

Introduction

Annals News and Perspective explores topics relevant to emergency medicine, in particular those in which our specialty interacts with the political, ethical, sociologic, legal and business spheres of our society. Discussion of specific clinical problems and their

management will be rare. By design, it will not be a “breaking news” section with the latest (and undigested) developments, but instead a reflective investigation of recent and emerging trends. If you have any feedback about this section, please forward it to us at feedback@acep.org.

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POLYHEME AND THE ETHICS OF INFORMED CONSENT

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Informed consent in out-of-hospital and resuscitation research will soon come under increased federal scrutiny in the wake of public outcry over a study of the blood-substitute PolyHeme.

The United States Food and Drug Administration (FDA) is launching a re-examination of the decade-old regulations allowing clinical emergency research under an exception from informed consent requirements. A set of standards, technically designated 21 CFR 50.24 and colloquially known as the Final Rule, were widely sought by researchers before their creation and have provoked repeated controversy since.

The effort, announced in an inconspicuous Federal Register posting just before Labor Day, was to go public October 11 with an FDA hearing on emergency research at the University of Maryland. The agency says it hopes to clarify language in the rule, examine the responsibilities of trial investigators, sponsors and institutional review boards (IRBs), and reopen the thorniest provisions in the original regulations—the requirement that institutions conduct public education and community consultation before a trial begins.

A RULE REVISED?

“On the 10-year anniversary of this regulation, it is appropriate that we review (it),” said Dr. Janet Woodcock, the FDA’s deputy commissioner for operations, in announcing the hearing. “It is critical that this type of research be conducted to help advance the practice of emergency medicine.”

The re-examination comes at a crucial moment and may have been carefully timed. Since the rule was promulgated, according to agency officials, approximately 60 waived-consent trials have been proposed to the FDA, and about 20 have been approved. But one waived consent study in particular recently has attracted notable controversy: the phase III trial PolyHeme, an oxygen-carrying blood substitute made by Northfield

Laboratories, Evanston, IL. The FDA hearing was announced less than a month after Northfield Laboratories completed enrollment of its envisioned 720 patients. The study’s top-line results are expected late this fall.

The PolyHeme trial is not the only waived consent effort in the public eye. In March, the journal *Nature* predicted that the National Institutes of Health’s 5-year, \$50-million Resuscitation Outcomes Consortium, a multi-pronged effort to treat trauma and heart attack patients, will also provoke questions. And in July, the United States Navy cancelled a meeting with the FDA on a waived consent trial of a different blood substitute, Hemopure, following court action by the watchdog group Public Citizen.

THE MEDIA MINEFIELD

But it is the PolyHeme trial, conducted in 19 states with the participation of thousands of medical personnel—and also dissected in the *Wall Street Journal*, on ABC’s “20/20” and in the *American Journal of Bioethics* and sharply criticized by a US Senator—that has brought home to the emergency medical research community the complexity and the sensitivity of doing waived consent studies.

“These trials involve really sick patients, most of whom cannot speak on their own behalf, none of whom can provide meaningful informed consent, most of whom cannot provide information to help us get in touch with proxies,” said Dr. Michelle Biros, professor of emergency medicine at University of Minnesota and Editor in Chief of *Academic Emergency Medicine*, who helped compose the original regulations. “All these things make IRBs and investigators nervous.”

The research that produced PolyHeme—technically not a blood substitute, but an oxygen-carrying red blood cell substitute derived from hemoglobin extracted from expired donated blood—dates back to Vietnam War-era changes in

trauma medicine. The increased ability to treat on the battlefield highlighted the critical need for a blood substitute that would do more than just restore volume as saline does. It also clarified the formidable challenges ahead. Oxygen-carrying capacity alone would not be sufficient; the ideal blood substitute would have a long shelf life to allow stockpiling, not require refrigeration so that it could be carried into the field, be universally compatible so there would be no need to type or cross-match, and not transmit blood-borne disease.

THE BIRTH OF A BLOOD SUBSTITUTE

Enter Northfield, a company formed in 1985 by five basic scientists and physicians. The group included Dr. Gerald Moss, a former Navy surgeon with an interest in blood substitutes who became dean of the University of Illinois at Chicago College of Medicine, and Dr. Steven Gould, a trauma and vascular surgeon and now the company's chief executive officer. Their interest in a safe and workable substitute dovetailed with research done by Dr. Ernest E. Moore, vice chairman of surgery at University of Colorado Health Sciences Center. His work on trauma patients who suffered multiple organ failure showed a strong correlation between the likelihood of death and the number of red blood cell transfusions the patients had received.

Trials of PolyHeme—the name is derived from “polymerized hemoglobin”—began in 1986. In 2001, Gould said, the company asked the FDA to approve the product based on results published the next year in the *Journal of the American College of Surgeons*: 171 trauma surgery patients who received PolyHeme compared with an historical control group of 300 surgical patients with religious objections to transfusion, treated at different times in different institutions.

The FDA turned back the application. “A major part of their response was that we had not tested the product in an ambulance, where blood was not available,” Gould said. “They felt the data we had published would lead to widespread use of the product in ambulances.”

THE TRAUMA CENTER TRIAL

Northfield's previous trials had conformed to standard informed consent protections. Trialing the product in an emergency medical services setting, though, would require using waivers of consent under the 1996 FDA rule. The company approached “about 50” of the US's then-192 Level 1 trauma centers, Gould said, ruling out any who did not have large patient volumes or robust research programs or were involved in competing studies. Thirty-two centers agreed to participate in a randomized trial that would administer PolyHeme, or the standard treatment of saline in the ambulance and donated blood in the emergency department (ED), to traumatically injured patients in hemorrhagic shock. Administration began during transport and continued for up to 12 hours in the ED.

“Hemorrhagic shock and the organ failure that results is something that I as a general surgeon, and every emergency

physician whether a surgeon or an emergency specialist, faces on an almost daily basis,” said Dr. Andrew Bernard, one of the study's principal investigators and an assistant professor of surgery at the University of Kentucky. “It's a common clinical problem that all of us feel challenged by.”

Participating in the trial meant abiding by the complex set of preconditions specified in the 1996 regulations. The patients who came to be enrolled would be people who were impossible to identify prospectively. At the time of their enrollment, they would have to be in a life-threatening condition and unable to provide meaningful informed consent. Their condition would have to be one for which available treatments are unproven or unsatisfactory. The intervention being tested would have to be administered in a short enough time period that obtaining patient or proxy consent would not be feasible, but the institution would be required to seek patient or proxy consent as soon as practicable.

And crucially, the IRBs having responsibility for the trial at each institution would commit to conducting “public disclosure and community consultation” to ensure that people who might become trial subjects could consider the project in advance. That meant seeking a wide array of tools—none of them specified in the regulations—to get news of the trial out to the public, from doing media interviews to speaking at churches and community groups to creating Web sites, hotlines and public education materials. One team, at the request of its IRB, set up a booth at a minor league baseball game.

SPREADING THE WORD

“We used every conceivable news vehicle,” said Moore, who became the study's lead principal investigator. “We held news conferences. We reported it to TV and on the radio. We got it into newspapers. We went to all the community groups we could.”

“The process is very intense and very difficult to do,” said Dr. Robert Cherry, a principal investigator who is chief of the section of trauma and critical care at Pennsylvania State College of Medicine and the Milton S. Hershey Medical Center. He described weeks of trekking to gatherings in the 6 counties Hershey draws from and reporting back to the center's IRB. But to respect the sacrifice of autonomy made by patients who are enrolled while not competent, “it should be difficult to do,” he said.

Moore enrolled the phase III trial's first patients in January 2003. By early 2006, when it had enrolled about 600 of the projected 720 patients, scrutiny of the trial abruptly shifted from local to national—and shifted attention back to the content of the then 9-year-old Final Rule.

In February, the *Wall Street Journal* reported that an earlier phase III trial of PolyHeme versus donated blood, conducted in consented patients undergoing aneurysm repair, had ended with poor results that had never been published: 10 heart attacks including 2 deaths among 81 patients who received the

substitute, versus no heart attacks in the 71 controls. The deaths, the newspaper said, had been disclosed to the current study's investigators and to the FDA but not at the community meetings held for potential participants in the new trial.

Northfield described the report as inaccurate, saying the heart attacks had been caused when personnel who misunderstood the protocol gave study participants not only PolyHeme but autologously donated blood as well.

THE SENATOR'S SALLY

Nevertheless, the story triggered Congressional response. Republican Senator Charles Grassley of Iowa—chairman of the Senate Finance Committee, which has jurisdiction over Medicare and Medicaid—fired a blistering letter to acting FDA commissioner Andrew von Eschenbach. He charged that the agency, company and investigators had all failed the regulations' "public disclosure" requirement, particularly in informing local communities of the existence of a colored "opt-out" bracelet. (Several thousand such bracelets were distributed, according to Sophia Twaddell, Northfield's vice president of corporate communications.)

"It is outrageous that, for all intents and purposes, the FDA allowed a clinical trial to proceed, which makes every citizen in the United States a potential "guinea pig," without providing a practical, informative warning to the public," said the letter, which demanded FDA staff make arrangements within a week for a Senate briefing. "I am skeptical that any participating medical centers managed to conduct effective, practical outreach to the community and to provide a meaningful, informative warning to the public."

In announcing his outrage, though, Grassley looked beyond the issue of informing the public of waived consent trials to the question of whether they should exist at all. He stated in a press release accompanying the FDA letter: "No reasonable person would expect to be treated as an experimental subject without consent."

THE ETHICIST'S WEIGH IN

Shortly afterward, the study drew criticism from another quarter: the medical bioethics community. In "An Open Letter to IRBs Considering Northfield Laboratories' Polyheme Trial" in the *American Journal of Bioethics*—published online in March and then printed in the May-June edition—3 authors asked the institutions conducting the study to suspend or end their participation unless the protocol was significantly changed. Dr. Robert Nelson of the University of Pennsylvania, bioethicist, attorney Nancy M.P. King of the University of North Carolina and Dr. Ken Kipnis, professor of philosophy at the University of Hawaii, argued that administering PolyHeme under waived consent rules in ambulances is appropriate, because nothing else can be done in that setting. But once in the hospital, a satisfactory alternative therapy, blood, does exist, they said—and therefore the protocol's provision of PolyHeme

for up to 12 hours post-arrival could not be justified under the waived consent rules.

"We can accept the legitimacy of a head-to-head randomized clinical trial comparing blood and PolyHeme, but only with consenting patients/subjects," they wrote. "Consent to an in-house, active-controlled trial—and not merely a good faith effort to obtain it—is plainly required before clinicians can forego the standard treatment, routine transfusion, and instead randomly substitute a promising experimental alternative."

The arguments found support in the broader bioethics community. "I would require a different consent process when the patient is in the hospital," said Nancy Neveloff Dubler, professor of bioethics at Albert Einstein College of Medicine. "At that point, the patient or family member needs to be given the option of the standard of care, because it is no longer an emergency."

20/20 HINDSIGHT

In a final blow, the ABC News program, *20/20*, examined the PolyHeme trial in a July 7th investigation that began:

"A medical experiment has been going on in more than 20 cities across the country using a product that may put people at risk. Maybe you were one of the guinea pigs, and you didn't know it." The program, which included an interview with Moore, sent a news crew into downtown Denver to ask passersby if they recognized the PolyHeme "opt-out" bracelet.

"Never heard of Northfield. Never heard of the experiment," said one interviewee, Pastor Paul Burleson of the Denver Alliance of Churches. "Something is wrong when people are not given a chance or a voice or a choice as to whether or not they want to be an experimental person."

In the wake of the program, several centers participating in the trial reexamined their participation, and at least one suspended participation for several days, though none dropped out. The trial appears to have concluded smoothly: Northfield announced the achievement of 720 enrolled patients August 29, and Gould told a financial analysts' meeting August 8 that the company plans to seek fast-track designation from the FDA.

COMMUNITY CONSULTATION CONUNDRUM

But the persistent concerns over what constitutes adequate community consultation, along with negative public and political reaction to the idea of waived consent, have left researchers apprehensive for the FDA's re-opening of the Final Rule later this fall—especially given recent tightening of waived consent rules in the European Union.

"What the FDA really wants is data," Biros said. "As it stands right now, the type of research that uses the waiver of informed consent is a sliver of all the research that is being done. They haven't seen the track record to say that the waiver works or doesn't work."

At the time of the FDA announcement, Northfield had not

decided whether to participate or submit testimony on their experience of the PolyHeme trial.

“We have a conundrum in this country,” said Gould, Chief Executive Officer of Northfield. “It’s the balance between the need to respect patients’ rights and the need to conduct rigorous scientific studies in emergency life-threatening situations. Those are the opportunities for some of the greatest

advances in care, and yet it is virtually impossible to do them with the traditional approach to informed consent.”

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ONE STOP HEALTH CARE SHOPPING? THE RISE OF “McCLINICS” AND THEIR IMPACT ON EMERGENCY CARE

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Special Contributor to Annals New and Perspective

In the last year or so, shoppers at supermarkets or drug and discount stores began noticing the hype for a not-so-traditional type of staple debuting near aisles once reserved for cereal, laundry soap or birthday cards:

“You’re Sick. We’re Quick!”

“Convenient Care When Your Doctor’s Not There!”

“Get Well. Stay Well . . . Fast!”

By late 2006, nearly 200 health care clinics had been added to grocery and merchandising giants such as Wal-Mart, Target, HEB, CVS, Kroger, and Piggly Wiggly. Their size and business models varied, but the clinics uniformly touted the advantages of speedy and economical treatment administered by nurse practitioners for common ailments.

That’s just the start of what some doctors refer to as the “McClinics” or even “Doctor Starbucks.” Ambitious expansion plans call for the retail clinics to spread faster than a flu virus, with more than 1,000 by the end of 2006, and twice that many next year.

The Madison Avenue-like pitches for clinic patients have spawned national media buzz. The *New York Times*, *Los Angeles Times*, *Time Magazine*, *USA Today*, and other publications have weighed in with largely favorable coverage on this newest trend in medical care.

Emergency physicians generally welcome the retail clinics as another point of access for medical care, but those surveyed stop far short of accepting contentions that the clinics could bring a cure to the longstanding problems of emergency department (ED) crowding.

Dr. Michael Bishop, an emergency physician and chief executive officer of the Bloomington, Indiana-based Unity Physician Group, said retail clinics have had no measurable impacts on the patient loads at the 10 EDs staffed or coordinated by Unity. They have about 270,000 combined visits annually.

“Obviously, any time there is another provider around, there is the potential to have an impact,” he said. Urgent care centers and primary care physicians may feel the effects of the clinics, he

said, “but I really don’t think it is going to have a great deal of impact on emergency departments.”

A QUESTIONABLE IMPACT ON EDs

Bishop explained that the bulk of emergency patients—who believe they have serious medical problems—will continue to rush to EDs rather than Wal-Marts. Most of the other ED visitors, especially at the safety net sanctuaries of public hospitals, won’t find retail clinics to be a viable alternative.

“Most of those [clinics] want cash, or if not cash, then at least insurance,” Bishop said. “They aren’t going to be of help at all to the uninsured and the under-insured cases that occur in emergency medicine.”

That assessment also came from Dr. Wesley Crowley, an emergency physician who is president of California Emergency Physicians group, which staffs more than 50 EDs.

Asked about the retail clinic movement, Crowley said, “I don’t think that it is a bad thing, but I don’t think that it is anything more than probably another point of entry of convenience” in the health care field. “I don’t think it is a business model that is necessarily going to fundamentally change medicine or anything like that.”

Crowley also said patient numbers at EDs served by his medical group had been unaffected by the onset of retail clinics. He also questioned the news media’s extensive and largely unchallenged coverage of the clinics’ claims of significant consumer savings over hospital or physician’s office costs, and of faster and more efficient care.

Articles on the retail clinics mostly overlook the trend by many hospitals and EDs to reduce wait times through innovative programs that expedite treatment, such as the California Emergency Physicians’ Rapid Medical Evaluation plan, Crowley said.

“I really take issue with the subject of cost,” Crowley said. While the bill for serious injuries or illnesses is obviously high in EDs, “for a minor treatment, the cost is low in an emergency room,” he said.