

Docket number 2006D-0331: Conduct of Emergency Clinical Research; Public Hearing

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Summary of Relevant Experience

In 1982 I began work at the Naval Research Laboratory on the development of a hemoglobin-based oxygen carrier or blood substitute for domestic emergencies and combat casualty care. Since that time I have worked with several blood substitute research groups, most extensively the Baxter DCLHb team. I was the Baxter delegate to the NIH/HHS meetings that led to the 1996 issue of 21 CFR 50.24, the so-called Final Rule permitting exception from informed consent (EIC) requirements for emergency research. In addition I worked with the Society of Critical Care Medicine to bring state regulations into line with the new federal regulations. As Director of Technical Communications for the Hemoglobin Therapeutics division of Baxter, I had responsibility for designing the community consultation and notification program for the DCLHb severe traumatic hemorrhagic shock trial. It was the first trial to be permitted under the new regulations governing EIC trials and there were no precedents to follow in designing the program. More recently I consulted on the design of the community consultation and notification program for the RESUS trial that the US Navy is hoping to initiate.

I am a community representative on the IRB of Northeast Hospital Systems and a volunteer representative on the Ethics Committee of Hospice of the North Shore. My involvement with various issues in medical ethics, beginning with those raised by emergency medical research and subsequent work in the field of stem cell research, in addition to serving on these boards, led to my desire for formal training in medical ethics. Currently I am a research fellow in the Division of Medical Ethics at Harvard. As part of the fellowship I am examining whether the approaches to community consultation and notification employed to satisfy the requirements of 21 CFR 50.24 have satisfied the original intention of providing additional protections for vulnerable research subjects. I am also exploring other approaches that might satisfy, perhaps more effectively, the original intention of the EIC regulations.

The Need for Additional Protections

The question that *should* now be addressed by FDA is whether the various additional protections provided by the 21 CFR 50.24 are demonstrably any more effective at protecting vulnerable patient populations than the practices in place previously or elsewhere. What *is* being addressed by FDA is how to better implement those additional protections. The July 2006 Guidance document¹ clarifies expectations regarding specifics of implementation, which is helpful, but I would urge, like many others who have contributed comments to this docket, that the specifics of the EIC regulations themselves be reconsidered with respect to several of the requirements. There is good reason to consider establishing an independent central IRB for scientific and ethics review, with members who are well trained on the specifics of 21 CFR 50.24; their deliberations should at least be available to potentially participating institutions and to the extent possible should be publicly available. There is good reason to consider broadening the research from life-threatening circumstances to severely disabling circumstances as emergency research in this area is stifled both by the difficulty of obtaining informed consent and by not qualifying for the exception to informed consent. Researchers are forced either to use excessively vulnerable patient populations to qualify for the

exception or insufficiently acute patient populations to assess a potential therapy's effectiveness.² And there is good reason to reconsider the requirement for community consultation. My specific comments will be limited to revisiting the community consultation requirement, widely considered to be the hardest part of implementing a clinical trial according to these regulations, as recently testified to FDA by attendees at the October 11th public hearing.³

When I developed the program of community consultation and disclosure for the Baxter DCLHb trial I was not formally trained in medical ethics but I was well aware of some of the history of abuses of research subjects – Nazi experiments in Germany and the Tuskegee syphilis studies in this country stand as hideous blots on the record of the medical research community. Never again. The *Nuremberg Code* (1949), the *Declaration of Helsinki* (1964) and the *Belmont Report* (1979), each more specifically than the one before, delineated protections for human subjects. The principle of autonomy, or respect for persons, rose during this period to reach equal status with the principles of beneficence and non-maleficence, or “do no harm.” More recently justice has been added to the list of principles that must be balanced as resource allocation issues become ever more problematic.

The first principle of the *Nuremberg Code* states: “The voluntary consent of the human subjects is absolutely essential.”⁴ By the time the Code was reformulated in the 1964 *Declaration of Helsinki* it was recognized that there may be exceptions to the requirement for informed consent. The *Belmont Report* led to 1981 regulations (45 CFR 46) permitting a waiver of the requirement for informed consent in some types of research involving “minimal risk.”⁵ The *Declaration of Helsinki* has undergone numerous updates, elaborations and clarifications since 1964: 1975, 1983, 1989, 1996 and most recently in 2000. In the 2000 edition it is recognized that it will not be possible to obtain consent from all patients or their proxies and it is specified that approval of review committees is necessary for research involving subjects with a condition that renders them unable to give informed consent.⁶ Further, consent to remain in the research should be obtained as soon as possible from the individual or their legally authorized

representative (LAR). Implicit is the perspective that the research should be permitted if it is likely to benefit the subjects to be enrolled, or the patient population represented by the subjects to be enrolled, and if the subjects can be judged as likely to give consent if they could. Similarly the International Council on Harmonization (ICH) guidelines on good clinical practice, issued in 1996, specify (section 4.8.15) that under emergency circumstances where prior consent by the subject or the subject's LAR is not feasible, protocol enrollment requires measures to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements.⁷ Documented approval/favorable opinion by the IRB/IEC [institutional ethics committee] is required. The subject should be informed of inclusion in the trial as soon as possible and "consent to continue" should be requested, a formalism sometimes referred to as "deferred consent."⁸

Development of the Final Rule

Deferred consent, however, was not in compliance with federal regulations, as recognized by Dr. Gary Ellis, Director of the Office for Protection from Research Risks (now the Office of Human Research Protections), when he alerted institutional officials and IRBs to the issue in his 1993 "Dear Colleague" letter.⁹ Emergency medical research came to a grinding halt.¹⁰ It is hard to calculate the cost of not doing emergency research but the earlier studies that led to the development of CPR and electrical defibrillation, now administered to hundreds of thousands of patients each year, were performed on unconscious patients unable to give informed consent. Three years of research time - and who knows how many lives - were lost while the various agencies struggled to resolve the regulatory and ethical conflicts.

Following industry-FDA meetings (1993), a Congressional hearing (May 1994), a Coalition Conference of Acute Resuscitation and Critical Care Researchers (October 1994), an FDA-sponsored public forum (January 1995), and publication of a consensus statement from the Coalition Conference¹¹ recommending that research without informed consent be selectively permitted with additional safeguards such as community

consultation (April 1995), FDA published in the *Federal Register* in September 1995, [60 FR 49086] a proposal to amend its regulations to permit a limited class of research in emergency settings without consent. Following a careful review of the comments received on the proposal, a final regulation was published October 2, 1996, [61 FR 51498], which came to be known as the Final Rule (21 CFR 50.24). The Department of Health and Human Services published in the same issue, its waiver criteria which match the FDA requirements [61 FR 51531]. Differences between the FDA and HHS regulations had, in fact, triggered Ellis's 1993 alert but these *Federal Register* documents established at last a single standard for this class of research.

European Approach

While the DCLHb severe traumatic hemorrhagic shock trial was being conducted according to 21 CFR 50.24 in emergency rooms across the US in 1997,¹² a multinational controlled trial of DCLHb was being conducted in the pre-hospital setting in Europe according to the ICH guidelines.^{13,14} Subjects were enrolled generally without their consent or consent of their proxies but were informed as soon as possible and consent to continue was requested, per the ICH guidelines. No program of community consultation and disclosure is required anywhere in Europe where the scientific review by IRBs and ethical review by institutional ethics committees is considered sufficient. Why is that not enough in the US? Is the lack of trust in the medical institutions in the US so great that communities really can't trust their hospitals to do the right thing? It would appear so. The regulations were greeted with grave concern among minority communities because of a sad history of exploitation by medical researchers.¹⁵ That concern has not dissipated much in the interim.^{16,17} Involvement by the community in the decision to conduct research on vulnerable members of that community was suggested by the Consensus Conference as a way to take that concern into account but the unintended consequences of that suggestion now need to be considered. If we are overly concerned with violating the principle of autonomy in our highly individual-centered culture, so much so that we place it ahead of doing what we believe is best, medically at least, for severely

compromised patients who might very likely benefit from being enrolled in a clinical trial of a promising new agent, device or procedure, we have not served the community well.

Despite the requirement for equipoise between the arms of a research protocol it can only be conducted if there is very good reason to believe the test article is likely to outperform the control or standard of care. According to the 21 CFR 50.24 section IV(3)(b) appropriate animal and other preclinical studies [and generally preliminary clinical studies as well] must have been conducted and the information derived from those studies and related evidence must support the potential for the intervention to provide a direct benefit to the individual subjects. Obviously neither sponsors nor investigators would seek to do such a trial if they didn't believe they were thereby advancing the practice of medicine and helping the patient population from which subjects were to be enrolled. I contend that a truly rigorous scientific evaluation of an emergency medical research protocol coupled with an equally rigorous ethical review *should be* sufficient to protect vulnerable patient populations. That is sufficient according to existing regulations in Europe. That is sufficient, too, according to the most recent (2000) edition of the Declaration of Helsinki. Unfortunately the perception in this country, rightly or wrongly, is that IRB and ethics committee review is still not sufficient to protect vulnerable patient populations from abusive medical experimentation.

Jay Katz, who vehemently opposed the EIC regulations,¹⁸ raised concern that beneficence as a first principle may overwhelm autonomy and be subverted into paternalism.¹⁹ With the advent of readily available information – the Internet age – the pendulum has swung very far from the paternalism of yesteryear, possibly even too far. What paternalism in medicine reflected was the superior training and knowledge of the physician compared to the patient, albeit without adequate respect for autonomy, but the knowledge differential remains. The Internet is no substitute for medical school.

There is a perspective emerging in biomedical ethics literature, in fact, that the increasing prominence of autonomy may actually have perverted this principle, pushing expectations regarding informed decision making by patients to a level that is unrealistic

and undercutting the role of the highly trained medical professional to advise the patient, share in the decision making, and direct treatment that is in the best interest of the patient.²⁰ Research presents additional issues. There is good evidence that few patients, following carefully conducted informed consent procedures in non-emergency circumstances, actually understand the concept of controlled clinical research or the actual risks to which they may be exposed in a randomized trial.^{21,22}

Relative to the conduct of emergency clinical research my point is that the current regulations as written, while affording important additional protections for vulnerable subjects in an attempt to respect their limited autonomy, may be contributing to the imbalance, subverting beneficence to autonomy. The cost and effort of community consultation has certainly been a barrier to pursuing many research protocols that might have resulted in advances in medical care for critically ill and injured patients. The rate of cardiac arrest trials, for example, has declined significantly in the US while it has increased in Europe since the issue of the Final Rule.²³

The extensive scientific and ethical review of protocols that FDA conducts before permitting research to proceed under the Final Rule, coupled with both the review by local IRBs and ethics committees and with the professional clinical judgment of well-trained investigators, together provide a great deal of additional protection to vulnerable subjects in acute circumstances who cannot give informed consent. Add to that the requirement for public disclosure to the community of risks, benefits, protocol specifics and demographics before and after the study; the requirement for a data monitoring committee; and the requirement that consent to continue be obtained from the subject or the subject's LAR as soon as feasible. The total package of additional protections is quite substantial. Community consultation as a means of feedback to the IRB from individuals who do not have a vested interest in the trial may add incrementally to the package of protections but, with all of the other safeguards in place, it can be argued that it need not be extensive. Input solicited from a small number of highly respected community leaders or delegates who function as consultants to the IRB may be more valid and sufficient in light of the rest of the package of protections.

Implementation of the Final Rule

There is a body of literature regarding implementation strategies and the effectiveness of various approaches to community consultation and notification.^{24,25,26} The consensus appears to be that despite extensive public communications remarkably few people within a community are aware of exception to informed consent EIC trials being run in their community. Public meetings held specifically for community consultation are poorly attended. For trauma research especially, where there is no expectation by anyone in the community that such a trial might ever apply to them, the lack of interest is understandable. For a trial of a potential therapy for heart attack or stroke victims, for example, it should be possible to identify a population of patients who, through past medical history, are known to be at risk and thus may be more interested in attending an informational session about such a trial.

When we prepared to initiate the DCLHb trial in trauma patients we sought the help of a professional communications agency, Fleishman Hillard. Community consultation we recognized as the first step, critical to initiation of the study, because IRBs needed that input before deciding whether to proceed. We identified civic and religious community leaders as well as local politicians in each city that could be contacted by investigators or IRBs; community boards and organizations that had regular meetings where investigators could make presentations; local radio and TV talk shows. We proposed in addition open community meetings, hospital outreach programs, telephone lines for questions and comments. Baxter funded a very extensive, and very expensive, program for community consultation as well as public disclosure. IRBs still made their own decisions which of the options to implement but they generally consulted with the communications officers of the hospitals and worked with Fleishman Hillard and Baxter to implement the best program they could design. Because it was the first EIC trial and the first community consultation program to be implemented we had no idea how much was enough. Thousands of dollars per patient were spent on the program. The company, the investigators, the IRBs and the research institutions made every effort to meet the spirit

and the letter of the new regulations. Though the trial itself had an untimely end and a very disappointing outcome, the consensus was that the community consultation and disclosure program, at least, was well done.

But was it effective? And how can that be measured? We still do not have benchmarks for such measures.²⁷ If the goal was for IRBs to have input from a broad cross-section of the community, in hopes that the geographic community would reasonably represent the population of accident and violence victims who were to be enrolled, then the goal was accomplished. If the goal was to protect vulnerable populations who by the nature of their injuries had lost much if not all autonomy at least temporarily, casual input from uninvested community members that was reported to the IRB can hardly be said to do that. The role of community consultation was not intended to be a proxy for consent. But perhaps it should be. If the community members do not have some official status for providing proxy consent, do not have a sense of responsibility to their community that such an official status would provide, do not have any training in medical research or research ethics, do not comprehend more than the most basic facts about the research being conducted that can be communicated in the few minutes people are willing to devote to learning about it, how useful can their input be?

Community-Based Ethics Committee

One option would be to draw a group from the community who could be vested with more responsibility and more training and whose input could be more formally provided to the IRB. IRBs and ethics committees have institutional affiliation and members are largely drawn from within the ranks of the institution with a minimal representation from the community. I serve as a community representative on an IRB and on an ethics committee and I do not have official affiliation with either institution. I do, however, have a background in medical research and medical ethics which enables me to participate much more fully in the discussions than other community representatives. But even a little training could go a long way.

In the preamble to the proposed rule (60 FR 49086, September 21, 1995) are several suggestions. “IRB’s should consider, for example, having a public meeting in the community to discuss the protocol; *establishing a separate panel of members of the community from which the subjects will be drawn; including consultants to the IRB from the community from which the subjects will be drawn; enhancing the membership of the IRB by adding members **who are not affiliated with the institution and are representative of the community*** [bold and italics mine]; or developing other mechanisms to ensure community involvement and input into the IRB’s decision-making process.”

Similarly, among the suggestions in the current (July 2006) Guidance document, in the section titled Type & Frequency of Community Consultation, is found the following: “...the IRB could consider, for example, having a public meeting in the community to discuss the protocol, *establishing a separate panel of members of the community from which the subjects will be drawn, 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. Alternatively, the IRB could use community members as consultants to the IRB*** [bold and italics mine]. While an IRB may appropriately decide to supplement its membership with consultants from the community, expanding the IRB membership would not by itself adequately substitute for the community consultation called for in 21 CFR 50.24(a)(7)(i); broad, public consultation with the community is needed for this type of research.”

What is suggested by the repeated phrase in **bold** is that input to the IRB needs to come from people who are not affiliated with the institution, i.e., do not have a vested interest in the decision to approve the trial; this reflects concern regarding the lack of trust by the community, or at least elements of the community, of the medical establishment. What is suggested by the other italicized sections, however, is that a panel of community members be established or other consultants drawn from the community to serve on or as consultants to the IRB. To my knowledge, judging from the limited research that has been published on community consultation and notification programs for EIC trials, the choice to establish and train a panel of community representatives, a kind of community-

based ethics committee, has not been implemented. Perhaps establishing and training such a panel for community consultation on a single EIC trial has been viewed as too labor intensive. But if such a panel were established as a standing community committee it could provide more valid input to the IRB and an enormously valuable service to the community and to the hospital ethics committee and IRB. Such a committee is in fact being established currently for the Harvard Medical School teaching hospitals.²⁸

The Community-Based Ethics Committee will be a resource to hospital ethics committees of the Harvard Medical School teaching hospitals. Such a Community-Based Ethics Committee (CBEC) will be comprised of members of the neighborhoods within the catchment area of the Harvard teaching hospitals. It is the intention of the organizers of the CBEC that the members will be diverse as to socio-economic status, religious affiliations, cultural and language groups, and educational backgrounds. The need for such a consultative group has been evident for a long time; community members currently serving on hospital ethics committees and IRBs are rarely truly representative of the communities they serve. As part of the formation of the Committee, the members of the CBEC will be given specific training in the area of bioethics; they will meet monthly to review issues and cases; and they will be a valuable resource to the various teaching hospitals' ethics committees by bringing a heretofore limited voice to the discussion. One role for the CBEC that has been discussed is to review and monitor the medical care of young children within the Department of Social Services protective system, particularly those with standing DNR orders. The organizers welcome the prospect that the CBEC could provide community perspective to the IRBs and institutional ethics committees regarding any protocols involving an exception to the requirement for informed consent, 21 CFR 50.24.

If the CBEC experiment at the Harvard teaching hospitals is successful it would provide a model for other large teaching/research hospitals or consortia of hospitals. Once such representative committees are in place the process of community consultation for important emergency research studies would be much less cumbersome and expensive. It would almost certainly be more effective as well because the CBEC would be both vested

in protecting the community and at least minimally trained in bioethics and principles of medical research, particularly emergency medical research involving an exception to the requirement for informed consent.

Summary

A reevaluation of the specific requirements of the Final Rule is in order. The additional protections for vulnerable research subjects are largely effective, ethically supportable and reasonably practicable. The exception is the requirement for community consultation, which has been very problematic. It is doubtful that the approaches that have been undertaken are in fact affording much in the way of protection, despite the great cost and time expended in the effort. This requirement may in fact be preventing advances in medical care of critically ill and injured patients because the cost and time are prohibitive, i.e., it may be doing more harm than good. The rationale for obtaining community input, however, is valid even if it is not effective in practice. An alternative approach, a community based ethics committee, is proposed.

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