note 175 at e60.

n178 See CIRB Home Page <http://www.ncicirb.org/> (last visited Dec. 5, 2007).

n179 See Silbergleit, *supra* note 101 at e63-68.

n180 The only way to determine whether investigators, sponsors and IRBs are complying with their responsibilities under the Emergency Research Rule (as well as other responsibilities for FDA-regulated studies) is to conduct onsite inspections that include interviews with key personnel and in-depth study/data audits to validate study findings and verify compliance with regulations. Such inspections could be arranged through FDA's BIMO program, which is a comprehensive program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA-regulated research. See FDA/ORA Bioresearch Monitoring Information Page, available at http://www.fda.gov/ora/compliance_ref/bimo/ (last visited Dec. 10, 2007). Because many emergency research studies are being conducted as part of a network, the results of a few clinical investigator inspections should be provided to all in the network. In addition, since the results of FDA inspections are publicly available, this will provide another layer of public disclosure.