Death Heightens Scrutiny of Clinical Tests

Concern About Volunteers' Safety Has Prompted Calls for New Rules, Expanded Protections

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She noticed the cough almost immediately, began feeling short of breath and achy. Two days after her visit for a research study at the Johns Hopkins Asthma and Allergy Center -- two days after inhaling the chemical hexamethonium during what was assumed to be a low-risk test for a healthy young woman -- Ellen Roche called back, obviously concerned.

Her symptoms were troubling enough that the staff quickly started monitoring her condition. That was May 7, and Roche's lungs already were functioning at two-thirds capacity. She was no better by May 9, when doctors admitted her to Johns Hopkins Bayview Medical Center in East Baltimore for observation.

The 24-year-old lab technician died there June 2, the university's first death of a research volunteer since 1986 and its first death ever of a healthy volunteer.

The tragedy, an "adverse event" that officials did not report publicly until mid-June, has raised anew questions about how adequately medical research participants are informed and protected during experiments. It has triggered an internal investigation, a special university review committee and probes by the federal Office for Human Research Protections and the Food and Drug Administration.

All will try to determine whether asthma researchers did anything wrong as they studied the physiological mechanics of a normal lung: whether they cut corners during the testing, for instance, or failed to fully disclose important details to Roche and other participants, or endangered their subjects from the start by using a substance that is not FDA-approved, possibly without the required permission.

Or the inquiries could find that, no matter the circumstances, the death could not have been foreseen.

"In the field of clinical investigations, the worst thing that can happen is the death, the *unanticipated* death, of a normal volunteer," said John Fletcher, professor emeritus of biomedical ethics at the University of Virginia's medical school and founder of the bioethics program at the National Institutes of Health.

"Where there's culpability, it's a life-changing and a career-changing thing. It's at least a 9 on a moral Richter scale. But we know in the total universe of human studies, these deaths are extremely rare."

Medical ethicists say the country has made great strides in the past three decades in its oversight of medical research. Institutional review boards must approve a project in advance. Scientists are expected to give research subjects truthful, clearly worded information about risk, which should be minimized as much as possible. And participants must be allowed voluntary consent that they can withdraw at any time.

Yet since 1998, a number of serious incidents have shown continuing weaknesses in the system. Concerns about patient safety stopped clinical trials at university medical schools in Oklahoma, Alabama, North Carolina and Massachusetts. After glaring breakdowns in its gene therapy studies, which only surfaced after a teenage participant died, the University of Pennsylvania announced last year that its genetic research would no longer use human subjects.

Just last month, as Roche lay in intensive care in Baltimore, a presidentially appointed panel recommended major changes in the protections afforded participants in a range of scientific studies. Review boards often are overwhelmed by the volume and technical demands of the work they judge, the panel said; guidelines about researchers' potential conflicts of interest need strengthening, as do provisions for especially vulnerable populations such as children and mentally incompetent elderly.

Though the scale of biomedical research has exploded since 1980, the National Bioethics Advisory Commission noted that there are no statistics on how many people are involved in clinical trials or the number of adverse events. It urged that a system be created for reporting those incidents. Some members also advocated that a fund be established to compensate individuals who are hurt because of their participation.

"It's a matter of simple justice that we cover them if they end up injured," said commission member James F. Childress, who teaches bioethics at the University of Virginia. They are, he pointed out, "putting their bodies on the line for research."

Ellen Roche did so understanding that she would receive no therapeutic benefit from whatever the Hopkins scientists learned. Theirs was a baseline investigation looking at how a normally functioning lung helps keep airways open even when they are exposed to irritants and allergens. If researchers can discover that, they can better grasp how the airways of someone with asthma begin to constrict and possibly develop a drug to prevent it.

Ten million Americans suffer from this potentially life-threatening condition. Roche did not.

Her family has not broken its silence in the weeks since she died. Perhaps she never told them why she decided to sign up for the study. Compared with the generally clear-cut motivation of a sick volunteer, a healthy person's reasons for taking part in a clinical trial can vary tremendously.

Scientific curiosity or simple altruism? A commitment to advancing an area of research or the need to make some extra money? Had Roche completed the seven- to nine-visit schedule specified in the research protocol that Hopkins posted on its Web site after her death, she would have been paid $365. Medical ethicists say that amount does not seem enough to coerce or unduly influence a volunteer's decision.

In keeping with her family's wishes, university officials have released no personal information about the young woman, a 1998 graduate of Frostburg State University. She lived in Reisterstown, northwest of Baltimore, in a two-story town house only a few miles from her father and stepmother. Just up from their house is Franklin High School, where a counselor remembers Roche as a quiet, involved student who was honored her senior year for academic accomplishments.

Roche worked at the university's allergy and asthma center. Butshe did not report directly to the principal investigators on the study, which is part of a $1.55 million grant from the National Heart, Lung and Blood Institute. Hopkins officials would not detail her employment or any other involvement in research projects. Workers and students are never solicited directly, they said; instead, fliers advertising a research trial are posted on campus.

The two-page "clinical investigation consent form" that Roche and eight other people signed explained the purpose of the project, its procedures and risks. During their first several half-hour visits, according to the form, they would inhale methacholine, a substance that usually causes mild coughing, shortness of breath and tightness in the chest. It is commonly used in doctors' offices to determine if a patient has asthma.

By a sixth visit, lasting up to four hours, study subjects would receive two substances, methacholine and either hexamethonium or a placebo. Hexamethonium was commonly prescribed during the 1950s for hypertension and to minimize bleeding during surgery. It later was supplanted by other drugs and taken off the market in the 1970s.

"This is capable of stopping some nerves in your airways from functioning for a short period," the consent form explains. It may reduce blood pressure "and make you feel dizzy, especially when you stand up. This effect may last up to three hours. During the visit you receive hexamethonium, you will be connected to a heart monitor and we will measure your blood pressure very often. You will also have an IV . . . placed only as a precaution."

The protocol application submitted to Hopkins' review board last summer by Alkis G. Togias, an associate professor, specified that participants would inhale up to 1,000 mg of the chemical during each of four visits. Based on published research from the 1980s, Togias wrote, "This dose . . . has been shown to be both safe and efficacious." He explained that a laboratory preparation would make the compound 99.6 percent pure.

Records show that the university is checking whether the chemical or the equipment used for Roche's test became contaminated. Two other volunteers who inhaled hexamethonium experienced little or no adverse reaction.

In the wake of Roche's death, Solbert Permutt, the pulmonary specialist overseeing this project alerted asthma specialists across the country to research from the late '50s linking hexamethonium -- albeit in higher doses over longer time -- to dramatic lung changes leading to individuals' deaths.

And last Tuesday, the director of the National Heart, Lung and Blood Institute suggested that lung investigators temporarily curtail research using the compound.

Hopkins suspended its experiment after Roche fell ill. In his warning letter, Permutt described how her symptoms "rapidly progressed" to acute respiratory distress syndrome, a dangerous medical enigma caused by acute injury to the lung. For three desperate weeks, doctors struggled to save Roche as her failing lungs precipitated a cascade of critical events ending with the shutdown of her kidneys.

"It is with deep regret that I report the death of the subject," Chi Van Dang, Hopkins' vice dean for research, informed the U.S. Office for Human Research Protection on June 6.

Results of Roche's autopsy, conducted at Hopkins, have not been released. In a statement Friday, the university announced that the findings of its special review committee will be sent to federal officials by July 13. Its statement disclosed that "some problems" relating to procedural issues and the review board have been discovered.

The impact of this case ultimately may be felt far beyond Baltimore.

"I worry about many people in clinical trials or other human research hearing about this and panicking," said Ruth Faden, executive director of the Phoebe R. Berman Bioethics Institute at Johns Hopkins. "Biomedical research, to succeed, really does depend on the confidence of the public."

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