Emergency trials of blood substitutes skirt ethical questions

Did you wear a thick, blue plastic bracelet with the words "I decline the Northfield PolyHeme study" splashed across it in bold black writing during the years 2004 to 2006?

If not, and had you been in a serious accident during that time, you could have been unwittingly enrolled in a phase 3 clinical trial for the blood substitute PolyHeme.

More than 700 patients at 32 trauma centers in 19 US states were—without consent—given the blood substitute, made from modified hemoglobin, to treat severe blood loss at accident scenes, in ambulances and even in emergency rooms.

The trial was allowed under a little known US Food and Drug Administration (FDA) rule that covers emergency research for which obtaining consent is impractical. Just over 20 such trials have been approved in the past decade. As Navy and civilian researchers push for approval to test another blood substitute, the FDA is trying to clarify the guidelines that govern the trials.

The public, meanwhile, remains largely unaware.

"How many people would even hear of this, much less brand themselves with a bracelet?" asks Harriet Washington, a journalist, ethics scholar and author, who says the opt-out bracelets are "repellent."

Recognizing that emergency treatments, particularly for trauma—the leading cause of death in Americans under 45 years of age—are understudied and poorly informed, the FDA adopted the current regulation in 1996, following a Congressional hearing and years of consultation with investigators, ethicists and the public.

The provision was "ethically mandated and ethically provided for patients that couldn't speak on their own behalf," says Michelle Biros, emergency medicine research director at the University of Minnesota, who helped draft the regulation.

In October 2006, the FDA held a public hearing to revisit the rule and get feedback on a July 2006 draft guidance document intended to interpret the regulation.

Proponents argue that emergency research may be impossible without such measures, but critics are unconvinced. "What these regulations do is dispense with the fundamental human rights laid down in the Nuremberg code," says Vera Sharav, president of the Alliance for Human Research Protection, a patient advocacy group.

Lack of informed consent is not the only issue. Critics objected to PolyHeme's use in emergency rooms where real blood was available. Others alleged that PolyHeme's Illinois-based manufacturer Northfield Laboratories withheld information from earlier trials indicating that the product increases the risk of heart attacks. The trial drew media attention from the likes of *The Wall Street Journal* and ABC News. Even Iowa Senator Charles Grassley expressed concerns.

Northfield Laboratories

Blood simple: PolyHeme has been used without informed consent to treat trauma patients.

Northfield has denied withholding information and maintained that PolyHeme's use in hospitals was warranted because there is insufficient evidence that real blood is superior, noting that not only the FDA, but also multiple institutional review boards, have approved the study.

Perhaps hoping to avoid similar controversy, investigators seeking approval to test another blood substitute, Biopure's cow blood–derived Hemopure, in trauma victims have proposed prehospital—that is, in an ambulance or at the accident scene—trials involving about 1,100 participants. In December, the FDA's Blood Products Advisory Committee voted against approving the trial, although a group of military and civilian investigators are still trying to hammer out a protocol to secure approval.

Those anxious to see the Hemopure trial proceed, including Yale University trauma surgeon Lewis Kaplan, note that data from previous trials—which some say indicate that Hemopure is unsafe—do not come from studies in trauma victims with severe blood loss, the study population now being proposed.

The FDA's regulation was carefully crafted but is easily misapplied, says Sidney Wolfe, head of the Public Citizen's Health Research Group, who testified against approving the Hemopure trial at the December meeting.

The statute specifies that experimental treatments should offer the patient direct potential benefit, treat a life-threatening condition for which available treatments are "unsatisfactory," and carry only a "reasonable" risk. Public input through community consultation before the trial, combined with public disclosure through press conferences, public presentations and newspaper and radio ads are meant to offer further protection.

"When you waive informed consent, you want there to be additional protections for those who are enrolled," says Sara Goldkind, a senior FDA bioethicist.

Although the FDA regulation does not explicitly address opt-out mechanisms, most participating companies, investigators and institutional review boards provide them, usually in the form of opt-out bracelets.

Even so, getting the public's attention is difficult. For example, in Oregon and Minnesota only five percent of those surveyed at hospital trauma centers had heard about an ongoing exception from informed consent trial at those centers, according to a 2003 study (*Acad. Emerg. Med.* **10**, 352–359; 2003).

Even those who support emergency research without consent recognize that community consultation and public disclosure are cumbersome, ineffective and poorly defined. It is also difficult for members of the public to determine whether studies are happening in their area. "You would really, really have to care about this to find out," says Richard Dutton, chief of anesthesia at Baltimore's Shock Trauma Center.

But the potential price of not considering research without consent may be a dearth of new treatments, Dutton notes. "Does society want to do this kind of research or not?" he asks. "You do the best you can under the circumstances."

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Correction: The headline for a news article in the May issue (*Nat. Med.* **13**, 517; 2007) incorrectly referred to a case of smallpox infection. The infection was instead with the closely related vaccinia virus.