

Trials and Errors: Barriers to Oversight of Research Conducted under the Emergency Research Consent Waiver

Despite the Nuremberg Code's assertion that "the voluntary consent of the human subject is absolutely essential," federal human research regulations permit both consent from legally authorized representatives (LARs) for incapacitated subjects, and waiver or alteration of informed consent for certain minimal risk research.¹ In 1996, the regulations were amended to permit a limited category of research bearing more than minimal risk to go forward without informed consent from either incapacitated subjects or their LARs. Known as the "emergency research" (ER) waiver rule, the regulation was codified in Food and Drug Administration (FDA) regulations² and adopted by the Department of Health and Human Services (DHHS).³

Though controversial and infrequently employed, the ER waiver rule is valued because it facilitates important research in settings where new, well-validated treatment options are needed and circumstances preclude obtaining informed consent from an incapacitated individual's LAR. The first clinical trial conducted under the ER waiver rule was a widely publicized study of an oxygen-carrying blood substitute: Baxter Laboratories' HemAssist.⁴ Another trial conducted under the rule involved placing automated defibrillators in public venues and tracking the outcome of their use from experimental and control sites.⁵ Individuals felled by cardiac arrest formerly had to wait for emergency medical personnel to arrive before receiving needed defibrillation. Because of the study, automated defibrillators are now common in airports and other public places.

The ER waiver rule permits Institutional Review Boards (IRBs) to waive the requirement for informed consent from an incapacitated individual's LAR when certain conditions are met.⁶ These include familiar protections such as evidence from prior research supporting the experimental intervention's potential to benefit

patient subjects and the establishment of an independent data monitoring committee. Additional conditions are specific to a narrow application of the waiver: patient subjects are in a life-threatening situation that necessitates intervention; obtaining informed consent from an LAR is not feasible within the time period necessary to initiate the experimental intervention (i.e., the therapeutic window); and available treatments are unproven or unsatisfactory. Finally, the conditions require researchers to 1) consult with representatives of the communities in which the research will be carried out and from which subjects will be drawn and 2) publicly disclose to those communities the research plan and its potential risks and benefits.

During the community consultation process, people can register their views about the proposed study. IRBs are expected to consider community views when reviewing a request for a waiver of consent under the ER waiver rule. After obtaining IRB approval for the study, researchers must disclose to the public that incapacitated individuals can be enrolled without consent from an LAR.⁷

Some time ago, we became concerned about the applicability of the ER waiver rule to the ongoing trial of PolyHeme, Northfield Laboratories' hemoglobin-based oxygen-carrying resuscitative fluid. If it were to merit FDA approval, the product could save the lives of trauma victims initially being treated in an out-of-hospital setting. Because blood transfusion is ordinarily unavailable in the field, trauma patients often succumb to hemorrhagic shock before reaching the hospital.

The Trial and Its Error

The PolyHeme trial has two stages: an ambulance stage and an in-hospital stage. Trauma patients in hemorrhagic shock are enrolled in the trial by emergency medical technicians at the scene of accident or injury. Patient subjects are randomized to receive either saline solution (the standard but admittedly unsatisfactory treatment) or PolyHeme. They are then

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transported to the hospital, where those who received saline continue to receive standard treatment, now including blood as needed. Those in the experimental group continue to receive up to six units of PolyHeme for up to 12 hours—instead of blood.⁸

Because blood is available at the hospital, and is an effective (albeit imperfect) standard treatment for hemorrhagic shock, denying half of the patient subjects blood for up to 12 hours does not, in our view, meet the criteria for the ER waiver rule, which requires that available treatments be “unproven or unsatisfactory.” In the hospital setting, blood is neither. An in-hospital trial comparing PolyHeme with blood could be valuable and legitimate, but consent from the patient subject or an LAR should be required.⁹

The research had been misleadingly described as an “ambulance trial.”¹⁰ When we finally appreciated the in-hospital problem, we corresponded with an official from the trial’s sponsor, Northfield Laboratories. The sponsor’s arguments for in-hospital use of PolyHeme were premised on the adverse effects of blood. Following a failed effort to persuade the sponsor’s representatives that the study design did not meet the ER waiver rule, we contacted the FDA. The FDA acknowledged our communications without comment. As we pressed on, we discovered three barriers to effective oversight of research conducted under the ER waiver rule.

Barrier #1: Proprietary Protocols

When we asked to see the protocol, we were told that its disclosure was limited to IRBs reviewing the study or researchers carrying it out, and then only pursuant to a confidentiality agreement. Although industry sponsors of research have legitimate interests in protecting trade secrets and confidential commercial information, little systematic attention has been given to the effects of this degree of information control in clinical research. When a commercial sponsor labels its research data as proprietary, a conflict arises between protecting competitive advantage and protecting subjects (and perhaps future patients as well). In research requiring community consultation and public disclosure, when an entire protocol is considered proprietary, the sponsor’s interest in protecting its competitive advantage also conflicts with the community’s right to transparency. It seems to us that if community consultation is to be adequate and effective, the community’s need for information must outweigh the commercial interests of a spon-

sor. Commercial secrecy thus appears directly at odds with the free and full discussion required by the ER waiver rule. The protocol should be available for review. Despite repeated requests, we have yet to see the protocol for the PolyHeme trial, or even any version of the consent form.¹¹

Barrier #2: Derailing IRB Disapprovals

If an IRB determines that it cannot approve proposed research—because it does not meet the criteria for the ER waiver rule or “because of other relevant ethical concerns”—the IRB must document and report its disapproval promptly to the sponsor and local investigator. The sponsor then must promptly report the IRB determination to the FDA, to the sponsor’s other investigators, and to other IRBs who have considered or are considering the study or substantially equivalent research.¹²

In communications with several members of IRBs that reviewed the proposed PolyHeme trial, we uncovered two strategies for sidestepping these reporting requirements. In both instances, the concerns IRB members had about the trial were essentially identical to the problem that troubled us: its in-hospital portion.

In one case, the principal investigator (PI) had been alerted in advance that some on the IRB had expressed reservations about the trial. Before the full IRB convened to review the proposed study, the application for review was withdrawn. The IRB neither completed its review of the proposed study nor reported a failure to approve. In a second case, the IRB notified the PI that there were problems with the study needing correction. The application for review was returned to the investigator with a request to amend and resubmit it. The IRB never received an amended version of the application, and no negative report was sent to the sponsor.

It could be argued that these examples are consistent with a narrow interpretation of “cannot approve” in the ER waiver rule because neither IRB made a final determination about the research. From our perspective, however, the requirement that the IRB’s findings be disseminated promptly appears intended to promote communication and learning among IRBs and investigators. We worry that IRBs and sponsors can too readily avoid reporting problems with proposed studies to those needing to be informed. If serious reservations about a study identified during IRB review were generally buried in this way, the national system of research oversight would be compromised.

Barrier #3: The Special Protocol Assessment

The PolyHeme study is being conducted under an FDA-granted Special Protocol Assessment (SPA). The 1997 FDA Modernization Act¹³ contains provisions designed to streamline the approval process for drugs and biologics, including the making of agreements between the FDA and sponsors about the amount and nature of the evidence required to establish safety and effectiveness and rapid assessment of protocols to determine whether they can produce adequate evidence. In May 2002, the FDA issued a guidance on SPAs. When granted, an SPA locks the FDA and the sponsor into an agreed-upon study design. The FDA can reconsider and order changes only if one of four conditions applies: 1) there is mutual written agreement to alter the trial; 2) there has been a subsequent identification of “a substantial scientific issue essential to determining the safety or effectiveness of the drug”; 3) the sponsor fails to follow the agreed-upon protocol; or (4) “the relevant data, assumptions, or information provided by the sponsor in a request for special protocol assessment change are found to be false statements or misstatements or are found to omit relevant facts.” The FDA can only grant an SPA before subject screening or enrollment begins.¹⁴

There is a tension between community consultation in trials under the ER waiver rule and the SPA's timing. The study can begin only after a sponsor has first received written permission from the FDA and, later, IRB approval. But IRBs can approve the protocol only after community consultation.¹⁵ If, as we believe, one purpose of community consultation is to uncover correctable problems, the prospect of having to reapply for an SPA discourages the sponsor from changing the protocol when errors are found. One would expect a “take it or leave it” approach to community consultation if a study design could not be altered without costly delay.

More important, the SPA appears to bar the FDA from taking corrective action. The identification of ethical concerns is missing from the list of four conditions warranting FDA reconsideration. Even if the FDA agreed that our ethical critique of the PolyHeme trial were sound, it is not clear it could require alteration of the study on that basis, having previously approved the study design under an SPA. We do not know how often sponsors seek SPAs for clinical trials, but can well understand the desire to clarify in advance what design and data will suffice for FDA approval. We are not the first to recognize that SPAs can constrain IRB review.¹⁶ We

suspect, however, that the PolyHeme trial is the first to uncover conflict between the requirements of an SPA and those of the ER waiver rule.

Discussion and Recommendations

In attempting to learn more about the PolyHeme trial, we found heretofore-unsuspected conflicts, tensions, and gaps in the oversight of research conducted under the ER waiver rule. Taken together, these appear to diminish responsiveness to ethical concerns arising in this unusual category of clinical trial. The proprietary sequestration of essential documents; the apparent side-stepping of the requirement to report IRB failures to approve; and the granting of SPAs that constrain community consultation and cripple FDA reconsideration: all three suggest a dysfunctional system.

The PolyHeme trial suggests that in an increasingly competitive atmosphere, the still-unfamiliar requirements of the ER waiver rule can too easily be interpreted away. We argue that when requirements of the ER waiver rule appear to conflict with other FDA provisions and procedures, more attention must be given to ensuring that the ethical integrity of the ER waiver rule is maintained. We recommend that, at the very least, IRBs reviewing such research should determine whether it involves a confidentiality agreement or an SPA, and disapprove the research unless those provisions are altered to ensure adequate and effective community consultation and public disclosure.

In addition, DHHS's version of the ER waiver rule contains language absent in the FDA's: “A periodic review of the implementation by IRBs of this Section 101(i) waiver will be conducted by [the Office of Human Research Protections (OHRP)], to determine the adequacy of the waiver in meeting its intended need or if adjustments to the waiver might be necessary and appropriate.”¹⁷ Although the FDA has exclusive jurisdiction over waived-consent trials conducted under FDA regulations, such as the PolyHeme trial, the OHRP appears to have the authority to conduct such a periodic review. We believe that a review of these broader issues, collaboratively undertaken by the OHRP and the FDA, is now necessary to ensure open discussion of the future of the ER waiver rule.

Properly conducted, waived-consent research can augment the capabilities of emergency medicine. It would be tragic if avoidable failures and conflicts in oversight compromised the promise of these trials.

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References

1. *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity. Volume I, Report and Recommendations of the National Bioethics Advisory Commission.* Rockville, MD: National Bioethics Advisory Commission, 1998:61-63. <http://www.georgetown.edu/research/nrcbl/nbac/capacity/Moving.htm#Informed>; see also sec. __.116(c) (the Common Rule) and 45 CFR 46.116(c) (DHHS) on minimal risk waivers of consent.
2. Food and Drug Administration. 21 CFR Parts 50, 56, 312, 314, 601, 812, and 814. Protection of Human Subjects; Informed Consent. Federal Register 1996;61(192):51498-51531.
3. Department of Health and Human Services. 45 CFR Part 46. Waiver of Informed Consent Requirements in Certain Emergency Research. Federal Register 1996;61(192):51531-51533.
4. Sloan EP, Koenigsberg M, Brunett PH, et al. Post hoc mortality analysis of the efficacy trial of diaspirin cross-linked hemoglobin in the treatment of severe traumatic hemorrhagic shock. *Journal of Trauma-Injury Infection & Critical Care* 2002;52:887-895.
5. Hallstrom AP, Ornato JP, Weisfeldt M, et al. Public Access Defibrillation Trial Investigators. Public-access defibrillation and survival after out-of-hospital cardiac arrest. *NEJM* 2004;351(7):637-646.
6. See ref. 2.
7. More extensive discussion of the ER waiver rule's history and implementation may be found elsewhere, including: Biros MH, Fish SS, Lewis RJ. Implementing the Food and Drug Administration's final rule for waiver of informed consent in certain emergency circumstances. *Academic Emergency Medicine* 1999;6:1272-1282; Biros MH. Research without consent: Current status. *Annals of Emergency Medicine* 2003;42:550-564; Shah AN, Sugarman J. Protecting research subjects under the waiver of informed consent for emergency research: Experiences with efforts to inform the community. *Annals of Emergency Medicine* 2003;42:72-78; Proceedings of the 2005 AEM Consensus Conference on Ethical Conduct of Resuscitation Research. *Academic Emergency Medicine* 2005;12:1019-1139.
8. Northfield Laboratories Inc. Press Release: Northfield Laboratories Announces Patient Enrollment in Phase III Urban Ambulance Trial to Begin Monday, December 22. Evanston, IL, Dec. 22, 2003. <http://phx.corporate-ir.net/phoenix.zhtml?c=91374&p=irol-newsArticle&ID=599107&highlight>.
9. We set out a more detailed examination and critique of the design and conduct of the PolyHeme trial in: An open letter to IRBs considering Northfield Laboratories' PolyHeme trial. *American Journal of Bioethics*, forthcoming.
10. See ref. 8.
11. Every study site must have an IRB-approved consent form available, in case informed consent can be obtained from a subject or an LAR. See ref. 2; Japsen B. Paper barred from using data: Northfield Labs sues on blood substitute. *Chicago Tribune*, January 7, 2006. <http://www.chicagotribune.com/business/chi-0601070106jan07,1,5904816.story?ctrack=1&csset=true>.
12. See ref. 2.
13. Pub. L. 105-115, 105th Congress, Nov. 21, 1997.
14. Food and Drug Administration. Guidance for Industry: Special Protocol Assessment. May 2002. <http://www.fda.gov/cber/gdlns/protocol.pdf>.
15. "Community consultation refers to ensuring that the community(ies) is (are) involved in the IRB's decision-making process. As such, the IRB needs to provide an opportunity for the community(ies) to discuss the proposed clinical investigation and its risks and potential benefits, and to provide feedback to the IRB. The IRB should consider this community discussion when reviewing the protocol." Food and Drug Administration. *Draft Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research*. March 30, 2000, p. 6. http://www.fda.gov/ora/compliance_ref/bimo/emrfinal.pdf.
16. Mann H. Clinical trial protocols: Agreements between the FDA and industrial sponsors. *Lancet* 2002;360:1345-1346.
17. See ref. 3.