BNA, INC.

MEDICAL RESEARCH LAW & POLICY

BNA Employee-Owned Since 1947

REPORT

FDA Draft Guidance on Emergency Research: Additional Issues Left Unanswered

BY MARK BARNES, ESQ., CLINTON D. HERMES, ESQ., AND SHARON RACKOW HERRICK, ESQ.

On Aug. 29, the Food and Drug Administration (FDA) released draft guidance to assist institutional review boards (IRBs), clinical investigators, and sponsors interpret and comply with regulations at 21 C.F.R. § 50.24, which sets forth, for ''emergency'' research, an exception from the requirements of informed consent.[1] The draft guidance seeks to clarify and elaborate on the language of the regulatory exception and on the FDA Information Sheet on this topic that was issued in 1998;[2] although the draft guidance does provide useful clarification on some areas of this exception, it also provokes new questions and leaves some existing questions unanswered.

[1] *Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors; Exception from Informed Consent Requirements for Emergency Research,* Aug. 29, 2006, *available at* http://www.fda.gov/OHRMS/DOCKETS/98fr/06d-0331-nad0001.pdf.

[2] *Guidance for Institutional Review Boards and Clinical Investigators, 1998 Update, Exception from Informed Consent For Studies Conducted in Emergency Settings: Regulatory Language and Excerpts from Preamble, available at* http://www.fda.gov/oc/ohrt/irbs/drugsbiologics.html#emergency.

Mark Barnes, Esq., is a partner and Clinton D. Hermes, Esq., an associate with Ropes & Gray, New York.

Sharon Rackow Herrick, Esq., is an associate with Ropes & Gray, Boston.

Background

The first provision of the Nuremberg Code, developed for the Nuremberg Military Tribunal as legal standards by which to judge human experimentation, states that ''the voluntary consent of the human subject is absolutely essential.'' This ethical imperative has been the universally recognized cornerstone of human subjects research ethics since at least World War II. However, there are narrow categories of interventional clinical trials in which the subject population—because of age, mental capacity, or other reasons—is not capable of providing voluntary informed consent, and in each such circumstance, ethical scrutiny of the research must be exacting.

Regulations at 21 C.F.R. § 50.24 provide a narrow exception to the informed consent requirements for subjects in need of emergency medical intervention who cannot give informed consent because of their life-threatening medical condition (e.g., head trauma, cardiac arrest, stroke) and whose legally authorized representatives (LARs) cannot be reached in sufficient time to provide consent. Because this type of research involves a particularly vulnerable population, the regulations impose numerous safeguards as a means to ensure the protection of participants and the integrity of the resulting data. In the nearly ten years since the regulations were implemented in November 1996, FDA has received approximately 60 requests to conduct clinical investigations under this exception. FDA issued its draft guidance in light of its experience with these requests and in consideration of comments informally received from the research community since 1998.

Numerous articles and press releases have accurately summarized the draft guidance and highlighted the ad-

ditional requirements proposed therein,[3] and we do not seek to repeat those summaries here. This article instead focuses on unresolved issues and concerns raised by the regulation and the draft guidance, occasionally through the context of the highly publicized and controversial PolyHeme study. The PolyHeme study, sponsored by Northfield Laboratories and performed at 31 hospitals throughout the United States, involved a randomized evaluation under the emergency research exception of an investigational oxygen-carrying blood substitute in 720 severely injured trauma victims experiencing hemorrhagic shock. This Phase III study, which has been criticized in the public media and has become the object of congressional and Securities and Exchange Commission investigations, may have been the catalyst motivating the FDA to take a closer look at the emergency research exception and to propose the new draft guidance. In any event, the PolyHeme trial serves as a useful case study of practical issues that arise under the emergency research exception.

Available Treatments are Unproven or Unsatisfactory

IRBs reviewing a proposed study under the emergency research exception must make a finding and document that the available treatments for the medical condition under investigation are unproven or unsatisfactory.[4] The FDA Information Sheet on emergency research explains that clinical equipoise must exist, meaning, ''[w]hen the relative benefits and risks of the proposed intervention, as compared to standard therapy are unknown, or thought to be equivalent or better, there is clinical equipoise between the historic intervention and the proposed test intervention.''[5] Neither the FDA Information Sheet nor the new draft guidance provides any further insight into what type of evidence is necessary to establish that an available treatment is ''unproven'' or ''unsatisfactory.'' Is a literature review or the concurrence of physicians with expertise in the relevant specialty adequate? Is the fact that a therapy is widely accepted as the standard of care, even if there are known risks, sufficient to demonstrate that the therapy is not ''unproven'' or ''unsatisfactory?'' What is the rationale that equates clinical equipoise—which is the ethical gold standard in most placebo-controlled trials—with an ''unproven'' or ''unsatisfactory'' treatment, since clinical equipoise between standard therapy and experimental therapy may exist even when the standard therapy is both proven and satisfactory? Without further guidance from FDA, it remains unclear how this threshold factor must be demonstrated.

This issue is at the core of the controversy with respect to the PolyHeme study. During the initial part of that study, subjects were enrolled in the field by emergency medical technicians (EMTs) providing initial treatment and were randomly assigned to receive either saline fluid (standard treatment) or PolyHeme (experimental treatment). Once at the hospital, the second part of the study commenced, and subjects who had previously received saline in the field then were provided saline and blood as needed; and those subjects who had received PolyHeme in the field continued to receive only PolyHeme for up to 12 hours following hospital admission. In an effort to voice concerns regarding the second part of the study design, Drs. Ken Kipnis, Nancy King, and Robert Nelson prepared an open letter to IRBs participating in the study.[6] This letter suggests that this second part of the study does not fall within the emergency research exception, since the use of blood to treat patients in hemorrhagic shock is neither ''unproven'' nor ''unsatisfactory,'' and therefore, they argued, that portion of the study may not be performed without first obtaining the informed consent of the subjects or their LARs. Kipnis, King and Nelson acknowledge in the letter that, like all medical interventions, blood has its risks and limitations; however, they assert that once blood is available to patients in hemorrhagic shock, as the current favored treatment, it may not be withheld under a study paradigm without obtaining appropriate consent. This raises the question: when a therapy is widely considered the favored method for treating a medical condition, can that therapy nevertheless be deemed to be ''unproven'' or ''unsatisfactory'' for purposes of this ''emergency'' research exception?

Dr. Anne Hamilton Dougherty addressed this very question in her own letter to the editor of the same journal, responding to the open letter from Kipnis, King and Nelson.[7] Dougherty queries whether the efficacy and safety of transfused blood has been proven, as ''[d]espite its widespread use and acceptance, the performance of banked blood has never been subjected to the level of scrutiny imposed on investigational new drugs.'' Additionally, Dougherty examines whether the transfusion of banked blood is ''satisfactory'' in light of extensive evidence demonstrating that such transfusions increase the incidence of organ and multi-organ failure and are associated with immunologic complications and infection transmission.[8]

While to some extent one must rely on the established IRB review system to resolve such issues, for studies in which the ethical stakes are especially high, IRBs benefit from clear standards on which to base their determinations. Either FDA or the Office for Human Research Protections (OHRP) (or both) should provide the research community with guidance on what standards a noninvestigational medical treatment must meet in order to be considered ''proven'' or ''satisfactory'' (*e.g.*, is the standard ''clinical equipoise,'' or something more demanding in this context?) and what forms of evidence must be used to confirm this finding for purposes of the emergency research exception.

---

[3] *See* FDA press release at http://www.fda.gov/bbs/topics/NEWS/2006/NEW01439.html (Aug. 29, 2006); Jeannie Baumann, ''Informed Consent: Updated Emergency Research Guidance Includes Key Changes, FDA Bioethicist Says,'' 5 *Medical Research Law & Policy Report* 583, 9/6/06.

[4] 21 C.F.R. § 50.24(a)(1).

[5] *See* FDA Information Sheet, note 2, quoting from 60 Fed. Reg. 49086, at 49093, 9/21/95.

[6] Ken Kipnis, Nancy M.P. King, and Robert M. Nelson, ''An Open Letter to IRBs Considering Northfield Laboratories' PolyHeme Trial,'' 6 *The American Journal of Bioethics,* 3/9/06.

[7] Anne Hamilton Dougherty, ''Letter to the Editor: In Defense of the PolyHeme Trial,'' 6 *The American Journal of Bioethics,* 2006.

[8] *See also,* Ted Agres, ''Controversial blood trial continues,'' *The Scientist,* 5/8/06.

   ISSN 1539-1035

Obtaining Informed Consent is Not Feasible

Subjects Cannot Give Informed Consent Because of their Medical Condition

Before approving a study under the emergency research exception, an IRB must find and document that obtaining informed consent from subjects is not feasible because: (i) the subjects cannot give their informed consent as a result of their medical condition; (ii) the experimental intervention must be administered before consent from the LAR may be obtained; and (iii) there is no reasonable way prospectively to identify individuals likely to become eligible for participation in the study.[9] Although these requirements may appear straightforward, there is disagreement about when a subject is deemed to have the capacity to provide his/her informed consent for research procedures.

When an individual is unconscious, it is evident that he/she cannot provide informed consent for any form of research or treatment. The issue of capacity is far less clear, however, when an individual is conscious but in an urgent or emergent medical or psychological state—for example, experiencing serious pain or shock. The FDA Information Sheet on emergency research provides that ''[s]ubjects do not have to be comatose, but the medical condition under study must prevent obtaining valid informed consent.''[10] In its recent draft, FDA offers no specific guidance for IRBs to follow in making this critical finding.

It is important to note that capacity to provide or refuse consent for medical treatment is an issue that has been addressed in numerous academic articles and reports. Often these writings focus on the capacity of individuals who suffer from long-term problems such as mental illness or Alzheimer's disease. Standard methods for assessing capacity typically involve validated instruments or questionnaires that are administered to the individual. Capacity in the emergency research context is unique in that it often involves individuals who may be limited in their ability to provide informed consent for a short period of time, and for whom the administration of capacity-testing instruments ''in the field'' is impracticable.

In the event a study proposed to be conducted under the emergency research exception involves subjects who will be conscious when enrolled into the study, IRBs should consider whether it is possible (even remotely possible) that some of these subjects will be capable of providing informed consent. If this possibility exists, can these subjects be enrolled in the study under the emergency research exception, or would a separate, parallel study need to be established (with a separate investigational new drug (IND) application) for these consenting subjects? Furthermore, IRBs would need to ensure that there are appropriate procedures in place for determining, prior to enrollment, whether each potential subject demonstrates capacity to provide informed consent. As emergency responders may be involved in making this initial assessment, as was the case in the PolyHeme study, these health professionals would need to be made aware of and carefully trained to perform these important initial evaluations.

[9] 21 C.F.R. § 50.24(a)(2).

[10] *See* FDA Information Sheet, note 2.

Contacting the Subject's LAR or Family Members

The emergency research exception requires that the clinical investigator commit to attempting to seek the written informed consent, if feasible, of the subject's LAR or make contact with the subject's family members and provide them with an opportunity to object to the subject's inclusion in the study before administration of the experimental intervention.[11] The draft guidance expands upon the scope of this requirement by making clear that the IRB must review the proposed plan and procedures for attempting to contact the LAR or family member and determine whether the plan and period for the attempted contact is appropriate in light of the length of the therapeutic window and the effect of delaying administration of the test article. The draft guidance does not, however, address who constitutes a LAR or an appropriate family member for this important contact.

The question of who constitutes a LAR for purposes of FDA regulations or the Common Rule is neither new nor unique to the emergency research context. Nevertheless, the practical difficulties associated with finding someone who meets the relevant legal requirements of a LAR are especially acute when the time frame for identifying the LAR is limited by a presumably narrow therapeutic window. Under FDA regulations and the Common Rule, LARs are defined as, ''an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in research.''[12] One need review only a handful of OHRP determination letters to realize that research sites often have difficulty in defining who constitutes an appropriate LAR under state law. Many states have enacted laws that permit certain individuals, such as spouses, to consent to medical treatment on behalf of their spouse, but these laws typically do not address who can provide consent to participation in a medical experiment as opposed to receiving standard therapy. Some states, including New York and Massachusetts, have no clear legal method for surrogate consent, even to medical care, in the absence of a health care proxy, court order, or guardianship. ''Unless a potential subject has signed a durable power of attorney for health care designating someone to make all health care decisions on his or her behalf, there is surprisingly little uniformity in state laws regarding who may make such decisions.''[13] Institutions and IRBs therefore must be familiar with applicable state laws regarding who is an appropriate LAR in the research context generally, and they should develop procedures specifically to identify LARs (and verify their authority as both a LAR and a ''personal representative'' under the Health Insurance Portability and Accountability Act of 1996) to provide appropriate consent and authorization under the emergency research exception.

The draft guidance provides that when a LAR is available, the LAR's decision as to enrollment of the patient in the ''emergency'' research will, of course, prevail. If, however, a LAR is not available, the clinical investiga-

[11] 21 C.F.R. §§ 50.24(a)(5) and (a)(7)(v).

[12] 21 C.F.R. § 50.3(l); 45 C.F.R. § 46.102(c).

[13] *See* Sandra P. Kaltman and John M. Isidor, ''State Laws Affecting Institutional Review Boards,'' 4 *Medical Research Law & Policy Report* 417, 5/18/05.

tor must attempt, if feasible, to provide a family member with the opportunity to object to an individual's participation in the emergency research study.[14] ''Family member'' is defined in FDA regulations 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.''[15] FDA makes clear in the draft guidance that if a family member objects to a potential subject's participation, the individual should not be entered into the study. Additionally, when the opportunity to object to participation is offered to more than one family member, and the family members disagree, FDA suggests that the investigator and family members ''work out the disagreement'' among themselves. Without further guidance from FDA, IRBs should pay particular attention to this issue and ensure that the clinical investigator's and sponsor's plan and procedure for contacting family members addresses the possibility that family members may disagree on this important decision, and consider stipulating a more specific method for resolving the dispute. The unfortunate outlier case would occur if, against the backdrop of family discord about the patient's study enrollment, the patient is enrolled and suffers a significant adverse effect of the study drug or treatment. In such cases, the investigators, sponsor, and IRB would be vulnerable to much second-guessing, and would be able to defend the decision to enroll the subject only if the exact family decision-making mechanism had been specified in the protocol, approved by the IRB, and documented contemporaneously by the investigators or study team.

This situation is relatively novel for most IRBs, but analogous situations can arise at institutions with organ transplant centers, when next-of-kin are relied upon to make very significant decisions on behalf of patients. Both decision-making rules and decision-making processes may be borrowed from this context and from the relevant state's version of the Uniform Anatomical Gift Act. A few methods for resolving an intra-family dispute over subject enrollment therefore may be as follows: (i) the decision of the closest family member prevails, as set out by a pre-established hierarchy (e.g., the hierarchy established in the Anatomical Gift Act); (ii) the decision is determined by majority (or super-majority) rule of the family members available; (iii) the decision to permit enrollment of the subject requires the concurrence of all family members to whom the issue is raised; or (iv) the decision is left to the discretion of the principal investigator. The last method is the most troubling and difficult to implement with consistency, particularly if the principal investigator cannot immediately be reached when the situation presents. As is suggested in the draft guidance, all efforts to contact LARs and family members should be summarized and recorded in each subject's medical record or study file so that it is accessible to be reviewed by the IRB and FDA, or by other authorities.

Community Consultation

The draft guidance elaborates upon the scope of and responsibilities for community consultation under the emergency research exception, particularly with respect to the role of the IRB. Prior to publication of the draft guidance, common practice was for the clinical investigator to perform the community consultation (sometimes with assistance from the sponsor), as reviewed and approved by the IRB, and to report the results of this process to the IRB. The new draft guidance sets a higher standard, providing that IRBs: (i) must review, request appropriate modifications in, and approve or disapprove the sponsor's and clinical investigator's plans for community consultation; (ii) have the responsibility to ensure that the community consultation is adequate; (iii) should consider being directly involved in community consultation activities to hear first hand the concerns expressed during the consultation process; and (iv) should discuss community opposition to, or concern about, the research and specifically document in the IRB meeting minutes what these concerns are and how the IRB resolved them. As a result, if and when the draft guidance is finalized, IRBs are likely to become significantly more involved in the community consultation process.

Despite the enhanced and welcome guidance in this area, there remain gaps in guidance on this important element of the emergency research exception.

What Information Should be Disclosed?

One of the most alarming allegations relating to the PolyHeme study has been that some significant information was not disclosed to the public during the community consultation process.[16] Northfield Laboratories previously had tested PolyHeme in a study of aneurysm-surgery patients. In this earlier trial, 10 of the 81 patients who were treated with PolyHeme suffered heart attacks, two of whom died, as compared with the 71 patients who received standard therapy, none of whom experienced heart attacks. Northfield terminated the study without ever completing the protocol or publishing the results. In defending its decision not to include this information in the community consultation process, the company argued that the heart attacks and other adverse events could have been caused by factors unrelated to the PolyHeme itself. Additionally, claims were made that the earlier trial results could not be disclosed to the public because they remained confidential.

As provided in the new draft FDA guidance, a key element of community consultation is to inform the communities about all relevant aspects of the study, including its risks and expected benefits. Still, the guidance does not require the disclosure of any specific categories of information, particularly about previous (or related) human and animal studies. Therefore, the concern remains that certain information may be withheld from presentation to communities, when this information could have a significant impact on whether the community would be willing to support the proposed study. Trial sponsors may argue that they should not be required to disclose information on halted or terminated studies because the results may not be conclusive or may not be statistically significant, yet the opposed ethical argument is that the community should have ac-

[14] 21 C.F.R. § 50.24(a)(7)(v).
[15] 21 C.F.R. § 50.3(m).

[16] *See* Thomas M. Burton, ''Blood-Substitute Study is Criticized by U.S. Agency,'' *The Wall Street Journal,* p. A3, 5/10/06.; and Thomas M. Burton, ''Red Flags: Amid Alarm Bells, A Blood Substitute Keeps Pumping,'' *The Wall Street Journal,* p. A1, 2/22/06; *But see,* Dougherty, *supra,* fn. 7.

   ISSN 1539-1035

cess to all relevant information that weighs on a risks and benefits analysis. Therefore, without more extensive guidance on the scope of information to be presented to the community in connection with the consultation process, IRBs will need to consider these competing interests and determine the appropriate amount and types of information that should be included in this process. This evaluation will be familiar to IRBs, as they regularly address the appropriate content of informed consent documents, particularly with respect to the disclosure of potential risks. One may ask, in fact, whether the dialog with the community in this context is qualitatively different from the discussions held with individual potential subjects prior to enrollment in a study. Should the types of information shared in these two contexts be the same, or are there distinct purposes for these procedures such that the scope of disclosures need not be equivalent? These are just some of the issues IRBs will face in evaluating and structuring the community consultation process.

What Should IRBs do with the Information they Receive?

Once the community consultation is complete, the draft guidance does not address what IRBs should do with the information they have received during this process. For example, if an IRB receives feedback from a survey of the appropriate community demonstrating that 30 percent of the community finds the study unethical and should not be performed without consent, 60 percent of the community finds the study would benefit the community and should be performed, and 10 percent do not know how they feel about the study—how should the IRB regard such results? Should either the disapproval of 30 percent of the community or some uncertainty in the community lead to IRB disapproval of the study? FDA has provided no guidance for how IRBs are to consider and resolve the issues raised during the community consultation process. Of particular concern is the situation in which a community demonstrates both strong support for and sharp opposition to the proposed investigation, as this is a reasonably foreseeable outcome in light of the controversial nature of studies conducted under the emergency research exception.

Use of Independent IRBs to Approve Emergency Research

The new draft guidance makes explicit FDA's expectation that emergency research usually will be performed at an institution with an ''internal'' IRB responsible for reviewing the study at that institution. While the guidance notes that ''independent'' IRBs (*e.g.*, Western IRB) also may review these studies, FDA cautions that IRBs must be knowledgeable about local conditions in order to adequately evaluate the plans for community consultation and public disclosure. While knowledge of the local research context is required of all IRBs,[17] the importance of this responsibility is heightened for research conducted under the emergency research exception. Considering the significance of the community consultation process and the expanded role that IRBs are expected to play in this process going forward, one must question whether an IRB located in another state or across the country can feasibly and effectively meet the responsibilities relating to the community-based processes.

Further, when multiple research sites use the services of a single independent IRB, this may lead to beneficial efficiencies by reducing the number of IRBs and the number of reviews required throughout the duration of a study. In the context of emergency research, however, any decrease in the number of IRBs weighing the risks and benefits of a study is a negative result, as each additional IRB that reviews the study provides another safeguard to the interests of the subjects. This protection provided by greater numbers of IRBs is particularly important in light of the regulatory requirement that sponsors inform all IRBs that have been (or are) asked to review a study under the emergency research exception of any IRB that disapproves the study. In this way, the disapproval of a study by any one IRB functions as a check on all other participating IRBs. Thus, for multicenter studies performed under this regulation, it is preferable that a greater number, rather than fewer, IRBs review and evaluate whether it is appropriate for a study to be approved to enroll subjects without obtaining informed consent.

While the PolyHeme study has faced considerable public criticism for some of the issues addressed here, one of the factors indicating that human subject protections were being sufficiently considered, and regulatory requirements adequately met, has been the fact that the study had been reviewed by 32 IRBs, and 31 of these boards voted for approval.[18] One can easily imagine that if the PolyHeme study had been reviewed by only two or three independent IRBs located in communities remote from the participating institutions, that more telling concerns about the review and approval process could have been raised.

State Law

It is important for sponsors and institutions to remember that notwithstanding the FDA waiver provisions, some states have determined that they will not permit the conduct of emergency research in any context. As an example, until July 2006, Rhode Island had a statute that was widely interpreted as prohibiting *any* research (including research that can only be performed in the emergency setting) to commence without first informing the potential participant of the study and offering the individual the option to refuse to participate.[19] This type of protective state law would trump the more permissive federal regulations, thereby making the conduct of emergency research in Rhode Island prior to July 2006 (or any state with a similar law in effect) technically impermissible. As IRBs should ensure that any research to be conducted under the emergency research exception meets the appropriate regulatory requirements, they must be familiar with applicable state laws that address whether emergency research is permitted.

Subject Exclusion

The draft guidance briefly addresses the issue of excluding certain subjects from participating in emer-

[17] *See* Letter from Director, Office for Protection of Research Risks (OPRR, now OHRP), *IRB Knowledge of Local Research Context*, 8/27/98, as updated 7/21/00.

[18] *See* Dougherty, *supra,* fn. 7.

[19] R.I. Gen. Laws § 23-17-19.1 (2006). As of July 3, 2006, the Rhode Island statute was revised to permit the conduct of emergency research without informed consent under certain limited conditions similar to those under the FDA regulations.

gency research. However, we question whether there are sufficient protections in place for individuals who arguably should never be enrolled in this type of clinical investigation, such as prisoners and pregnant women. In waiving the applicability of informed consent requirements in the limited context of emergency research, the Office for Protection from Research Risks (the precursor to OHRP) made clear that this waiver does not apply to research involving pregnant women or research involving prisoners.[20] The draft guidance, however, does not adequately ensure that individuals in these protected groups do not become participants in emergency research. In pertinent part, the draft guidance 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.'' The concern here, is that prisoners and pregnant women may not be obvious members of these categories (*e.g.*, a prisoner in partial correction custody in a community release program or a woman who is in the early months of pregnancy). Therefore, how do researchers ensure that members of these groups do not become enrolled in research under the emergency research exception? Furthermore, if such an individual is enrolled into an emergency research study, once the subject is identified as being a prisoner or pregnant, what does this mean for the subject's continuation on the protocol and use of the data? These might be infrequent events, but they are issues FDA has yet to address.

[20] OPRR Report, *Informed Consent Requirements in Emergency Research*, 10/31/96.

Conclusion

While FDA has provided valuable guidance regarding the emergency research exception, this article has sought to highlight some areas that the research community will need to grapple with in addressing the many lingering state law uncertainties and federal law ambiguities. In light of FDA's breadth of experience with studies performed under these regulations during the past ten years, some of these issues and concerns likely would benefit from FDA direction. On the other hand, IRBs offering a fresh look at each study proposed under the exception may be in the best position to respond to and resolve many of the concerns raised here. The public hearing and comment opportunities ahead surely will foster a healthy debate about this emotionally charged type of human subject investigation.

   ISSN 1539-1035