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Duke's hazards

Did medical experiments put patients needlessly at risk?

BY SHEILA KAPLAN AND SHANNON BROWNLEE

In the hierarchy of the nation's elite research institutions, Duke University Medical Center has long ranked near the top. Nestled in the middle of a 210-acre campus in Durham, N.C., the center's gleaming glass tower has served as a beacon for top-flight researchers, who bring in \$175 million of federal biomedical research funds annually, and for patients. More than 1 million come to Duke from all over the world each year.

But Duke's reputation suffered a big ding last week when the federal government forced the university to shut down all 2,000 of its medical experiments involving human subjects. In a stern letter that criticized the university for failing to adequately protect patients who enter research trials—either in hope of being cured or for altruistic reasons—the government ordered Duke to make drastic changes before admitting any more subjects. After medical school dean Edward Holmes and his associates flew to Washington and pledged to make immediate improvements, regulators told them they could resume a limited program. "Our concern was for the people in experiments facing risks they didn't know about or understand," said Gary Ellis, director of the Office for Protection From Research Risks (OPRR), which closed the program. Duke is not out of the woods yet. Another agency, the U.S. Food and Drug Administration, plans to inspect Duke's programs this week.

The deficiencies cited by OPRR, which ranged from failing to monitor ongoing research to ignoring federally mandated rules designed to protect children, are unusual for their sheer number—20 in all—and for their occurrence at such a prestigious institution. But similar problems are found with surprising frequency elsewhere. Federal audit reports obtained by *U.S. News* show that the safety net designed to protect patients in research trials is riddled with holes at scores of institutions around the country. Last year the FDA,

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The Office for Protection from Research Risks, which is part of the National Institutes of Health, monitors human clinical trials and is dedicated to human subject protection.

Duke University Medical Center. Responding to the OPRR directive, the DMC's news office issued press releases on [clinical trials](#) and [strengthening](#)

which oversees research sponsored by private companies, cited nearly 150 institutions for problems ranging from neglecting to inform patients that an experimental treatment could blind them to recruiting patients by offering them money. And OPRR, which is investigating compliance with human protection rules at 60 institutions, has already noted violations at such well-known research centers as the City University of New York, Scripps Clinic in California, and Mount Sinai School of Medicine in New York.

Crackdown. Last week's suspension of Duke's research privileges lasted only five days. But the incident signaled a new toughness on the part of OPRR, a tiny office at the National Institutes of Health that oversees patient safety at more than 500 institutions. Duke's temporary closure follows disciplinary actions against Rush-Presbyterian-St. Luke's Medical Center in Chicago last October and West Los Angeles Veterans Affairs Medical Center in March for similar lack of oversight. Among the most egregious lapses, the federal agency found that some patients at Rush-Presbyterian were enrolled in studies even though they were too sick to be eligible. Others were enrolled in studies for which they did not give full, informed consent. At the veterans hospital, researchers failed to obtain consent from patients before performing experiments on them during heart surgery.

Protection of people in research has come a long way since the cold-war-era experiments in which veterans were injected with plutonium and students at Fernald School for the Retarded in Massachusetts were fed radioactive oatmeal. Such unethical experiments prompted the federal government to develop guidelines to protect people whose willingness to participate in research benefits the rest of society. Most important, participants must understand that they are research subjects and must be told of all the benefits, alternatives, and risks. This notion of informed consent lies at the heart of human protection.

Perils unknown. It is also the underpinning for the rules regulating clinical trials. It was for violation of such rules that Duke was cited by OPRR. A December 18 OPRR letter to Ralph Snyderman, Duke chancellor for health affairs, said Duke failed to adequately inform patients of the "purpose, risks, and benefits of the research."

While officials at Duke agreed to make necessary changes and conceded that there were problems at the medical center, they denied that patients were ever in jeopardy. "I am not aware of any situation in which there was an approval of a research protocol that has led to any harm," said Holmes, Duke's medical school dean, last week. That's precisely the flaw in Duke's system, says OPRR. Duke failed to keep track of patients once studies were underway. As a result, OPRR doesn't know if patients were hurt; but the university can't guarantee that they were not. "Duke

procedures for human subject studies.

Duke was reprimanded due, in part, to problems with its institutional review board. The Food and Drug Administration provides "Guidance for Institutional Review Boards and Clinical Investigators." This document includes a guide to informed consent and an FAQ about review boards.

Learn about clinical studies from the National Institutes of Health. Review a patient bill of rights from NIH's Clinical Center.

For information on cancer trials, try the National Cancer Institute.

CenterWatch is a listing service for clinical trials. It has information for potential participants in clinical trials.

has a dysfunctional process for the protection of human subjects," says John Fletcher, emeritus professor of biomedical ethics at the University of Virginia, who worked on the government audit.

Duke's troubles began just last year, when OPRR, which normally inspects research centers only in response to allegations of wrongdoing, decided to review the 15 institutions that receive the most federal dollars. "We went around the table, and I asked the staff to speak up," said OPRR Director Gary Ellis. "Could they vouch for these institutions? Did they know someone there? Duke drew blank looks around the table. Our office had not had contact with officials there in several years."

Biased? The December 1998 visit turned up a score of serious concerns. At the nexus was Duke's Institutional Review Board, or IRB, the panel of doctors, scientists, and community members responsible for approving the design of research involving human subjects, monitoring the studies, and ensuring that patients are told about potential benefits and risks. Such panels must be composed of members who can assess the scientific merit of research and independently represent the interests of patients. In a system that relies on local research institutions to police themselves, review boards are critical.

In a series of letters following the visit, OPRR cited the review board's deficiencies: The board often approved research projects without having sufficient information, OPRR said. The board also failed to monitor serious side effects in trials. Informed-consent documents had patients waiving their legal rights, in violation of federal rules. Moreover, the ability of the review board to make independent, unbiased decisions was compromised, charged OPRR, because two members had a conflict of interest. They were the director and assistant director of the Office of Grants and Contracts, whose primary mission was to bring in federal research dollars. "It's in their best interest to see study proposals move forward," says Michael Carome, OPRR compliance chief. Duke has barred the two officials from voting on board decisions. Carome and his team also found that the review board, which is charged with monitoring patients' safety as studies progress, often failed to do so. "There were so many violations of procedure and administrative issues, it was hard to believe," says OPRR consultant Fletcher.

Nonetheless, the medical center's administration brushed off the agency's complaints as "administrative errors" and record-keeping problems. Last March, pediatrician John Falletta, who chairs Duke's review board, downplayed the agency's concerns in an interview with *U.S. News*. "Cancer in children is serious. Lack of respect for human research is serious. This didn't rise to that level." OPRR's Ellis says otherwise. "We found them unsatisfactory on three occasions in the last five months," said Ellis. "You don't

occasions in the last five months, said Ellis. "You don't get four strikes."

Duke is taking OPRR seriously now. Last week, university officials scrambled to enlist volunteers to serve on a second review board, while Holmes and Snyderman were in Washington hammering out the action plan with federal investigators. Documents suggest Duke should have seen it coming. In 1995 and in 1997, auditors from the National Cancer Institute uncovered major deficiencies in the conduct of cancer trials. And the FDA issued a formal warning to Duke in 1994 for renewing research programs without first assessing their progress. Falletta told the FDA that Duke's strategy for correcting the deficiencies was "still evolving."

The FDA did not follow up to ensure the medical center actually complied, and the problems persisted until OPRR'S inspection last year. Paul Goebel Jr., the FDA official who oversaw review boards for many years, says the agency inspects each facility about once every five years—more if there are ongoing concerns. He acknowledges, however, that field offices have had to cancel some inspections because of a lack of travel funds.

The problems at Duke highlight a national failing. Bioethicists say many review board members do not understand even the most rudimentary ethical rules that form the foundation of the human protection system, or are overburdened by too many research proposals, or both. In a report released last June, the inspector general of the Department of Health and Human Services, which oversees both the FDA and OPRR, reported that the "effectiveness of Institutional Review Boards is in jeopardy." With the rise of HMOs, money from research provides a larger proportion of medical center budgets than ever before—putting pressure on review boards to approve protocols quickly. Many review boards are overwhelmed by the numbers of protocols, leading them to rubber-stamp study proposals and to fail to keep track of side effects. The inspector general's report noted that IRBs "review too much too quickly" and that "there may be widespread abuses."

The inspector general also expressed concern about the growth of independent for-profit review boards, which travel around the country to review protocols for a range of research centers, rather than one institution.

A review of recent audits by OPRR and FDA reflects all these concerns. In a February 26 letter to the City University of New York, OPRR criticized the university's human research review board for approving consent forms with a host of problems, including the phrase "there are no risks," when the research project could, in fact, endanger patients. OPRR even criticized the National Cancer Institute, which also conducts human research, for slowness in informing participants in the

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tamoxifen breast cancer prevention trial that tamoxifen heightened their risk of developing endometrial cancer. In a notice to Scripps Clinic in November, OPRR said that the review board was approving too many research experiments on children without following the special rules designed to protect them—something the agency also cited at Duke. A Scripps official says the clinic did follow the rules—it just didn't document it.

What many patients fail to understand, bioethicists say, is that medical experiments can pose dangers. Mechanisms like informed-consent forms and review boards were established to make sure that patients considering taking part in experiments are aware of both possible benefits and the dangers. Says law Prof. Anna Mastroianni of the University of Washington, a leading bioethicist, "What's important in research is protection of people."

