The San Diego Union-Tribune

March 4, 2000, Saturday

SECTION: LOCAL;Pg. B-10:7; B-7:1; B-2:2

LENGTH: 614 words

HEADLINE: FDA looks into **clinical-trial** selections

BYLINE: Cheryl Clark; STAFF WRITER

BODY:
Federal officials are stepping up their investigation into the methods physicians use to recruit participants for **clinical trials,** especially when large drug company payments may be at stake, a top official of the U.S. Food and Drug Administration said here yesterday.

"We're going to be focusing a great deal of attention in coming months," said Dr. David A. Lepay, the FDA's director of scientific investigations in Rockville, Md. "We're going to be looking at whether recruitment practices are appropriate, and at advertisements as the beginning of the informed **consent** process."

The concern is that participants in a **clinical trial** to test a drug or a medical device be thoroughly informed about the physician's potential financial gain, which could be thousands of dollars per participant, and that the participant's personal physician could receive a finder's fee for the referral.

Lepay made his remarks to more than 150 physicians attending an ethics session sponsored by the American Academy of Allergy, Asthma and Immunology during the first day of its six-day meeting at the San Diego Convention Center. The conference has drawn more than 6,000 physicians from around the world to discuss the latest techniques in the field.

The ethics session was organized by a UCSD pediatric allergy expert and drug researcher, Dr. Eli Meltzer, who said he had increasing concerns about physicians "who are scam artists."

The topic of **clinical-trial** ethics has been especially hot since disclosures about the practices of Dr. Robert Fiddes, a Whittier-based physician who went to prison for enrolling fictitious patients, fabricating test results and substituting another person's bodily fluids to get a patient enrolled who otherwise would have been ineligible.

In exchange, Fiddes received thousands of dollars from drug companies for each subject enrolled.

Lepay said the number of complaints about physicians and **clinical trials** "has been increasing." And, even though only 2 percent to 4 percent of the number of complaint inspections result in FDA action, "when it does occur, it does affect confidence and raises questions about trial oversight and professional ethics."

The FDA is increasingly concerned when drug companies pay physicians on the basis of trial outcome or sales of the product, or when the investigator shares in the patent or has equity interests in the sponsoring company, Lepay said.

As managed care keeps reducing physician reimbursement, more doctors are launching side-line businesses as **clinical-trial** investigators of potential drug remedies.

Meltzer, chairman of the academy's ethics committee, said planning yesterday's ethics meeting was "a painful process." During a question period, several physicians said they see drug companies trying to influence how they prescribe drugs.

An American Medical Association official said drug companies spend between $8,000 and $13,000 per year per physician trying to influence medical practice. Elaborate dinners, tickets to games or theatrical events, clothing, airline tickets, Christmas trees and computers are among items drug companies buy for doctors.

Arjun Rajaratnum, representing Glaxo Wellcome Inc., acknowledged the problems and increased scrutiny.

"Is it education, or is it entertainment?" Rajaratnum said. "That's the question we all need to pose every time we have an interaction.

But he added that drug companies are only trying to tell the physician about their products' proven capabilities.

"Many positive benefits are obscured by the negatives," he said, and physicians receive free drug samples, which they often give to medically indigent patients.

LANGUAGE: ENGLISH

LOAD-DATE: March 6, 2000

FOCUS™
Search: General News;human subjects and clinical trials and consent

To narrow this search, please enter a word or phrase:

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Example: **House of Representatives**

The Chronicle of Higher Education

March 17, 2000

SECTION: GOVERNMENT & POLITICS; Pg. A31

LENGTH: 3399 words

HEADLINE: An Inside Look at How a University Tries to Protect **Human Subjects**

BYLINE: JEFFREY BRAINARD

BODY:

Seventeen men and women who watch over human experiments at the Duke University Medical Center began their February meeting with a working lunch around a 30-foot conference table. They would need fuel for the five-hour marathon, with no scheduled breaks, to clear their mound of paperwork.

But at least the meetings have been getting shorter.

The members of the medical center's Institutional Review Board, or I.R.B., have been under the gun since May, when federal regulators stunned Duke officials -- and researchers nationwide -- by suspending all **clinical trials** at the center for four days. The U.S. Office for Protection from Research Risks voiced concern that Duke's board was overworked to the point it was no longer meeting its responsibilities. Even more seriously, the regulators said, the board had violated federal rules on how to conduct its deliberations.

Duke has since gone on a crash drive to improve its review process and ease the board's load. Across the nation, I.R.B.'s are under similar pressures. The federal government has suspended research at four other institutions in the past 10 months, citing violations similar to those found at Duke.

The actions have added weight to a spate of government reports declaring that I.R.B.'s everywhere are stretched. The consistent finding: Too often, the boards give perfunctory reviews to research in which the rights and health of **human subjects** hang in the balance.

At the request of The Chronicle, officials at Duke's medical center recently allowed a reporter to observe an I.R.B. meeting, which is normally closed, and to explore how the review of **human-subject** safety works. Duke officials allowed the visit on the condition that The Chronicle not divulge confidential details, such as patients' identities (unless the patients agreed), or techniques that might be named in patent applications.

That snapshot revealed a paperwork-driven process that places great faith in the precision of language, and in the careful review of documents that scientists submit to justify research projects. The process does not involve direct oversight by board members of the research itself. All of those features are typical of review boards at other universities.

As Duke and other institutions try to improve the monitoring of experiments involving humans, many researchers and bioethicists continue to wonder: Does the current system of oversight adequately protect patients?

No reliable statistics reveal how often research volunteers are harmed by experimentation. Thus, the safety of clinical research is often judged by appearances, and by crises, such as the death of a teenage subject during a gene-therapy experiment at the University of Pennsylvania in September.

But even if most volunteers are not physically harmed, shortcomings in project reviews threaten their rights, which could cause equally serious damage to universities over time, some observers have said.

"What you see is a fear by administrators and researchers that if the public's confidence in their research and ethics is undermined, [scientists] will in the future no longer be able to support their research, because they depend on tax money," said Mary Faith Marshall, director of the bioethics program at the Medical University of South Carolina. "And I think that's appropriate."

Along with determining safety, I.R.B.'s ensure that **consent** forms have adequate information for volunteers to understand the risks and benefits of participating. There are an estimated 3,000 to 5,000 such boards nationally, supervising both **clinical trials** at academic medical centers and research in the social sciences involving **human subjects** conducted by colleges of arts and sciences.

After Duke's suspension, "I got e-mail every day from people at other universities who said, 'There go we, but for the grace of God,'" said Jeremy Sugarman, an associate professor of medicine and philosophy here and a bioethicist who advised the administration on improving the oversight of medical experimentation.

Last year's four-day shutdown of Duke's medical research was all about procedure. The board had failed to review some continuing research projects at least once a year. Among other problems, the I.R.B. lacked formal training for researchers and board members on regulations covering human volunteers. Duke was scolded as well for such seeming minutiae as failing to keep sufficiently detailed minutes of I.R.B. meetings.

Regulators did not allege that volunteers had been physically harmed in experiments by Duke researchers, who study a broad range of treatments for cancer, heart disease, and many other illnesses.

The annual caseload here has grown from 400 **clinical trials** a decade ago to 2,200 last year. After the suspension, Duke administrators set up a second I.R.B., and they plan to add at least two more this year. Many universities had just one I.R.B. before the flurry of suspensions, but they are now moving to add more.

The Chronicle visited Duke's new board, whose 17 members evaluated 33 research proposals over an afternoon last month.

Most of the members are researchers at the medical center, and many also care for patients. Several served on the medical center's original I.R.B., whose practices had triggered the federal sanctions. The board includes a sociologist, a medical student, and, as required by regulations, a community representative not affiliated with the university -- in this case, a lawyer.

For lengthy stretches of the meeting, the members seemed more like manuscript editors than researchers. They parsed nuances of wording in proposed **consent** forms -- but spent much less time analyzing the potential risks for **human subjects.** Their goal was to make the forms easily understood to anyone reading at an eighth-grade level.

Take, for example, a proposed test of an experimental drug that might detoxify carcinogens in cigarette smoke. Should the **consent** form tell prospective volunteers -- all of them smokers -- that the carcinogens might damage "your DNA and other large molecules"? A member recommended substituting "your body."

Or, one panelist wondered, was "drowsiness" clearer than "sedation"?

A panelist said the **consent** form in the smoking trial should not refer to the participants as "patients." That could imply that they would receive some benefit from the experimental drug -- the very question being studied. He recommended "volunteers." Everyone agreed.

Some of the board members find that scrutiny excessive. "There's a lot of nitpicking that goes on," said Patrick D. Kenan, a professor emeritus of head, neck, and throat surgery, in an interview after the session. But other questions, he said, must be asked. During the meeting, Dr. Kenan noted that

researchers proposed to stick a tube down volunteers' windpipes to retrieve lung tissue so they could study the experimental drug's effects. Researchers planned to use the less-invasive of two possible techniques, and Dr. Kenan insisted that the **consent** form describe that technique in detail.

The wordsmithing continued as members munched on chicken-breast sandwiches, pasta salad, and cake, off plates scattered among stacks of papers. Board members occasionally left the room for a moment to answer pages about patients' care.

Such discussions take time, relatively. The review of the lung study lasted 17 minutes, one of the longest of the meeting. But that was enough to slow the board's progress through its long agenda.

The board's chairman, Joseph C. Farmer, a professor of head, neck, and throat surgery, said in an interview that he hoped the board's editing duties would decrease. The I.R.B.'s newly expanded staff will begin asking Duke investigators to rectify routine errors or omissions in their applications before the committee's meetings, he said.

Nevertheless, Dr. Farmer added, "We really think this [editing] is one of the most important things we can do. If people can't understand the informed-**consent** form, what good is it?"

Indeed, proper informed **consent** is a bedrock requirement of the Nuremberg Code, which physicians in many countries adopted following World War II as a standard of ethics for medical experimentation. Neither I.R.B. members nor federal regulators are present when doctors explain experiments to prospective volunteers. The informed-**consent** form, then, is a kind of proxy.

However, the editing left less time for another major area of the board's responsibility: determining whether experiments had enough promise of useful results to justify risks to the participants.

That's not unusual for I.R.B.'s nationally, said Jeffrey P. Kahn, director of the Center for Bioethics at the University of Minnesota-Twin Cities. Semantic details preoccupied them even before federal regulators stepped up enforcement of procedural requirements, he said.

"Oftentimes, I.R.B.'s get very mired in wordsmithing **consent** forms," he said. "That should not be their main focus. They need to keep their eyes on the prize, which is the protection of subjects of research." Federal rules require **consent** forms to contain many details, so "that's an easy place to spend time," Mr. Kahn said. "To try to assess risks and benefits is a more difficult and ongoing challenge."

An I.R.B. is hardly the sole arbiter of the potential risk of experiments. Before reaching the board, project applications, which can run several dozen pages, must first pass muster with an I.R.B. member from the same department, as well as with the department's chairman. At Duke, unlike many other universities, every clinical department has a member on an I.R.B.

Then, before each meeting, I.R.B. members -- generally from other departments -- are asked to evaluate three or four of the study proposals. Those members summarize the proposals for the full board, including risks and benefits, and recommend approval or other action. Some panelists said they have time only to skim the proposals before the meeting, other than those they have been assigned to review.

The reputation of the researchers provided the panelists additional cues, in some cases.

For example, John M. Falletta, a professor of pediatrics, questioned the risks posed by a planned experiment using a drug to treat social phobia in adolescents. A possible side effect was kidney failure.

Cynthia C. McCaskill, a registered nurse who conducts research in the department of psychiatry and behavioral sciences, said the scientist who had proposed the experiment, and who is in her department, "is a safe investigator. He watches the patients carefully."

Dr. Falletta, who heads the medical center's other I.R.B., said he was reassured because the Food and Drug Administration had approved the drug for treatment of a different psychiatric disorder. He also

noted a directive from the National Institutes of Health telling federally supported biomedical researchers not to exclude children from studies unnecessarily, because children and their medical needs have been underserved by clinical research.

Dr. Falletta said in an interview that while those points had influenced him, he would not have supported the experiment if he had unresolved questions about risks.

It's common for I.R.B.'s to weigh this melange of considerations. Minnesota's Mr. Kahn said it was not inappropriate to consider an investigator's reputation -- as long as the board didn't base its decision solely on that assessment.

The I.R.B. rarely rejects projects outright as presenting too much risk. If they have remaining doubts after discussions, they ask the researchers -- who do not usually attend I.R.B. meetings -- to provide more information in writing.

"In most cases, the investigator can give a straightforward answer that's convincing," said Dr. Farmer, the board chairman. The panel also has the option of bringing in an expert consultant, but that kind of assistance is rarely used.

Although the board tinkers more with the wording than the substance of proposed experiments, some researchers at Duke and elsewhere say clinical research has become so specialized that I.R.B. members -- especially the community and medical-student representatives -- lack sufficient expertise to adequately evaluate risks posed by research proposals.

"All over the U.S., you have amateurs reviewing professionally done clinical research," said Robert Califf, chief executive officer of the Duke Clinical Research Institute, which coordinates multi-site **clinical trials** in 50 nations. "That doesn't seem to make a lot of sense. Maybe we're entering an era when the relationship between clinical ethics versus clinical research needs to be reexamined."

Dr. Califf said questions from I.R.B.'s have led to needless delays of useful research and, in some cases, have made the institute miss deadlines to participate in **clinical trials** involving other institutions.

He and other researchers said in interviews that national peer-review panels, such as those that advise the National Institutes of Health about grant proposals, should also evaluate the safety of research proposals. Experts in specific fields are best equipped to understand the science in those areas, Dr. Califf suggested.

But Dr. Falletta of the I.R.B. insisted that local review boards should continue. The medical center bears ultimate accountability for its patients' welfare, he said. "I'm afraid that would be lost if there were some oligarchy overseeing all of this."

When questions are raised about risk, "in most cases, there's a member who has some knowledge in that area, and who can boil the issue down and say whether this is a reasonable scientific approach," said Dr. Farmer, the panel chairman.

Researchers contribute as much to the delays as I.R.B. members do, or more, added Joel Smith, a professor emeritus of sociology. Delays can arise because an application is incomplete or offers a poorly designed study, which triggers the I.R.B. to request changes or information, he said.

In the end, board members said, assessments of risks and benefits depend partly on common sense. Thomas F. Slaughter, an assistant professor of anesthesiology who joined the I.R.B. last year, following the federal shutdown, applies that yardstick to applications and his own ideas for research as well: "I would never do any study that I wouldn't be comfortable putting my father in."

Even for scientists on the board, grappling with the workload can be a challenge -- with a resulting burden on their careers.

Duke requires I.R.B. members to attend five or more hours a month of training, besides the hours-long monthly board meetings. Then there is the time spent wading through applications. Over all, members spend up to 25 hours a month for the job, and only the chairmen and vice chairmen are paid.

"I had no idea [the workload] was so staggering," said Dr. Slaughter. "I'm at the point in my career where, in addition to patient care, I need to be working in the lab and getting grants."

Although the medical center gives faculty members 11 years to make tenure, promotions occur during that period. Dr. Slaughter is up for one this year.

As at other academic medical centers, Dr. Slaughter's department expects him to generate revenue by caring for patients and securing money for research projects. Revenue flow is an increasingly urgent concern for those centers because of the constraints of managed care. There are no quotas per se. The medical-center administration allows the departments to decide whether to allow I.R.B. members to bring in less revenue. Dr. Slaughter's department does not make such an allowance.

The lack of such recognition has made it harder for I.R.B.'s nationally to recruit and retain experienced members, said Ms. Marshall, the bioethicist in South Carolina. "I think that the institutions should, because they're looking out for the interests of the institution. You can't expect a busy academic to do that when there's nothing in it for them."

Given those pressures, why does anyone volunteer to serve for what seems to be a thankless task? Several members said I.R.B. service provided opportunities to expand their knowledge of the universe of research going on at the medical center. For some, that form of networking could give them ideas for future research collaborations with Duke colleagues.

"It's difficult to interact with people around here, because we're all so busy," said Michael A. Morse, an assistant professor of oncology who serves on the I.R.B.

Protecting research subjects wasn't always the first reason members cited for serving. In fact, a formal background in medical ethics is not mandatory to join the I.R.B. at Duke or most other institutions. But given that many members also have patients, "we're starting with a panel of people who are committed to protecting patients," Dr. Falletta suggested.

The time demands on I.R.B. members also mean that the boards do not often include research institutions' top academic stars. Dr. Falletta conceded that not all of the Duke boards' members would fit that description. Several are junior faculty members, and others are retired.

However, he and others reiterated that the degree of scientific expertise needed to assess research risks is not the same as that required to conduct high-level research. "You want a mix of people, because you always want to be training new members," said Ms. Marshall, the bioethicist.

But some critics of the I.R.B. process have said that a board made up mostly of scientists may be too skewed toward the interests of researchers to look after the rights of patients adequately. Others say that review boards have an inherent conflict of interest because they are part of the institution whose researchers they are monitoring. One solution would be to increase the number of community representatives on such boards.

Members of the I.R.B., however, said they represented many types of people and backgrounds. "I think society has a tendency to stereotype individuals," said David K. Walmer, an associate clinical professor of reproductive endocrinology who has done missionary work in Haiti. Researchers on the I.R.B. are also "citizens like everyone else."

Scholars who study I.R.B.'s say little research has been done about whether the boards' work, and the rules they interpret, have actually produced better-informed research subjects and lower risks.

"This process involves people sitting in a room, talking about papers," said Ms. Marshall. She and other

scholars have suggested that I.R.B.'s expand their oversight by sending representatives to hospital wards and doctors' offices to directly observe interactions between researchers and volunteers.

Administrators and I.R.B. members nationwide have argued instead that federal regulations should be changed to give the boards the flexibility to focus on research proposals presenting the greatest risks. That could be accomplished, they said, if I.R.B.'s were not required to review all continuing projects, including ones presenting minimal risks, at least once a year.

Other ideas for improving I.R.B.'s may come from research sponsored by the National Institutes of Health on informed **consent** and the ethics of **human-subject** protection. The National Bioethics Advisory Commission, which advises President Clinton, expects to report later this year on its study of the system of protections.

In the end, no matter how much the boards fine-tune **consent** forms, there will be a continuing need for effective oversight whenever scientists recruit sick people as research subjects. Although many **consent** forms emphasize that an experimental treatment may not help volunteers, ill patients may become desperate when other therapeutic options fail.

Consider the faith of Harry L. Snyder, a 77-year-old retired farmer from Virginia Beach, Va. He had been treated at Duke for a heart attack, and returned for care last month, after suffering another one. After reviewing a six-page **consent** form, he agreed to participate in a **clinical trial** of an experimental drug for heart failure.

"I had nowhere to go but up," he said. Of the doctors who asked him to participate, he said: "I trust them implicitly. I don't know what's best. That's their department."

LANGUAGE: ENGLISH

LOAD-DATE: April 17, 2000

The Associated Press State & Local Wire

View Related Topics

March 4, 2000, Saturday, PM cycle

SECTION: State and Regional

LENGTH: 666 words

HEADLINE: FDA says leader of fatal gene therapy experiment violated rules

BYLINE: By PAUL RECER, AP Science Writer

DATELINE: WASHINGTON

BODY:

The Food and Drug Administration is accusing a University of Pennsylvania researcher of violating safety regulations in a gene therapy experiment in which a patient died.

In a stern warning letter, the FDA said that Dr. James M. Wilson of the University of Pennsylvania "violated regulations governing the proper conduct of clinical studies" in a series of gene therapy experiments designed to correct a liver disease.

Wilson headed a gene therapy experimental study that was halted after the death of 18-year-old Jesse Gelsinger of Tucson, Ariz. The teen-ager is the first patient known to have died as a direct result of a gene therapy experiment.

In Friday's letter, the FDA ordered Wilson and the University of Pennsylvania's Institute for Human Gene Therapy to continue cessation of all current human experimental drug trials and not to apply for new studies until "corrective actions have been implemented."

A warning letter is an FDA procedure that notifies a researcher or institution of what the agency considers to be violations of federal law. It means that unless the offending actions are corrected, the agency can take some enforcement action without further notice.

The University of Pennsylvania said in a statement that it takes the FDA letter "extremely seriously."

The statement said the university had already answered many of the allegations contained in the letter and was "disappointed" that the FDA discounted or rejected those earlier responses.

The warning letter said the university had 15 days to report on steps it plans to correct the violations.

Gelsinger suffered from an inherited liver condition caused by a genetic flaw. He was enrolled in an experiment designed to test if such disorders can be corrected with new genes. In the experiment, a virus modified to carry the corrective gene was infused directly into the liver.

The teen-ager died last September just four days after he was injected with the gene therapy drug. An autopsy report blamed his death on the effects of the experiment.

The 20-page letter sent to Wilson said than an inspection showed that the University of Pennsylvania researchers failed to properly report serious reactions experienced by patients who had the gene therapy before Gelsinger.

The letter also said the university failed to make a timely report about the death of at least two lab monkeys in similar gene therapy experiments.

The warning letter accused the university of:

-Failure to properly report changes in the experimental protocol. Among the changes was elimination of a provision to stop the experiment if two patients experienced serious liver toxicity. "These protocol revisions reflect significant changes that affect the safety of study subjects," the letter said.

-Failure to immediately notify or properly report serious adverse reactions in four patients. An annual report by the university, the letter said, "misrepresented the true nature of the toxicities experienced by these four subjects."

-Enrollment of new patients in the experiments using higher doses despite adverse reactions experienced by earlier patients at lower doses. "Your actions demonstrate a disregard for the protocol stopping rules you had agreed to follow that were designed to protect the safety of study subjects," the letter said.

-Failure to properly report liver damage found in a laboratory monkey even though the results suggested "a significant risk for **human subjects.**"

-Failure to revise informed **consent** documents for new patients after some earlier patients had serious side effects. This meant, the letter said, that some patients were not told "new information about the possible risks of participation."

-Failure to properly conduct the required laboratory tests on patients either before or after the experiment. "We conclude that the (institute) did not exert due diligence to ensure that the follow-up tests were performed according to the protocol," the letter said.

LANGUAGE: ENGLISH

LOAD-DATE: March 5, 2000

The Record (Bergen County, NJ)

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February 8, 2000, TUESDAY; ALL EDITIONS

SECTION: NEWS; Pg. A4

LENGTH: 610 words

HEADLINE: CLINICAL TRIALS MISUNDERSTOOD, PANEL SAYS1 NEW3 SUBJECTS VIEW RESEARCH AS TREATMENT

BYLINE: BOB GROVES, Staff Writer

DATELINE: NEWARK

BODY:

People who give their "informed **consent**"to take part in **clinical trials** of experimental drugs are, in fact, often misinformed, self-deluded, or too scared to focus on what they are getting into, a panel of medical experts cautioned on Monday.

"The patient and the scientist want to believe they're involved in treatment, when it's actually research,"George J. Annas, a professor of health law at Boston University, said at the University of Medicine and Dentistry of New Jersey.

Clinical trials produce a"therapeutic illusion"in which people "mix up research with treatment, see scientists as doctors, and medical study subjects as patients,"Annas said at a conference at UMDNJ-New Jersey Medical School on informed **consent** and human research.

About 70 physicians and other health professionals attended the event aimed at members of institutional review boards (IRBs), the hospital committees that oversee patient safety in **clinical trials.** In 1970, Congress mandated IRBs and informed-**consent** forms, the agreements that volunteer subjects sign saying they understand the drug study.

The death in September at the University of Pennsylvania of an 18-year-old man enrolled in an experimental gene therapy for an inherited liver disorder was the fault of the **clinical-trials** system, not the school, Annas said.

"It's endemic. We don't pay attention to informed **consent.** We treat research as treatment,"Annas said.

The father of the teenager told a Senate subcommittee hearing last week that when he permitted his son to take part in the test, he 1 NEW3 was not aware of the true medical risks or the possible serious side effects.

The death triggered a government investigation, the suspension of eight gene therapy trials in Pennsylvania, and a Senate hearing last week. This week, Beth Israel Deaconess Medical Center in Boston announced it has suspended its gene therapy tests because of safety concerns about the death.

Parents of sick children are particularly vulnerable to enrolling in studies, Annas said.

"Ninety-five percent of parents think their kids will benefit from research. The illusion is extremely powerful. We're fooling ourselves if we think we researchers are getting informed **consent,**" he said.

"Subjects have to protect themselves by getting a second opinion" before becoming involved in **clinical trials,** Annas said.

Patients diagnosed with a fatal disease are often too traumatized to understand the experimental therapy they are signing up for, said Dr. Richard F. Levine, a professor of medicine at George Washington University.

There is a huge amount of vulnerability among patients who present themselves as subjects for **clinical trials,** Levine said.

"People with illness, particularly cancer, get afraid and distracted and can't pay attention. Informed **consent** is an illusion," said Levine, a hematologist."As soon as you tell them they have leukemia, they think they'll die, and can't concentrate. They're not informed. They're not giving informed **consent.**"
Informed **consent** also affects organ transplant recipients, said Renee Fox, a fellow with the Center For Bioethics at the University of Pennsylvania.

The fact that every organ transplant, except in the case of identical twins, will ultimately be rejected after a period of time"is not well understood by recipients, and is deliberately not told to them,"Fox charged.

"How much and what should the recipient be told about organ rejection and serious side effects?"she asked.

This story contains material from The Associated Press.

LANGUAGE: English

LOAD-DATE: February 8, 2000

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Knight Ridder/Tribune News Service
The Philadelphia Inquirer

February 5, 2000, Saturday

SECTION: DOMESTIC NEWS

KR-ACC-NO: K2251

LENGTH: 1619 words

HEADLINE: Patient in gene-therapy study feels betrayed

BYLINE: By Susan Fitzgerald

BODY:

In June 1998 Dolores Aderman became Patient No. 11 in a groundbreaking gene- therapy experiment at the University of Pennsylvania.

Researchers inserted a small tube and infused her liver with viral particles loaded with a gene to correct a rare metabolic disease that ran in her family.

Aderman left the hospital thinking that the experiment went off without a hitch and happy that she had done her part in possibly finding a cure for the disease that killed her son Michael two weeks before his fourth birthday and now affected two other sons.

But that was not the case, according to an investigation after the death last September of Jesse Gelsinger, Patient No. 19 in the same gene-therapy experiment.

And in the months that have ensued, Aderman, 36, has been rethinking her role as a volunteer on the frontiers of medicine. The Bucks County woman remains committed to helping researchers find a cure for her sons' disease, but she also feels betrayed.

Records of the experiment showed that after her gene treatment, Aderman's liver had a bad reaction. Key enzymes that serve as gauges of liver-cell injury rose to levels high enough that the researchers reported the toxicity to the federal Food and Drug Administration and were obligated to get permission to proceed to the next patient.

From a medical standpoint, Aderman was not in danger, and her enzyme levels returned to normal by the time she left the hospital.

But researchers write such toxicity standards into experiments to serve as warning signs. The three patients who followed Aderman also experienced liver toxicity, and the FDA has criticized Penn for not promptly reporting two of the "adverse events."

Penn did not return phone calls from The Inquirer requesting comment on Aderman's story.

In the aftermath of Gelsinger's death in Penn's gene-therapy experiment, Congress was scheduled to hold a hearing Wednesday on whether the safety of patient volunteers is being adequately protected in this highly unproven but still promising field of medicine.

Are patients fully informed of the risks before they sign up for gene-therapy trials? Do they understand that in this early testing phase the therapy will not likely offer them any benefit? Are they kept up-to-date on unexpected developments in the experiments? Is there rigorous oversight by the FDA and the National Institutes of Health?

The FDA found numerous violations in the way the Penn experiment was being conducted. Last month the FDA shut down all gene-therapy trials at Penn's Institute for Human Gene Therapy, headed by Dr. James M. Wilson, saying there were not adequate systems to ensure the safety of patients.

Penn is expected to officially respond to the FDA this week.

Aderman said she knew nothing about her liver reaction until she pieced it together from news accounts of FDA reports in December.

Aderman said she was shocked because the doctors had never told her that her enzymes had spiked.

"The patient has the right to know everything going on," she said. "It's my body. It's not your body. I lent them my body."

Aderman's friends and family thought she was crazy to volunteer for the gene- therapy experiment.

"What if something happens and for the rest of your life you have to pay for it?" Aderman says her mother asked her.

She learned about the experiment on the Internet while researching ornithine transcarbamylase (OTC) deficiency. Mark Batshaw, a doctor at Children's Seashore House in Philadelphia who had treated one of Aderman's children, was one of the researchers.

Michael, her firstborn, had died in 1986, within hours of eating a high-protein meal of three pieces of fried fish.

It was only after the autopsy report came back that she learned of OTC, a rare genetic disorder in which the liver is unable to rid the body of ammonia, a natural byproduct of metabolism.

Since then, Aderman has learned that the disease, which is inherited through the mother's genetic code, probably killed two of her brothers, who died inexplicably at a young age. Two of Aderman's other sons have the disease. Aderman and her two daughters are carriers.

People with OTC must eat a special low-protein diet and take medication. But even a little cold can put their ammonia levels dangerously out of whack. At age 2, Aderman's son Jonathan fell into a coma for a week after drinking a glass of milk intended for a sibling.

Aderman was eager to volunteer for the experiment.

"The only thing I thought about was if I could just help kids who were so sick," Aderman said. "I went into it so I could save just one more mom or dad from what I went through."

Penn's gene-therapy trial was unusual because the patients were relatively healthy.

When scientists first ventured into this new approach to disease _ which involves giving patients corrective genes piggybacked onto viruses _ they focused on conditions in which patients were very ill or near death.

Wilson's research team had wanted to test the technique on babies dying of OTC, but a university review of the proposal determined that it would be unethical since parents who were about to lose a child could not make a clear-headed decision to allow their baby to take part.

The plan shifted to using adults who were carriers or had mild symptoms of the disease.

But Aderman was far from a dispassionate participant.

"It had to be done," she told her mother. Twelve years after his death, Michael was still the first thing

she thought about each morning.

As Aderman went through the screening to see if she met the criteria for the trial _ answering questions, giving every detail of her medical history, having her blood drawn for DNA testing, drinking a nasty concoction to see how her body handled ammonia _ she only knew that she wanted to be in the experiment.

When it came time to sign the **consent** form on April 27, 1998, Aderman did not dwell on the form's mentions of potential dangers _ inflammation of the liver from the virus used in the therapy or an immune response that could cause liver damage.

"OK, Michael, you didn't die in vain," she remembers thinking. "Mom is going to do something to help all the kids with OTC."

When Aderman, a nursing aide in a nursing home, checked in for her gene therapy, she was the first person in "Cohort 4," a group of patients who would get the fourth- highest level of the drug.

In keeping with the experiment's protocol, Aderman was placed in isolation after the two-hour procedure. She developed aching symptoms similar to the flu, but she was not worried because previous patients had felt the same way.

For a week after the gene infusion, doctors and nurses methodically monitored Aderman in the hospital, checking her blood and urine for a long list of factors, including liver enzymes, that would indicate whether she was having a reaction to the gene therapy. Doctors also did a liver biopsy, snipping a small piece of her liver to get a firsthand look.

"They said everything went good," she recalled.

Under federal rules, patients in **clinical trials** have the right to request adverse-event reports emerging from the research, according to an FDA spokesperson, and **consent** forms are supposed to spell out all possible risks and complications.

Beyond that, there is little clarity about what details patients should be told.

"If a patient experiences a serious toxicity in a study, whether it's a clinical toxicity or a laboratory toxicity they might not know about, I think researchers ought to tell the subject what is happening," said LeRoy Walters, head of the Kennedy Institute of Ethics at Georgetown University.

After news broke of Gelsinger's death, Aderman requested her medical records from the University of Pennsylvania. She had gotten health insurance and wanted her new doctor to have her complete medical history.

She said Penn gave her lab reports from her hospital stay, a biopsy report and copies of **consent** forms she had signed. She wanted more. What she got, she said, was not enough to cover more than a week in the hospital. There was nothing to say her case was reported to the FDA.

Last week she called Dr. Philip Noguchi, who oversees gene research for the FDA, to make another request for her records. She said he told her that he would have to check on it.

The FDA spokesperson said the agency would not discuss individual patients.

Aderman figures she gave Penn her all and, in return, "all I ask for is a little respect, a little common courtesy, and the truth."

"You give your whole self," she said. "It's not something you take lightly.

"You don't say, 'I think I'll go down to the University of Pennsylvania and have them stick something up

my artery.' "

Aderman was also offended by the form letters that kept coming for months after the researchers informed patients of Gelsinger's death.

"I am very pleased to update you that the OTC gene therapy study is progressing very well. We have now dosed 18 volunteers!" said letters sent to Aderman in November and December requesting blood samples.

A month after Gelsinger's death, she was at Penn for follow-up lab work and she had to sign a **consent** form for the experiment because the previous one had expired. The 11-page form, in detailing the experiment's risks, did not specifically mention the liver toxicity experienced by patients in Cohort 4, or Gelsinger's death.

Still, Aderman remains a believer in Penn's gene-therapy experiment.

She would do it again. In fact, "if Michael was alive," she says, "I would let him go and do it."

PHOTO (from KRT Photo Service, 202-383-6099):

Visit Philadelphia Online, the Inquirer's World Wide Web site, at http://www.philly.com/

LANGUAGE: ENGLISH

JOURNAL-CODE: PH

LOAD-DATE: February 5, 2000

The Associated Press State & Local Wire

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February 2, 2000, Wednesday, AM cycle

SECTION: State and Regional; Washington Dateline

LENGTH: 973 words

HEADLINE: Father of dead teen says he not told of true gene therapy risks

BYLINE: BY PAUL RECER, AP Science Writer

DATELINE: WASHINGTON

BODY:

The father of a teen-ager who died after being injected with experimental genes said he and his son were not informed of the true risks and the serious side effects that could be caused by the treatment.

Paul L. Gelsinger of Tucson, Ariz., said that before he let his son participate in a gene therapy experiment, he was not told that a monkey had died in a similar experiment and that another patient had had serious side effects.

Gelsinger's son, 18-year-old Jesse, died at the University of Pennsylvania in September after being injected with genes designed to correct an inherited liver disease. Jesse was recruited for the experiment because he was born with ornithine transcarbamylase deficiency syndrome, a liver disorder.

"It looked safe. It was presented as being safe," Gelsinger testified Wednesday at a Senate subcommittee hearing. "Since it would benefit everybody, I encouraged my son to do this.

"I was misled," he added. "That's what hurt the most. This was not as it was presented."

Jesse Gelsinger went into a coma and died within hours, becoming the first patient whose death was directly linked to experimental gene therapy.

The testimony came in a hearing by the Senate Health, Education, Labor and Pensions Committee's panel on Public Health, which is investigating patient safety in gene therapy **clinical trials** and whether there is a need for more vigorous supervision of the trials by the government. The hearing follows reports that some researchers have failed to tell the National Institutes of Health about some serious health conditions experienced by patients taking part in gene therapy trials.

Sen. Bill Frist, R-Tenn., a physician and chairman of the subcommittee, said the death of Gelsinger "has sobered us all" about the promising field of gene therapy.

"Jesse's death is not merely a pothole that we can simply ride over on the road to find genetic cures," said Frist. "We must take a new path that ensures that no family will be forced to endure what the Gelsinger family has experienced."

Judith Rodin, president of the University of Pennsylvania, in a letter Frist read at the hearing, called the death of Gelsinger "a terrible tragedy."

"We deeply regret Jesse Gelsinger's death and we want to learn everything we can about how and why he died," wrote Rodin. She pledged a thorough investigation into the causes of the death and to finding

ways of improving the university's research program.

"We intend for our research programs, particularly those involving **human subjects,** to meet the highest standards," Rodin said in the letter. "Nothing less is acceptable."

Dr. Amy Patterson, head of a NIH office that oversees gene therapy, said that researchers are required to report any serious adverse event among patients in the gene therapy trials, but that this requirement has been frequently ignored.

"There has been widespread noncompliance," Patterson said in testimony.

Over a seven-year period, she said, there have 691 adverse events, but only 39 had been reported to the NIH within the time required by the regulations. Patterson said that the agency was aware of the other 652, "but they were not reported in a timely way to the NIH."

All gene therapy proposals once required approval of the NIH's Recombinant DNA Advisory Committee, but that approval authority was shifted in 1997 to the Food and Drug Administration.

After this shift, "there was widespread noncompliance with NIH reporting guidelines (of adverse events)," said Patterson.

Patterson and Dr. Jay P. Siegel of the FDA said there have been other deaths among patients involved in gene therapy experiments, but only the death of Jesse Gelsinger was directly caused by the therapy. Others deaths, such as among cancer patients taking part in the experiments, have been attributed to the underlying disease, they said.

FDA adverse event reporting guidelines are different from those the NIH, and FDA regulations also require the agency to not publicly reveal the reports. NIH regulations, however, make all adverse event reports open to the public.

Siegel said the FDA, starting in December, now requires that the NIH would be notified of all adverse event reports filed to the FDA by researchers, along with any changes in the research protocols.

He said the FDA also has sent letters to researchers reminding them of the requirement to report adverse events to both the NIH and the FDA.

Siegel said the death of Gelsinger prompted an FDA investigation of the University of Pennsylvania gene therapy research program. The program was halted after inspectors found a number of violations, Siegel said. The findings continue to be evaluated by the FDA, he said, and further action may be taken.

University of Pennsylvania researchers have declined interviews about the Gelsinger death, but in a public meeting at NIH last December the scientists said that the teenager's reaction to the gene injection was unexpected and unexplained. They said Gelsinger died after a developing a high fever, slipping into a coma and experiencing general organ failure. Side effects had been much milder in 18 patients injected with the genes earlier, they said.

Another witness, Eric Kast of Norman, Okla., said he is a cystic fibrosis patient who has taken part in drug trials.

He said patients should be fully informed about research risk and that researchers should be told of all adverse events that occur in the field. This is essential, he said, to build trust and confidence.

Kast said he believes that gene therapy offers the promise of possibly curing cystic fibrosis. He urged that the research continue, but that adverse events be made public through the NIH.

However, he cautioned that the personal medical histories and identification of patients should be protected.

Capital Times (Madison, WI.)

November 22, 1999, Monday, ALL EDITIONS

SECTION: Lifestyle, Pg. 1D

LENGTH: 865 words

HEADLINE: SPELLING OUT RISKS IN **CLINICAL TRIALS; CONSENT** FORMS PACKED WITH INFO

BYLINE: By Debra Carr-Elsing The Capital Times

BODY:

Many people agree to be in medical studies for altruistic reasons. After all, research is the way that we advance our knowledge and improve health care for the next generation.

There are a few things consumers should know, however, before agreeing to participate in a **clinical trial,** and most of this information is spelled out in a **consent** form.

"A ***consent*** *form should say why the research is being done and what the procedures will be,*" says Dr. Norman Fost, a professor of pediatrics and chairman of the **human subjects** committee for health sciences at the University of Wisconsin-Madison.

These procedures can be spelled out in as much detail as consumers want, Fost says. They can even know how many blood tests or X-rays to expect, for example, and how much time may be involved.

Besides that, a medical study **consent** form typically lists possible benefits and any risks that can be reasonably anticipated.

"If it's a research project involving some type of experimental treatment, the form also should let people know how to find alternative treatment for the disorder," Fost says.

The name and phone number of a study's lead investigator also should be on the **consent** form, as well as the name and number of another official from the institution, such as a patient representative. Then, if you think you haven't been treated well, there's someone outside of the study you can contact.

"**Consent** is not forever -- you can change your mind," Fost says. "A form should say that you can withdraw from the study at any time."

Before they sign on the dotted line, consumers also may want to know whether or not a particular study is being regulated by an institutional review board. These boards also are known as **human subjects** committees.

It's mandated that IRBs oversee any research that receives federal funding, and a primary purpose of these committees is to make sure that **consent** forms are available to consumers.

Another purpose of **human subjects** committees is to make sure that research is being done ethically, says Dr. Leslie Taylor, medical director of **clinical trials** at the Dean Foundation for Health Research and Education.

Basically, these committees protect the rights of patients, she adds, and all research at the Dean Foundation falls under committee review.

In turn, IRBs are under the scrutiny of the Food and Drug Administration and the Office for Protection from Research Risks, which is under the federal Department of Health and Human Services at the National Institutes of Health.

"The OPRR recently shut down some research clinics, in part because it didn't feel that the particular IRBs were spending enough time reviewing studies and documenting the research," Taylor says.

Ongoing research is required to be reviewed annually, she adds.

"Medical research is a well-regulated and safe enterprise," Fost says.

For example, UW-Madison has four IRBs, and Fost's particular committee for the UW Health Science Center is currently overseeing about 1,400 research protocols.

In any study, the most important piece of paper is the informed **consent,** Taylor says.

"If there's any sense that research staff aren't answering your questions clearly, then that document shouldn't be signed," she cautions.

What usually happens, however, is that study participants Taylor who have a particular disorder are generally better informed than others with the same condition because potential risks and benefits -- as well as treatment options -- are listed in the **consent** form.

"Study participants often get much more time and attention than they would otherwise," Taylor says. "Particularly in the field of psychiatry, patients often feel like they don't routinely get enough time to describe what's going on in their lives."

But one of the benefits of being in a study is that researchers ask a lot of questions -- they want to know how patients are feeling.

"We learn from participants, and they gain a great deal of insight about their particular illness," Taylor says.

There also can be monetary compensation, especially in research protocols calling for volunteers who aren't sick and have no medical reasons of their own for participation in the study.

The cash benefit could be $ 20 per visit, plus travel pay. Some studies that require participants to keep track of daily symptoms could pay as much as $ 60 per weekly visit.

In treatment studies where participants have a condition that could benefit, compensation typically is the free medical care.

With end-stage cancer studies, for example, participating in research may be the only way to get something that can help a condition after standard therapies have failed.

Besides that, anyone who has been on a placebo in a double blind study usually is given the opportunity to take the "real drug" after the study is completed.

Clinical trials also are monitored by independent review boards that have been known to end a study prematurely if a particular treatment clearly is shown to be superior.

"It's simply not ethical to continue a study where some people are denied a treatment that could help them," Taylor says.

GRAPHIC: Consumers should clearly understand what the procedures will be -- and what alternative treatments are available -- before agreeing to participate in a medical study or **clinical trial.** Photo of Leslie Taylor

LOAD-DATE: November 23, 1999

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The Associated Press State & Local Wire

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March 11, 2000, Saturday, BC cycle

SECTION: State and Regional

LENGTH: 708 words

HEADLINE: Research suit settled for **$3.8 million**

DATELINE: TAMPA, Fla.

BODY:

Tampa General Hospital and the University of South **Florida** each has agreed to pay more than $1 million to settle a class action suit contending experimental procedures were performed on poor pregnant **women.**

The $3.8 million settlement, announced Friday, could affect 3,000 **women.**

The 1990 medical research suit alleged thousands of pregnant **women** weren't told of the risks, benefits and alternatives of various experiments conducted between 1986 and 1990.

USF doctors working at Tampa General gave about 3,000 **women** with high-risk pregnancies drugs that the doctors thought would enhance the lung development of their fetuses.

The **women** then were given regular **amniocentesis** to monitor the effectiveness of the drugs. Between 1 and 2 percent of **women** miscarry immediately after undergoing an **amniocentesis.** That is when a needle is inserted into the uterus to extract amniotic fluid for analysis.

In the suit, none of the **women** claimed they were harmed by the experiment or that it was ineffective in improving the outcomes of their pregnancies.

But they said they were never told the drugs were experimental or that they could choose not to take them.

There was no admission of wrongdoing in the settlement.

The settlement calls for the hospital and the university each to pay $1.1 million and a state insurance plan to pay $1.6 million over a four-year period to about 3,000 people who could collect from the class action suit.

U.S. District Judge Henry Lee Adams Jr. must still sign the settlement, said Stephen Hanlon, attorney for the plaintiffs.

Hanlon's law firm, Holland & Knight, is to receive $1.1 million, and plans to donate $80,000 to consultants working to solve the hospital's financial woes.

USF and TGH officials said both institutions have initiated safeguards sought by the plaintiffs since the suit was filed.

"A lot of what was raised in this case, is now routine," said Michael Hoad, USF director of Health Sciences Public Affairs.

Tina Perritt was 26 weeks pregnant when her water broke and she was admitted to TGH.

Perritt, who was 18-years-old at the time, said she was already woozy from Demerol taken to ease her labor pains when she was asked to sign a three-page, single-spaced form giving consent for an experiment allowing doctors to use steroids to spur fetus lung development and to increase survival chances of her premature baby.

Perritt, admitted to TGH for nine days in March 1987, was given three different types of experimental medicines, the lawsuit said.

After being discharged, the suit says she was told to return every two weeks to TGH's High Risk Clinic, where on 11 occasions she had **amniocentesis.**

Perritt says the **amniocentesis** procedures caused an infection resulting in the premature birth of her daughter, born when she was eight months pregnant.

Perritt's daughter is now 12 and is healthy, Perritt said at Friday's news conference.

Pregnant **women** usually receive **amniocentesis** only twice throughout their terms, said Karen Perrin, a former TGH nurse who noticed on the charts that a number of pregnant **women** were receiving multiple **amniocentesis** as part of a research study.

She said the **women** told her that if they didn't receive the **amniocentesis,** their babies would die.

After finding no answers at the hospital, Perrin went to Hanlon in 1987.

"It's scary to be a whistleblower, but it's worth it because that is how things get changed," said Perrin, now a USF associate professor for the college of public health.

"I would like nurses to know that they are the watchdogs of medicine," Perrin said. "If they see something that looks unethical, they need to pursue it."

In addition to the financial penalty, TGH has agreed to produce consent forms that are easier to read; a California organization will assist in preparing a more readable one, Hanlon said.

The hospital also will assist in trying to find the estimated 3,000 **women** who participated in the experiments - a process that could last four to six months.

Perritt, Flora Diaz and Marian Taylor, whose names are on the suit, each will receive $50,000. The remaining $2.55 million will be split among the rest of the **women** in the class action.

LANGUAGE: ENGLISH

LOAD-DATE: March 12, 2000

Los Angeles Times

May 1, 2000, Monday, Home Edition

SECTION: Metro; Part B; Page 6; Editorial Writers Desk

LENGTH: 592 words

HEADLINE: BAD MEDICINE FOR THE POOR;
THE PROBLEMS COULD UNDERMINE PATIENT CONFIDENCE IN KING/DREW MEDICAL CENTER.

BODY:

There's an ugly history in this country of unethical medical research, most notoriously the long-running Tuskegee experiments, begun in 1932, that allowed poor African American men to develop end-stage syphilis so government scientists could research the progression of the disease.

That history makes it all the more crucial that researchers in hospitals serving poor and minority populations uphold the highest standards when conducting **clinical trials.** One such center is the **Charles R. Drew University** of Medicine in South Los Angeles, the only black-operated medical school west of the Mississippi and a national leader in studying problems particular to poor, urban Americans, such as the growth of HIV infections among African Americans and Latinos.

The recent voluntary shutdown of 250 research studies at Drew and its affiliated Martin Luther King Jr. Hospital, however, makes it clear that some of its researchers were not sufficiently heeding history. Federal inspectors found researchers concealing their studies from the scrutiny of the required Institutional Review Board and denying patients the information they needed to make an informed decision about whether to volunteer as research subjects. The problems could undermine patient confidence in a medical facility that provides desperately needed care in South Los Angeles.

To be sure, none of Drew's violations approach those of Tuskegee, but they are emblematic of what was found in studies by the federal inspector general earlier this month and by the Food and Drug Administration and the General Accounting Office last year: Researchers, not just at Drew but nationally, have skirted safety protocols required by the government since 1974 by failing to submit their studies' designs to a review board and not fully informing patients of the treatment's benefits and risks.

Researchers, under intense pressure to enroll ever larger numbers of patients in **clinical trials** for the burgeoning drug and biotechnology industries, complain about review-board bureaucracy. But research protocol violations are often far from trivial. Reform clearly is needed. Last month, for example, a Florida jury awarded $ 3.8 million to a group of mostly indigent women who had been told that they had to submit to several potentially dangerous amniocentesis procedures to keep their babies from dying when, in fact, all of the babies were healthy.

The immediate solution is for Congress to increase funding for federal oversight, which hasn't remotely kept pace with the explosive growth in the drug and biotechnology industries in the last two decades.

Over the longer term, Congress should consider some systemic changes. Currently, federal regulators--the few there are--conduct on-site visits of research centers only after complaints of egregious violations. The best idea comes from USC law and medicine professor Alex Capron, an advisor to previous presidents and a member of President Clinton's National Bioethics Advisory Commission. Capron proposes an independent body to accredit each university's system of research oversight, much as an outside group now accredits hospitals. Until reforms are in place, the 5 million Americans participating in medical trials should think about getting a second opinion from a medical

expert with no stake in the research. Until federal oversight improves, some patients may have to protect themselves.

It's a shame to suspend the research conducted at Drew. But better to lose some research than the trust of a community.

LANGUAGE: English

LOAD-DATE: May 1, 2000

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Example: **House of Representatives**

The New York Times

View Related Topics

May 4, 2000, Thursday, Late Edition - Final
Correction Appended

SECTION: Section A; Page 20; Column 1; National Desk

LENGTH: 1015 words

HEADLINE: F.D.A. Says Researchers Failed to Report a Second Death Linked to Gene Therapy

BYLINE: By PHILIP J. HILTS

DATELINE: BOSTON, May 3

BODY:

Researchers at St. Elizabeth's Medical Center here failed to report the death of a patient in gene therapy experiments and might have contributed to the growth of cancer in another patient, whose condition was also reported improperly, investigators for the Food and Drug Administration have said.

Their accusations were made in April in a letter to the hospital and the chief researcher in the experiment, Dr. Jeffrey M. **Isner,** and were recently posted on the agency's Web site. The experiment has been stopped.

The news comes as scientists, hospitals and companies sponsoring gene therapy experiments have been working to assure the public of the safety of the experiments after the death of a patient in a gene experiment at the University of Pennsylvania last year.

Jack Cumming, president of the Vascular Genetics Inc. of Durham, N.C., the company sponsoring the experiment at St. Elizabeth's, acknowledged today that there had been some "problems" in the gene therapy experiment. Mr. Cumming said the company would do everything it could to satisfy the F.D.A. in correcting the problems. He said he was "very optimistic" that positive results would be presented to the agency this summer.

Mr. Cumming said he would not dispute the agency's findings and said that his company had hired two outside groups to audit and monitor all the experiments it had begun around the country, including the one at St. Elizabeth's. The groups were hired after the company learned that the federal agency was writing a warning letter, he said.

Sonia Hagopian, a spokeswoman for the St. Elizabeth's, said the hospital took the warning letter very seriously, and added: "We are focusing all our resources on producing a thorough and thoughtful response to the F.D.A."

The hospital's public relations office said Dr. **Isner** would not be available for comment at this time.

The problems in the experiment were reported on Tuesday in The Washington Post and The Boston Herald.

About 300 gene therapy experiments are under way around the country. Troubles with some of the experiments have become public, especially since the death of a patient, Jesse Gelsinger, 18, in the University of Pennsylvania experiment.

In the experiment at St. Elizabeth's, which was jointly sponsored by Tufts University, a gene that makes a substance called V.E.G.F. (for vascular endothelial growth factor) was injected directly into the hearts

of patients with blocked heart vessels. Researchers hoped the gene would start making the growth factor, which is the body's natural substance to make blood vessels grow.

Inspectors for the federal agency said they found several violations of the rules of the experiment in a routine check in March. One patient in the experiment died two months after receiving the experimental therapy, but the researchers did not report the death to the agency. The agency is investigating to determine if the treatment was the cause of the death.

In another case, a patient was included in the study although he should have been kept out under the rules of the experiment. The patient was a heavy smoker and a small mass had appeared in one lung, the agency said. Because the experimental therapy used a chemical designed to increase the growth of blood vessels, the agency said, it was possible that it increased the supply of blood to the growing **tumor.**

The agency's warning letter noted that the St. Elizabeth's researchers saw the mass when it was less than a centimeter in July 1999, then again in August when it was two centimeters in diameter, but went ahead with the treatment on Sept. 21, 1999. Two months later, the agency said, the patient was hospitalized with chest pain, and the mass was found to have grown to five centimeters.

There was no evidence in the patient's records or the experiment records that either the patient or his doctor was notified of the growth of the mass, investigators said.

Instead, one of the researchers sent a letter to the patient's doctor saying that the patient was doing better with his heart problem since receiving the therapy. The letter did not mention the lung mass.

In addition, the agency noted that in the experiment records the growth in the mass was noted and marked as a "severe" change for the patient. This word should have set off an immediate call to the F.D.A. Instead, the agency said, the word "severe" was struck out and the word "mild" substituted.

The agency's letter also noted that because the researchers apparently did nothing to notify the patient or his doctor, "your site appears to have failed to provide adequate medical care for this subject."

In another case, a patient in the study had a heart attack just after getting the experimental injection. The attack led to multiple organ failure, a long hospitalization, and death a few months later.

But the researchers reported to authorities only that the patient was hospitalized, not that she had died.

Such events are required to be reported because it is possible the therapy itself was the cause of death, and it would be urgent to consider whether to take precautions with other experimental subjects.

In addition, the agency reported that Dr. **Isner** himself carried out an autopsy on the woman's heart, although he is not a certified pathologist and has no hospital privileges to carry out autopsies.

The inspectors also cited several other problems with the methods of enrolling patients in the experiment: needed tests were not done in some cases, and other patients enrolled might not have been eligible for the study.

The hospital and the researchers have 15 days to tell the agency how they will correct the problems in the experiment. There is no set punishment for the violations, but the F.D.A. has the authority to ban the researchers from future work using federal money.

This and three other experiments carried on by Dr. **Isner** were stopped when the agency first began its inspection in February and have not resumed.

Dr. **Isner** is a founder of the company leading the trials and is a major stockholder in it.

http://www.nytimes.com

CORRECTION-DATE: May 6, 2000, Saturday

CORRECTION:
An article on Thursday about the death of a patient in a gene therapy experiment at St. Elizabeth's Medical Center in Boston misidentified the authority to which the hospital failed to report the death. It is the institutional review board of St. Elizabeth's, not the Food and Drug Administration.

An article on Thursday about the death of a patient in a gene therapy experiment at St. Elizabeth's Medical Center in Boston misidentified the authority to which the hospital failed to report the death. It is the institutional review board of St. Elizabeth's, not the Food and Drug Administration.

LANGUAGE: ENGLISH

LOAD-DATE: May 4, 2000

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Los Angeles Times

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April 27, 2000, Thursday, Home Edition

SECTION: Part A; Part 1; Page 1; Metro Desk

LENGTH: 1396 words

HEADLINE: KING/DREW MEDICAL RESEARCH SUSPENDED;
HEALTH: VOLUNTARY ACTION COMES AFTER REGULATORS FIND TWO DOZEN VIOLATIONS OF RULES DESIGNED TO PROTECT HUMAN SUBJECTS AND ENSURE CREDIBILITY AT SOUTH L.A. FACILITY.

BYLINE: NICHOLAS RICCARDI and TERENCE MONMANEY, TIMES STAFF WRITERS

BODY:

The **Charles R. Drew University** of Medicine and Science and its affiliated health care center, Los Angeles County's Martin Luther King Jr. Hospital, have stopped hundreds of clinical studies after federal officials found more than two dozen violations of regulations and rules protecting people who take part in research.

The university's unusual order, issued in conjunction with a visit by officials from the U.S. Office for Protection From Research Risks, centers on flaws in the legally required oversight meant to ensure that studies are scientifically credible. The regulations also are supposed to ensure that patients and other subjects are fully informed of the risks of participation and thus are protected from undue harm.

Medical center officials suspended research activities two weeks ago, the day after federal officials confronted them with a long list of violations both large and small, according to interviews and internal hospital documents.

Drew University's president, Dr. Charles Francis, did not return a call for comment.

About 250 studies have been halted, officials say, though they could not pinpoint how many subjects that affected. The King/Drew Medical Center in Willowbrook receives $ 32 million annually in federal research grants, which could be jeopardized if the self-imposed suspension is prolonged. Studies whose interruption would harm patients will be allowed to continue.

Although the suspension may threaten the millions of dollars in federal research funds, Drew officials said they believe that the problems will be resolved before any financial troubles befall the institution.

Drew officials said the research operations will be overhauled and fully restored by the end of May. A few studies already have been reevaluated and will resume shortly.

Those include a project to measure blood levels of lead in pregnant women, another to track the health of patients with high blood pressure and kidney disease who are at risk for dialysis treatment, and another educating children with asthma to better manage the disorder.

The officials said they voluntarily suspended the research because they are sensitive to the institution's role in serving the vulnerable, mainly poor populations of South Los Angeles.

"No subject has ever had an adverse effect" from Drew research, said Dr. Tony Strickland, associate dean of research. "Clearly, as an institution that is committed to an underserved population, we hold the protection of human subjects at a highest regard."

Strickland said that about 20 ongoing research projects will continue because halting those studies could harm patients, and other studies may be revived if researchers find similar dangers in stopping them.

Studies Attract National Attention

Studies at Drew, some of which have drawn national attention, include testing new treatments for HIV and hypertension, as well as studies of different diagnoses of dementia in the African American and Latino populations. All 250 research projects involving human subjects are conducted by Drew's more than 600 faculty members.

Earlier this month, according to documents obtained by The Times, federal inspectors at the medical school found that, contrary to federal regulations, some research projects were not reviewed by the internal committee charged with approving them, a "major violation."

Among the other violations listed in documents, the medical center lacks adequate guidelines for conducting research on the most vulnerable of subjects: prisoners and children. Consent forms omitted information necessary for prospective subjects to make informed decisions. Some forms were not in Spanish, the native language of many subjects. And the forms did not always include all the procedures that a patient would undergo.

Hospital spokeswoman Mary Schnack said the risk office's mid-April visit to the medical center was prompted by concerns that had been raised by university officials.

But other sources pointed out that the risk office already had been investigating possible problems with the university's compliance with human research regulations for nearly two years.

Similarly, a Drew University statement released late Wednesday described the shutdown as resulting from a "self-study of policies and procedures," which Strickland said had been completed earlier this year. But an internal document listing the 28 findings of problems in procedures is titled "OPRR Citations to Drew."

Strickland said the weaknesses in reviewing human subject research may be the result of an increase of studies at Drew and King/Drew. "We used to be just a clinical campus, and now our thrust has been toward being leaders in urban medical research," he said.

Drew University's College of Medicine is the only black-operated medical school west of the Mississippi. Many of its 600-plus faculty members also work across the street at King/Drew, a 480-bed, county-run facility that is the only major hospital and trauma center for much of South Los Angeles.

Physicians at King/Drew deal with a host of urban woes and run one of the busiest emergency rooms in the county. The hospital has come under repeated fire for inadequate care, and its physicians last year spearheaded a successful attempt to unionize county doctors, the nation's largest unionization of physicians in the past decade.

The suspension of research has rocked the faculty and hospital staff. "More bad news," one grumbled Wednesday.

Drew's shutdown feeds into the growing national concern over the poor performance of the research review committees that are supposed to protect people in clinical studies.

Known as institutional review boards, the legally mandated committees consist of physicians, other health care providers, researchers and laypeople. The boards evaluate proposed studies for scientific validity and ethical standards and monitor continuing studies. Any midstream change to a study requires board approval.

Review Boards Overwhelmed

A scathing 1998 report from the U.S. Department of Health and Human Services declared that the nation's 3,000 to 5,000 research review boards were overwhelmed and dramatically losing effectiveness. And a follow-up report this month said little has changed in the past two years--with the notable exception of increased vigilance by the federal risk office.

Over the last two years, the federal risk office made news and generated controversy by shutting down research activities at seven medical centers, including Duke University and the University of Illinois. In March 1999, it canceled the federal research contract at the Veterans Affairs Greater Los Angeles Healthcare System, prompting VA officials in Washington to take yet more sweeping action--a move from which the West Los Angeles facility and affiliated centers are still recovering.

Dr. Donald Thomas, associate director of the county's health department, said that because Drew officials voluntarily halted research, the situation there is far less severe than at other facilities that have had trouble with federal regulators. "A lot of very reputable institutions have gotten smacked that way with involuntary cessation, so it's pretty good that didn't happen to them," he said.

Drew's voluntary research shutdown is virtually unprecedented, experts on human research rules said Wednesday. Whether the risk office would have stopped research activities at the medical center anyway is not known, but sources insisting on anonymity said the regulators were poised to cancel or suspend the medical center's federal research contract.

Some medical center insiders saw the move by university administrators as an attempt to preempt such a drastic action and avert the ensuing negative publicity.

George Annas, a professor of health law at Boston University, said the problems with Drew's review boards typify the failure of many medical center officials to take seriously the regulations and procedures for protecting research subjects' physical health and rights of self-determination.

But a violation cited by Drew (and described to Annas by a reporter) was rather extreme--especially the admission that clinical studies went ahead without any prior review from the research review board. "That's a major problem," he said. "That's the only reason the boards exist."

GRAPHIC: PHOTO: Research studies have been halted at King/Drew Medical Center.
PHOTOGRAPHER: ROBERT DURELL / Los Angeles Times

LANGUAGE: English

LOAD-DATE: April 27, 2000

The Chronicle of Higher Education

April 14, 2000

SECTION: GOVERNMENT & POLITICS; Pg. A45

LENGTH: 2403 words

HEADLINE: Could Better Reports by Researchers Have Prevented a **Clinical-Trial** Death?

BYLINE: JEFFREY BRAINARD

BODY:

A patient in a **clinical trial** of an experimental brain-cancer medication suffers a series of headaches. The cause is unclear: Did they result from the medication, which has some toxic effects, or from the patient's poor health? Do the headaches qualify as "serious"? As "unanticipated"?

The answers to those questions are key to treating the patient. But they are tremendously important for another reason as well: They help determine whether the researchers must report the headaches to the federal government. If the symptoms are not reported, the researchers might find they have their own headaches with U.S. officials.

The death of 18-year-old Jesse Gelsinger last September, in a gene-therapy experiment at the University of Pennsylvania, has raised an array of issues for scientists and government officials, who desperately want to avoid a repetition. Among the most vexing is the question of when clinical researchers should report that study volunteers suffered unusual health problems -- referred to in the dry lexicon of federal rules as "adverse events," which includes deaths but also such less-serious reactions as numbness.

Recent discussions about the reporting of adverse events have suggested that gene-therapy researchers tell the government about far too few such incidents. In most other biomedical fields, however, the reporting rules differ, and the problem is not that too few adverse events have been reported, but too many, scientists and ethicists say.

The intensified talk about adverse events has come at a time when some observers are already questioning whether the university panels and federal agencies that review those reports are equipped for the job. In trying to solve the problem, some experts believe that institutions should seek out reports from independent safety panels, which statistically analyze adverse-event data in some **clinical trials.**

At stake for researchers are the welfare of patients and their willingness to volunteer for medical experiments that could lead to new treatments for illness.

"Our system for protecting human research subjects has evolved in response to relatively isolated events. Jesse Gelsinger's death is another of these, and will spur people to address problems that aren't new at all, but have been burrs under our saddles for some time," says Daniel K. Nelson, an associate professor of social medicine and pediatrics, and director of the Office of Human Research Studies, at the University of North Carolina at Chapel Hill.

Deciding what is and is not an adverse event can involve tough judgments.

Many experimental drugs cause toxic effects, and thus some adverse events are expected. Indeed, a major goal of clinical studies is to measure those toxic effects. Researchers can then compare a treatment's benefits with its risks.

Another complicating factor is that some patients, especially in cancer trials, may be close to death when they enter a trial. They volunteer as a last resort, after conventional treatments have failed. Many of the participants die during such trials -- but they may have died anyway, researchers say.

Scientists have to figure out which complications and deaths are caused by an experimental treatment, and which by the underlying disease.

Once scientists have spotted an adverse event, federal agencies have detailed, differing rules about how it must be reported.

Scientists must promptly tell the Food and Drug Administration about problems that are serious, unexpected, and possibly related to an experimental treatment. A separate report is required each time such an incident affects any individual patient. Less-serious problems can be summarized in annual reports to the F.D.A., which has sole authority to approve new medical treatments.

By contrast, the National Institutes of Health requires researchers to promptly send all reports of "unanticipated" problems to universities' institutional review boards, or I.R.B.'s. Those panels, formed mostly of volunteers, are responsible for evaluating the risks and benefits of experiments involving **human subjects.**

The N.I.H. has a separate standard for experiments in the controversial field of gene therapy, in which scientists hope to repair or replace damaged genes to cure a variety of illnesses. All serious adverse events in those studies must be reported immediately to the agency and to the appropriate I.R.B. Some researchers say confusion over the N.I.H. and F.D.A. requirements has contributed to the underreporting of adverse events in gene-therapy trials.

Interpreting the meaning of adverse events can be difficult for both the researchers and the officials who review the reports.

To aid in that task, pharmaceutical companies that sponsor large **clinical trials** at universities often set up independent panels, called data-safety-monitoring boards. Those panels apply statistical analysis to find safety trends in the adverse-event reports, and advise the companies of any problems.

However, some observers say, pharmaceutical companies do not always share those analyses with university I.R.B.'s or federal officials promptly, if at all. Instead, companies send a torrent of reports about individual volunteers -- documents that often lack vital context.

The reports "have created a great deal of work for I.R.B.'s, but it's questionable whether there's been commensurate benefit to research subjects," says Moira A. Keane, director of a program on research-subjects protection at the University of Minnesota-Twin Cities.

The difficulty is compounded because **clinical trials** of new treatments are increasingly being conducted at dozens of academic medical centers around the world. That creates a group of volunteers large enough to yield statistically meaningful results, but also produces a flood of adverse-event reports.

Regulations require each American institution to evaluate reports received from every other participating institution -- even those that lack context. For example, medical researchers frequently give placebos, or dummy medications, in trials designed to study the efficacy of new medicines. But to promote objectivity, scientists do not know which volunteers are receiving placebos; that information is kept secret by assistants. Thus, reports of adverse events typically do not note whether the ill volunteer was receiving a placebo.

Moreover, reports often do not indicate how many patients are participating at a university, making it difficult for I.R.B.'s elsewhere to judge whether an adverse event is common or rare. I.R.B.'s consist mostly of faculty members who volunteer their time, and many board members complain that they are overworked. The boards tend to focus instead on the adequacy of **consent** forms given to research subjects, and the risks presented by proposed research (The Chronicle, March 17).

"Frankly, I.R.B.'s are not well-equipped to handle the reports they're seeing," says Gary L. Chadwick, executive director of the review board at the University of Rochester. "You see one piece of the puzzle,

not all the pieces. . . . You feel there may be some information here, but you don't know what to do with it."

The reports can run several pages, and over the course of a trial, one volunteer may experience 20 or more adverse events. The largest medical centers typically run as many as 2,000 **clinical trials** at once. As a result, some university officials say they receive up to 200 reports of adverse events a month, filling several boxes.

The underreporting of adverse events in gene-therapy experiments appears to have occurred because of a special rule for that type of research: The National Institutes of Health makes the reports public. By contrast, I.R.B.'s and the F.D.A. keep reports from ordinary **clinical trials** confidential.

N.I.H. officials say the public disclosure is necessary because gene therapy is so novel and ethically sensitive that the experiments demand a higher level of public scrutiny. But some observers believe the rule has led gene-therapy researchers to underreport adverse events for financial reasons. Pharmaceutical companies have said the disclosure of some details in the reports could reveal their trade secrets.

Some experts say that expanded use of the independent data-safety-monitoring boards could help everyone who reviews adverse-event reports.

The monitoring boards get the crucial information that I.R.B.'s often do not, such as which patients are receiving placebos. The panels consist of statisticians and medical experts who are not part of the research team conducting the **clinical trial.**

Companies that sponsor such boards benefit because they can present the findings to the F.D.A. when they submit the experimental therapy to be approved for marketing. Although the agency does not require safety-monitoring boards, they are increasingly common in large trials.

The N.I.H. has for years required safety-monitoring boards for many types of large **clinical trials** it finances, including for treatments of cancer and AIDS. And in June, the N.I.H. required the monitoring boards to send their findings to I.R.B.'s at participating universities, in lieu of immediate reporting of adverse events in each patient. N.I.H. officials said that would help cut down on the number of reports burdening I.R.B.'s.

But at many academic medical centers, many if not most multicenter trials are financed by pharmaceutical companies, I.R.B. officials say. And too often, the companies do not send the monitoring boards' reports to the I.R.B.'s reviewing those experiments, says Jeremy Sugarman, a bioethicist and associate professor of medicine and philosophy at the Duke University Medical Center. That's probably because the F.D.A. does not require pharmaceutical companies to do so, he says.

For its part, the F.D.A. does not review adverse-event reports as extensively as the data-safety-monitoring boards can, observers say.

The F.D.A. also does not record adverse events from **clinical trials** in an electronic database, making it difficult to analyze the information statistically, as the safety-monitoring boards do. And like members of I.R.B.'s, F.D.A. staff members do not always know which patients are receiving placebos.

As a result, the agency tends to follow up mainly on the most-serious individual adverse events -- and may be missing trends suggested by less-serious ones, says Roger L. Williams, who until January was director for pharmaceutical science at the F.D.A.'s Center for Drug Evaluation and Research. He left the agency to work for a nonprofit organization that recommends standards for drug quality.

"Drugs are in **clinical trials** for three to five or more years," Dr. Williams says. "If you think about monitoring all of those adverse events, I think it's difficult for F.D.A. reviewers to do that."

In 1993, an F.D.A. panel urged the agency to establish a database of adverse events in **clinical trials.** The panel made that judgment after studying the deaths of five patients in a trial of fialuridine, an

experimental drug to treat hepatitis.

The F.D.A. is building a system that will allow sponsors of clinical drug trials to send adverse-event reports to the agency electronically. The system, which has been delayed by a lack of financing, should be in place by 2002, says Janet Woodcock, director of the F.D.A.'s Center for Drug Evaluation and Research.

The electronic submissions will replace printed reports, and thus should allow agency officials to better keep track of adverse events and offer more-effective oversight, Dr. Woodcock says.

Most clinical drug trials proceed without reports of serious adverse events, she says. But she encourages sponsors of **clinical trials** to use safety-monitoring boards more widely. That view is endorsed by LeRoy Walters, director of the Kennedy Institute for Ethics at Georgetown University.

Safety-monitoring boards can "serve as an independent, external check on the F.D.A. and its work," he says. "If for whatever reason, the F.D.A. is missing things, I don't want that to be a situation that jeopardizes the safety of **human subjects.**"

Mr. Walters and others have suggested that a board could also help alert the N.I.H. to the kinds of problems in gene-therapy trials that led to Mr. Gelsinger's death -- although that idea has its critics.

The promise and risks of gene-therapy trials are evaluated in public by an N.I.H. panel, the Recombinant DNA Advisory Commission -- RAC, as it is known.

The panel now has more adverse events than ever to consider. After Mr. Gelsinger died, the N.I.H. reminded gene-therapy researchers of their reporting responsibilities. N.I.H. officials said in December that scientists responded by sending the agency 691 reports, only 39 of which had been properly submitted to the agency before. Scientists have followed up with more than 460 reports so far this year.

But members of the RAC -- which includes scientists, bioethicists, and others -- were unable to agree last month on a proposal to create a national safety-monitoring board for gene-therapy trials.

Some researchers on the committee suggested that safety-monitoring boards were not well-suited to evaluating gene-therapy trials, because such experiments tend to involve fewer patients than the large trials that such boards typically review. Even had such a panel been in place for the Pennsylvania trial, it probably would not have prevented Mr. Gelsinger's death, says M. Louise Markert, an associate professor of pediatrics at Duke's medical center.

Disagreement among committee members also arose over a proposal that the N.I.H. require prompt reporting of a wider variety of adverse events than that required by the Food and Drug Administration. Under the proposal, for example, problems that were unexpected but not serious would have to be quickly reported. Supporters of such expanded reporting said it could reveal obscure safety trends in time to affect gene-therapy trials as they were occurring.

Several scientists on the committee suggested instead that the N.I.H. rely on the reports now submitted to the F.D.A. That agency is working on a new regulation to allow the public disclosure of some details of adverse-event reports it receives.

The committee is expected to consider a revised proposal at its June meeting.

LANGUAGE: ENGLISH

LOAD-DATE: May 15, 2000

FOCUS™

THE BALTIMORE SUN

April 28, 2000, Friday ,FINAL

SECTION: TELEGRAPH ,3A

LENGTH: 873 words

HEADLINE: Pondering medicine's moral issues
More Hopkins doctors are turning to institute about ethics questions

BYLINE: Diana K. Sugg

SOURCE: SUN STAFF

BODY:

The questions keep coming, through e-mails and phone calls, in formal meetings and chats: Should fetal tissue be used in research? Should the hospital allow couples to pay exorbitant prices for the donated eggs of women with beauty and intelligence? When does life begin?

Across the Johns Hopkins Medical institutions, scientists and physicians are trying to make sense of the moral questions that haunt their work. And increasingly, they are tapping the Hopkins Bioethics Institute.

Established a few years ago, the institute's faculty are grappling daily with some of the toughest and most pressing issues in modern medicine. They're getting so many requests for help that its director worries they won't be able to reach them all. But quietly, the center is influencing the way scientists do research and physicians practice medicine.

"It's not like we have a pipeline to the moral truth, and we're going to give it to you. It's, you've got the wisdom, you live it, and we have some tools that can help you think through it," said Ruth Faden, the institute's director. "Our moral reflection has to keep pace with our scientific and medical advances."

New efforts

That broad mission translates into many new efforts across the university and health system. A physician is teaching the ethics of the end of life to undergraduates at the School of Arts and Sciences. Researchers are investigating how seriously ill patients give **consent** to be in early phase **clinical trials.** Scholars are developing an ethics curriculum for researchers who work in developing countries.

To infuse ethics into the culture of the institution, the bioethics center is working on a strategic plan to train everyone engaged in patient care at Hopkins, said Faden, a widely respected scholar who led the national committee that investigated the human radiation experiments.

Lecture today

Today, the institute will be the host of a public lecture on the ethics of Medicare reform, followed by a two-day, off-the-record symposium next year involving key national players on all sides of that debate. The program, sponsored by the family of Robert H. Levi, a Baltimore businessman and philanthropist who was on the board of trustees at the hospital and university, aims to spark a dialogue and influence public policy.

The center has quickly moved to the forefront nationwide, making its mark with its work in contentious areas such as international research and genetic privacy.

"Hopkins was late to the gate for its ethics program, but they've really exploded once they made the

decision to go for it," said Thomas Murray, president of the Hastings Center, one of the country's oldest and most prominent bioethics centers. "They're really in the top tier."

Larger operations

Though all hospitals have bioethics committees that deal with specific cases and policies, bioethics centers are more like think tanks that do research and education. About 50 of the country's 125 academic medical centers have these institutes, but most are small operations of just a few people. A handful, such as the University of Chicago and University of Pennsylvania, have larger operations like Hopkins', which has 24 faculty members.

The institute just launched a five-year, $26 million fund- raising initiative, and leaders say they are about a third of the way to their goal.

The center's unusual structure, being universitywide and independent of all the schools, gives it freedom to comment on the cutting- edge, often politically sensitive work of researchers.

For instance, when the Hopkins School of Public Health came under fire for **clinical trials** in Africa that compared experimental therapies to prevent mother-to-baby HIV transmission with placebos, the bioethics institute jumped into the fray.

Scholars brought attention to often-neglected elements: the moral perspective of researchers from developing countries, as well as those countries' political and economic conditions.

Stem cell debate

Faculty members of the Bioethics Institute also got involved in the firestorm of debate over stem cells. (These parent cells, from which all tissues develop, could someday be used to help diseased organs.) Using private funding, Hopkins researchers isolated these cells from the tissue of aborted fetuses. They were donated by women who had made up their minds to have abortions and who had no connection to the scientists.

But the Hopkins work, along with that of another team's, sparked a national controversy. In the aftermath, the Hopkins researcher who did the work, Dr. John D. Gearhart, a professor of obstetrics and gynecology, turned to Faden and her colleagues.

"We needed help," he said.

Now, he seeks their counsel routinely.

There were no laws or guidelines in place for obtaining fetal tissue, so he said the bioethics scholars came up with a series of five or six procedural recommendations on how to do that.

"You just can't go shooting from the hip," Gearhart added. " You want to make sure that what you're doing is right with a capital R."

Madison Powers of Georgetown University will deliver the Robert H. Levi Lecture at 3: 30 p.m. today at Shriver Hall on Hopkins' Homewood campus.

LOAD-DATE: May 1, 2000

FOCUS™
Search: General News;human subjects and clinical trials and consent

The Washington Post

View Related Topics

April 13, 2000, Thursday, Final Edition

SECTION: A SECTION; Pg. A06

LENGTH: 631 words

HEADLINE: Protection of Patients In Research Is Faulted; Report: HHS Progress Minimal Since '98

BYLINE: Rick Weiss , Washington Post Staff Writer

BODY:

The Department of Health and Human Services has made "minimal progress" in the past two years toward implementing suitable protections for people enrolled in medical experiments, according to a report by the department's Office of Inspector General.

The new analysis is a follow-up to the office's high-profile June 1998 report on the nation's human research enterprise, which found numerous shortcomings in the protections afforded research subjects. That report focused especially on the Institutional Review Boards (IRBs) that judge the scientific and ethical aspects of human research at federally funded institutions, whose members it deemed to be overworked and often underqualified.

The 1998 report made numerous specific recommendations to the National Institutes of Health, the Food and Drug Administration and other agencies, aimed at improving the situation. The new report, released yesterday, sought to determine whether HHS had implemented the recommended changes.

The report applauds the NIH's Office for Protection From Research Risks (OPRR) for its "substantial increase" in enforcement of patient protections at research universities since the summer of 1998. It notes that the OPRR has significantly increased its on-site investigations and has suspended research at seven institutions with serious shortcomings. Those moves have had a "ripple effect" beyond the institutions involved by signaling that the agency is serious about patient protections, the report concludes.

The report also credits the FDA for increasing the frequency of its routine on-site investigations of IRBs.

But overall, the HHS report concludes, "minimal progress has been made in strengthening continuing protections for **human subjects** participating in research."

Among the report's criticisms:

* IRBs are still failing to conduct ongoing reviews of research they had previously approved. "IRBs know little of what actually occurs during the **consent** and research process," the report concludes.

* Although the 1998 report called for new standards of education for clinical researchers and IRB members to ensure they are familiar with the basic concepts of patient safety, "no educational requirements have been enacted for investigators or IRB members."

* There has been "no progress" in creating bureaucratic fire walls that would insulate research reviewers sitting on IRBs from conflicts of interest that can compromise their objectivity as they review colleagues' proposals.

* "Minimal progress" has been made in reducing workload pressures on IRBs, leaving these crucial bodies "hard-pressed to give each review sufficient attention."

The report acknowledges that many of the changes the inspector general's office had hoped to see by now would have required not only changes within HHS, but also changes in the "Common Rule," which provides standards for human research for 17 federal agencies. The rule is structured such that any overarching changes must be individually approved by all 17 agencies. In most cases, those approvals require implementing long and complicated sets of internal procedures.

"In view of this reality," the report concludes, "legislative change may well be necessary to achieve a timely implementation of many of our recommendations."

In response to yesterday's report, the FDA and the NIH released a joint statement saying that the agencies "are committed to ensuring the protection of participants" in **clinical trials** and that "numerous educational outreach activities" for IRB members and researchers are underway. Underscoring the agencies' concern for patient protections, the statement said, the OPRR will soon be elevated from an NIH office to one within the Office of the Secretary of HHS.

LANGUAGE: ENGLISH

LOAD-DATE: April 13, 2000

View Related Topics

March 29, 2000, Wednesday, 0 South Pinellas Edition

SECTION: CITY & STATE; Pg. 3B

DISTRIBUTION: CITY & STATE; METRO & STATE; TAMPA & STATE

LENGTH: 400 words

HEADLINE: USF says its trial of gene therapy likely to resume

BYLINE: WES ALLISON

DATELINE: TAMPA

BODY:

The University of South Florida plans to reopen a gene therapy trial for terminal cancer patients after reviewing more information about the death of a patient in Arkansas who had the same treatment.

Dr. Richard Heller, chairman of USF's Institutional Biosafety Committee, said the committee voted on Tuesday to lift the suspension on the **clinical trial** after the therapy's developer, Vical Inc. of San Diego, provided more details about its safety and about the death of the patient in Arkansas.

The committee agreed the treatment is reasonably safe, but it also changed the patient **consent** form to reflect that it could, potentially, lead to death; it dropped a sentence that said no one had suffered any serious side effects from the drug, and it cut the word "remote" from a sentence explaining that death was a possible side effect.

The changes must be approved by USF's Institutional Review Board, which oversees all trials at the school, before the trial again can recruit patients, but Heller expects that to happen soon.

"They're not really significant changes, but they're changes that need to be made so that the correct information is relayed to the patient before they enroll in the study," Heller said.

The USF College of Medicine was the only one of about 40 participating centers to stop the trial after learning in January of the patient's death, which the lead researcher at the University of Arkansas had indicated was "probably" related to the gene therapy.

The trial involves a drug called Allovectin-7 and is being tested in patients around the United States who have severe forms of skin cancer, called melanoma, that have not responded to other treatments. It uses altered genes to help the body's immune system better target the cancer.

Fewer than 10 people have gotten injections of Allovectin at the H. Lee Moffitt Cancer Center and Research Institute at USF in Tampa, and none has suffered adverse affects, school officials said.

Vical said that USF overreacted by stopping the trial last month and that the therapy has been used safely in more than 500 patients.

Heller said the company has now provided data that show the Arkansas patient, who died about two months after the treatment, likely died from other causes.

Experimental gene therapy has come under scrutiny since the death last fall of teenager at the University of Pennsylvania.

The Associated Press State & Local Wire

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March 19, 2000, Sunday, BC cycle

SECTION: State and Regional

LENGTH: 545 words

HEADLINE: AIDS drug research on inmates questioned

DATELINE: ORLANDO, Fla.

BODY:

Dozens of inmates at a central Florida prison are being treated for HIV and AIDS with combinations of medications that could have unknown dangers, a newspaper reported.

Some worry prisoners don't fully understand the risks or may be pressured to become research subjects, but many prisoners say the research has greatly improved their health, the St. Petersburg Times reported in its Sunday editions.

At issue is a voluntary testing program at the South Unit of the Central Florida Reception Center, 10 miles east of Orlando International Airport. The facility is among only a handful of the nation's prisons to allow such research.

There, free drugs and health exams are available for prisoners whose care would otherwise cost the state thousands of dollars per inmate per year.

Under the study rules, HIV-positive inmate volunteers get combinations of more than a dozen drugs. The aim is to see which drugs work best in which doses for which kinds of patients, Department of Corrections officials said.

Many inmates said the drugs have greatly improved their lives.

That includes Julius Samuel, 44, a burglar with HIV who was losing weight before going on the drug regimen.

"They have more drugs at the South Unit than where I was at," Samuel said. "I don't have a trace of the virus."

The drug testing program is relatively new. For years, the Florida prison system did not use inmates as subjects in medical experiments. Many states, including Florida, banned the practice after revelations in the 1970s that researchers working for drug companies exploited inmates in the name of science or profit.

That changed during the AIDS epidemic of the 1980s. Gravely ill people, including Florida inmates, began demanding access to experimental therapies that might save their lives.

A Florida prison official lifted the research ban on inmates and in December 1997, Dr. Margaret Fischl, a pioneering AIDS researcher, was allowed to set up a screening and testing site at the South Unit.

The prison system told her that inmates had to receive good treatment and couldn't take part in initial experiments to determine whether a drug is toxic.

But despite signing **consent** papers, some inmates do not seem particularly well informed about potential risks of the drugs, the newspaper reported.

Raymond McGee, 31, a former inmate now living at an Orlando halfway house, said he never asked, nor was told, about details of what the **consent** form calls a "potentially life-threatening" hypersensitivity reaction that the drug, abacavir, sometimes causes.

That can include fever, fatigue and skin rash.

Still, McGee says he's not concerned.

"I never had a reaction to it," he said. "If I didn't think it was working, I'd stop taking it."

Fischl said the combinations she gives inmates have successfully reduced the virus without negative impacts. Prisoners have had fewer adverse reactions than non-prisoners participating in the **clinical trials,** she said.

Fischl and Department of Corrections officials said that inmates are under no pressure to volunteer.

"There is no coercion," said Dr. David L. Thomas, the prisoner system's director of health services. "There are no promises of better treatment or easier life" at the South Unit.

LANGUAGE: ENGLISH

LOAD-DATE: March 20, 2000

St. Petersburg Times

March 19, 2000, Sunday, 0 South Pinellas Edition

SECTION: NATIONAL; Pg. 1A

LENGTH: 4526 words

HEADLINE: Questions raised over AIDS research on inmates

BYLINE: SYDNEY P. FREEDBERG

DATELINE: ORLANDO

BODY:

In a prison in the shadow of Disney, inmates are getting the AIDS drugs of tomorrow. But are they informed of the risks, and is the study under oversight?

It was once strictly taboo, evocative of the Nazis and Nuremberg: doing medical experiments on prisoners, often without their full knowledge.

Yet today, about 35 miles from Walt Disney World's Tomorrowland, dozens of inmates are being treated for HIV and AIDS with combinations of medications that could have unknown dangers.

The prisoners - murderers, rapists, burglars and drug dealers - are human lab rats.

Inmate advocates worry that prisoners may be pressured to become research subjects or don't fully understand the risks.

The top scientist on the project, a University of Miami professor with a world-renowned reputation and financial support from several drug companies, says she is careful and plays it straight with inmates. Her studies, she says, could help find a cure for AIDS.

The prisoners? Most think they've been blessed with everything from comfortable shoes to a chance to take anti-HIV drug combinations, not yet available to the public, that may improve and prolong their lives.

"I'm a living, breathing, walking miracle," said Yakab Dennis, a 33-year-old convicted rapist who readily volunteered for the research, then saw his health rebound dramatically. "I thank God for the study."

The potential for abuse is still there, however. It has been only two years since Florida finished changing its rules to allow research on some of its 3,250 HIV-positive inmates.

Within a year, questions had begun. And then last July, a state prison official wrote a letter assuring an oversight board that the research would easily comply with the Nuremberg Code, adopted after 16 Nazi doctors were found guilty of torturing concentration camp prisoners deemed "unworthy of life."

Recognizing the potential for exploitation, the Florida prison system says it agreed to the testing only after putting in place a system of oversight and creating a watchdog group to protect the inmates.

Yet the watchdog group has been disbanded.

Critics say the Department of Corrections has failed to adequately monitor the studies.

The University of Miami, citing federal confidentiality requirements, declines to release records about

the research or safety reports it compiles if an inmate gets a bad reaction to a medication.

And the person originally selected to look after inmates' interests is a state prison official who has championed the research project - a dual role that ethicists find troubling.

What's more, two pharmaceutical companies involved in AIDS research say they have given that official, Dr. David L. Thomas, honoraria for his work with the companies. Thomas did not respond to questions about those honoraria. But in an interview in December, he stressed that he follows Florida's financial-disclosure requirements.

The Department of Corrections, which has been under fire in recent months amid reports of inmate abuse and inadequate medical care, defends Thomas and the state's oversight of the research project.

"I'm sure you will find someone, whether it's a prisoner rights advocate or a so-called expert on medical ethics, to criticize us, especially on the issue of informed **consent,**" spokesman C.J. Drake said, adding that the research is ethical, proper and voluntary.

Drake hailed the research site, located in an AIDS prison, as a national model. He said the St. Petersburg Times, in asking questions, is "nitpicking issues of secondary importance."

After questions from the Times, however, federal regulators began an inquiry into whether Florida's prison studies, which are run by the University of Miami and financed by drugmakers and the National Institutes of Health, comply with rules to protect **human subjects.**

Dr. Norman Altman, the University of Miami's vice provost for research, says the university is cooperating with the Office for Protection from Research Risks, a tiny arm of the NIH that oversees **human subjects** at hundreds of institutions.

"It's our intention to do this right," Altman said, adding that the university would look into complaints about informed-**consent** procedures. "And if things aren't being done right, it's our intention to correct them."

Two or three times a day, several dozen inmates in freshly starched white uniforms line up outside nurse Ernestine Forbes' cubicle at the South Unit of the Central Florida Reception Center, 10 miles east of Orlando International Airport.

One by one, they swallow a raft of capsules and tablets that Forbes puts into their outstretched hands. One inmate gulps 53 pills a day: 17 in the morning, 19 in the afternoon and 17 in the evening.

For years, the Florida prison system did not use inmates as subjects in medical experiments. Many states, including Florida, banned the practice after revelations in the 1970s that researchers working for drug companies exploited inmates in the name of science or profit.

Prison reformers likened some of the studies, which included tests of cancer and hepatitis drugs, to inhumane experiments conducted by German doctors during World War II. Some ethicists contended that even though the research might hold great promise for society, inmates could never give truly informed **consent** because they live in a closed environment that can never be free of coercion.

Then came the AIDS epidemic. When it struck in the 1980s, the stakes for medical science suddenly rose dramatically. Gravely ill people, including Florida inmates, began demanding access to experimental therapies that might save their lives.

Enter Dr. Margaret Fischl, a pioneering AIDS researcher. She says she received letters from HIV-positive prisoners who clamored to enter drug studies.

As a young doctor at the University of Miami, Fischl was among the first to report that AIDS was not exclusively a gay disease. She also played a key role in the creation of AZT, America's first anti-AIDS drug.

A hero to some, Fischl was vilified by others who questioned her AZT research. As the epidemic intensified and AZT didn't live up to early hopes, some AIDS activists accused Fischl of jiggering study results to make AZT's manufacturer, Glaxo Wellcome plc, look good.

Fischl, now 50, denies fudging scientific data to get positive results, and federal regulators never found evidence of wrongdoing. "There was never any truth whatsoever to any of it," Fischl said. "I remain proud of that work."

Like many AIDS researchers, Fischl receives financial support for her experiments from pharmaceutical companies, including Glaxo. She says grant money would never sway her objectivity about a new drug, and besides, the University of Miami says, the money goes to a restricted university account, not to Fischl.

Even so, critics contend that such financial relationships, especially over time, can exert a seductive pressure on some scientists.

Fischl's studies made her one of the most powerful members of the AIDS research establishment in Washington. She brings prestige and millions in federal grants to the University of Miami, and Glaxo reaped a fortune off its global AZT sales.

By 1995, however, Glaxo competitors had begun to introduce new classes of AIDS drugs that patients seemed to tolerate better than AZT. The new drugs, given in combinations known as drug cocktails, sent AIDS deaths plummeting.

Even with HIV-positive patients living longer, the second generation of AIDS drugs had a host of problems. Drug companies remained eager to develop medications that were cheaper, less toxic and had less complex dosing schedules. A month's supply can cost $ 15,000.

In the race to get new drug cocktails on pharmacy shelves, the NIH and drug firms spend billions on testing. Typically, companies provide the medication used in a study at no charge. NIH or drug company grants, given to research institutions, cover the costs of test subjects' clinical visits, blood draws, lab tests and X-rays.

But drug experiments need patients, and some drugmakers, working with researchers like Fischl, soon learned where to find a ready supply: prisons.

For the researchers, inmates are ideal test subjects: a constant, controllable group, eating the same food, following the same routine, always taking the medication. Making them even more attractive commodities, some inmates have never taken HIV drugs. Such "drug naive" patients, or "treatment virgins," tend to do better on new drug therapies, experts say.

Only a handful of the nation's prisons now allow such research, but the benefits are obvious. They get free drugs and health exams for prisoners whose care would otherwise cost the state thousands of dollars per inmate per year. They also gain reputations as penal pacesetters.

And so it happened that a small group of Florida prison officials quietly lifted the research ban on prisoners.

Fischl agreed to donate her services, and without advertising for research proposals, the Department of Corrections let her set up a screening and testing site at the South Unit in December 1997.

The prison system told her that inmates had to receive good treatment and couldn't take part in initial experiments to determine whether a drug is toxic.

Corrections officials say Fischl enrolled 64 inmates in nine studies. Six are ongoing. Four of the research trials were funded by the NIH, three by Glaxo Wellcome, one by Merck & Co. and one by Pharmacia & Upjohn Inc.

Under the study rules, the Corrections Department says, HIV-positive inmate-volunteers get combinations of more than a dozen powerful drugs from nine drug companies. The aim is to see which drugs work best in which doses for which kinds of patients.

With her research team, Fischl began showing up at the South Unit, sitting with inmates and sometimes, she says, going over **consent** forms line by line, again and again. On some of the forms, inmates are told, "We cannot assure you of any benefits."

Many prisoners liked it when a famous doctor showed up in the Florida prison system, where they often complain about bad doctors and bad care. Some inmates saw Fischl as a sort of goddess and took what she said as gospel.

One of them is 44-year-old Julius Samuel, a burglar with HIV. Before becoming a research subject, Samuel was losing weight and spiraling downward. He says he joined a study because he wanted access to new drug combinations that weren't available at his other prison.

"They have more drugs at the South Unit than where I was at," Samuel said, adding that he feels as if he has come back from the dead. "I don't have a trace of the virus."

Prisoners do not earn money for joining research trials, which can last up to three years. But, like Samuel, several inmates told the Times they were partly attracted by other inducements, including the prospect of quality drugs and good care that they couldn't get at other Florida prisons. One inmate's mother says her son enrolled in a South Unit study after she complained to politicians about his mistreatment at a North Florida prison.

And some inmates mention the nice amenities at the South Unit, such as air conditioning and comfortable sneakers.

"All you got to do is say, "Look, my feet hurt,' and you get brand new, soft shoes," said Raymond McGee, a 31-year-old former inmate who jumped at the chance to lend his body to medical science. "Compared to other prisons, the way they take care of you at the South Unit is like a newborn child."

In interviews, many prisoners played down the drugs' side effects, which can include muscle pain, nausea, vomiting, fatigue, sleep disorders, ingrown toenails, tingling legs and numb feet. That's why they get the sneakers.

At the South Unit, where all but a handful of the 124 inmates are HIV-positive, prisoners say they don't feel like outcasts. The nurses are kind. The doctors know what they're doing. And the guards are under strict orders not to block access to medical care.

Dave Whiters, a convicted cocaine dealer with a cross tattoo on one arm and "Demon Dave" on the other, was a "treatment virgin" before joining a three-year study last year. "If you want yourself taken care of, you go to the South Unit," he said.

But when pressed about the study, Whiters, 36, doesn't seem particularly well-informed.

He's not sure what questions researchers hope to answer. And, unlike HIV patients in the community, Whiters isn't in a position to get a second opinion about his treatment options.

He shows a reporter a medication sheet indicating he gets an anti-HIV drug combination that includes at

least one placebo, or dummy medication. Asked if he knows what a placebo is, Whiters replied: "No, ma'am."

Former inmate McGee, now living in an Orlando halfway house, claimed to understand key safety information when he signed up for a potent drug combo that includes Glaxo Wellcome's controversial abacavir (Ziagen). But McGee also says he never asked, nor was he told, about details of what the **consent** form calls a "potentially life-threatening" hypersensitivity reaction that abacavir sometimes causes.

Nationwide, scientists have investigated eight deaths associated with abacavir, though there was no way to prove if the drug was the cause, according to the Associated Press.

After abacavir came on the market in December 1998, the FDA mandated that every patient receive a detailed notice explaining the hypersensitivity reaction, plus a wallet-sized card to carry that describes symptoms. These can include fever, fatigue and skin rash.

McGee says he's not concerned. "I never had a reaction to it," he said. "If I didn't think it was working, I'd stop taking it."

Questions about the research at the South Unit are not isolated. As more vulnerable patients, including children, prisoners and people without medical insurance, enroll in research studies, reports of lax oversight and dubious ethics in medical experiments have sparked investigations by Congress.

The Food and Drug Administration and the federal Office for Protection from Research Risks have cited research institutions for problems ranging from faulty informed-**consent** procedures to fraudulent practices in recruiting test subjects. Just last month, the NIH revealed that researchers under-reported adverse events in gene therapy studies.

In Florida, Dr. Fischl says the drug combinations she gives inmates have successfully reduced the virus without negative impacts. In fact, she says, she thinks she sees fewer adverse reactions among prisoners than non-prisoners in **clinical trials.**

Fischl and Department of Corrections officials say emphatically that inmates are under no pressure to volunteer.

"There is no coercion," said Dr. Thomas, the prison system's director of health services. "There are no promises of better treatment or easier life" at the South Unit.

Thomas, a lawyer, ophthalmologist and former Republican whip in the Florida House of Representatives, has become Fischl's chief advocate. After joining the Department of Corrections in 1994, he became known as a compassionate conservative who cut costs creatively. He earns $ 132,251 a year.

But Thomas, 54, says he did not promote the research to save the state money. Rather, he wanted to "bring inmates opportunities for the best care possible," and he says if there are savings, they are "minuscule."

In a letter to the University of Miami last July, Thomas wrote to Fischl's colleagues that prisoners felt no pressure, not even subtle pressure, to enroll. "We always attempt to exceed the guidelines of the Nuremberg Code," he said.

Thomas' role as a disinterested observer is debatable, however. In April 1999, a Brown University newsletter listed him as a consultant and speaker for Agouron Pharmaceuticals and Bristol-Myers Squibb. Spokesmen for the firms, which make anti-HIV drugs used in the prison research, say they gave Thomas honoraria for his advice on AIDS in prisons.

After the two drug companies told the Times about the honoraria, Thomas did not return telephone calls or e-mails seeking comment about the honoraria. In an interview in December, he said he owns no drug-company stock and always follows the state's financial disclosure laws. He told corrections spokesman Drake that he is not a drug-company consultant and that "his primary source of income" comes from the Corrections Department.

"Dr. Thomas is required to report any such things that might be covered by the law in his annual financial disclosure form, if he did in fact receive any," said John Burke, the prison system's health care administrator.

"Dr. Thomas has a medical degree, a law degree and is a former member of the Legislature," added department spokesman Drake. "If anyone knows what a conflict of interest is, he does. He is not involved in any conflict of interest."

It was Thomas and his predecessor who created a watchdog committee, with no association to Dr. Fischl or the University of Miami, to make sure the research complied with federal patient-protection rules.

But soon after the committee began meeting in 1998, it ran into problems. It had trouble finding members who could attend regularly, so Thomas suggested that his wife, Chris, join the group.

That raised some eyebrows, but the committee went along and voted to include her, according to Karol Lucken, a University of Central Florida criminal-justice professor who was chairwoman of the committee.

"I knew if we'd ask somebody like my wife, we'd have a quorum," Thomas said.

The committee, also composed of ministers, an AIDS activist and a former inmate, among others, had one setback after another. Lucken says its members lacked the expertise to weigh the scientific merits of the studies. They also had trouble getting answers to questions that went to the heart of informed **consent:**

How were inmates recruited and screened? Who was on which drugs and why? Was there enough staff at the South Unit, and were they trained to notice possible adverse reactions?

"We went around and around on some of these things," Lucken said, "but the procedures seemed nebulous."

When the group examined informed-**consent** forms signed by the inmates, some members felt they might as well have been written in Greek.

One form is titled: "A phase II, randomized trial of AMPRENAVIR as part of dual protease inhibitor regimens (placebo controlled) in combination with ABACAVIR, EFAVIRENZ and ADEFOVIR DIPIVOXIL versus AMPRENAVIR alone in HIV infected subjects with prior exposure to approved protease inhibitors and loss of virologic suppression as reflected by a plasma HIV-1 RNA concentration > 1000 copies/ml."

At the request of the Times, Education Programs Associates, a California company that writes easy-to-read documents, examined a **consent** form for a nationwide study that enrolled both prisoners and non-prisoners; in Florida, only non-prisoners took part.

"The format was very difficult to read," the company wrote in a three-page report, concluding the form is written at a 15th-grade level, well above the average inmate's education. "Important information was buried in densely written paragraphs. . . . Clinical jargon was rarely explained. The typical reader, even if well-educated, would have no way of comprehending the content of the **consent** form."

Problems understanding **consent** forms are common in and outside prisons, and Dr. Jay Sosenko, a member of the University of Miami's institutional review board, says the forms are "made as understandable as possible."

Miami's review board, he adds, rigorously reviews and tracks Dr. Fischl's research.

But in March 1998, Lucken wrote a letter to the Department of Corrections, saying that without more information, the watchdog committee couldn't give its assurance that inmate rights were protected.

Other potential problems turned up when members of the committee interviewed the inmates.

While some committee members thought the prisoners looked healthy and clearly understood what was going on, other members suspected some inmates had been pressured into the trials. They were told if they didn't sign up that day, the study might be closed to them, according to minutes of a committee meeting.

No one responsible for enrolling inmates in studies said that, corrections officials replied.

They promised to look into an allegation that an inmate was taken off his medication for a week and given other drugs without being told why. (Changing regimens or skipping anti-HIV drugs even for a few days can allow the virus to re-emerge.)

And correction officials said inmates enrolled in studies would continue to receive HIV drugs after they were released from prison. Despite their good intentions, however, they inadvertently lost track of two former inmates enrolled in studies: One was transferred out of state, and the Immigration and Naturalization Service deported another.

AIDS activist Peter Uitdenbosch, a member of the watchdog committee, discovered other problems. He said that one prisoner, a "treatment virgin," had been placed on a potent, mega-drug cocktail and didn't know he had other, less risky treatment options. And several prisoners weren't fully informed about the dangerous reaction that Glaxo's abacavir sometimes causes, according to Uitdenbosch, who is HIV positive and takes abacavir himself.

He says that when he informed one inmate, he "went into a panic" and complained to the administration.

Thomas accused Uitdenbosch of dispensing "invalid medical information" and threatened to "close down" the research if the committee felt it didn't comply with the Nuremberg Code.

Nobody wanted that. "It's the process that's bad, not the studies," Uitdenbosch said.

Last fall, the process took another hit when the Department of Corrections suddenly disbanded the watchdog committee. Thomas said he intended to name a new oversight panel, but for months, none was appointed.

Finally, a few weeks ago, the Corrections Department released the names of 10 new committee members. Seven are Corrections Department employees.

The selections promptly drew more criticism. "That panel should contain no state officials at all," Lucken said. "Evidently, the Department of Corrections thinks it is immune from oversight."

Federal rules require that the University of Miami appoint an inmate or inmate advocate to represent the prisoners' interests. When the university picked Thomas, critics charged that the selection was fraught with potential conflicts of interest.

"It smacked of cronyism," said Uitdenbosch, noting that Thomas is not only the man in charge of inmate

medical care but is also a University of Miami alumnus. "Who represents the prisoners?" Uitdenbosch asked.

Ruth Macklin, a bioethicist at Albert Einstein College of Medicine in New York City, says any prison official serving as an inmate advocate creates a conflict of interest. "Even in the most humane and enlightened prison, it's utterly preposterous to claim that any individual who is either from a corrections facility or the state is an advocate," she said. "They are adversaries."

Dr. Altman says the university picked Thomas because of his extensive knowledge of prison health care.

"I thought I was an appropriate person," Thomas said. "I've got a background in ethics."

- Times researchers Kitty Bennett and Caryn Baird contributed to this report.

University of Miami studies with inmate enrollment:

ACTG 384

Participants: 15 active.

Length of study: Three years maximum.

The aim: Study of protease inhibitor and/or non-nucleoside reverse transcriptase inhibitor with dual nucleosides in initial therapy of HIV infection.

Drugs involved: Combivir; efavirenz; Nelfinavir; Didanosine/Stavudine.

NZTA 4007

Participants: Four active; 13 have completed studies in the penal system.

Length of study: 54 weeks.

The aim: A phase IIIB, open label, pilot study to evaluate the efficacy, tolerability and health care resource use in HIV-infected incarcerated subjects treated twice daily for 24 weeks.

Drugs involved: Ziagen (abacavir); Combivir (lamivudine and zidovudine).

MK-094

Participants: Four active.

Length of study: 24 weeks.

The aim: A multicenter, open label 24-week pilot study to evaluate the safety and efficacy of indinavir Sulfate in combination with Ritonavir in HIV-infected individuals.

Drugs involved: indinavir; Ritonavir; Stavudine; Lamivudine.

ACTG 398

Participants: Three active.

Length of study: Approximately 1 1/2 years.

The aim: A phase II, randomized study of amprenavir as part of dual protease inhibitor regimens

(placebo controlled) in combination with abacavir, efavirenz and adefovir dipivoxil versus amprenavir alone in HIV infected subjects with prior exposure to approved protease inhibitors and loss of virologic suppression as reflected by a plasma HIV-1 RNA concentration > 1000 copies/ml.

Drugs involved: amprenavir; abacavir; efavirenz; L-Carnitine; saquinavir.

ACTG 388

Participants: 15 active; one has completed the study in the penal system.

Length of study: 96 weeks.

The aim: A phase III, randomized, controlled study of efavirenz or Nelfinavir in combination with fixed dose combination Lamivudine/Zidovudine and indinavir in HIV-infected subjects with < 200 cells/mm3or > 100,000 HIV RNA copies/ml in plasma.

Drugs involved: Combivir; indinavir; efavirenz; Nelfinavir.

PROAB 3006

Participants: One active; two have completed studies in the penal system.

Length of study: 48 weeks.

The aim: A phase III trial to compare the safety and anti-viral efficacy of amprenavir with indinavir in combination with nucleoside reverse transcriptase inhibitor therapy in NRTI experienced, protease inhibitor naive, infected patients.

Drugs involved: amprenavir; indinavir; abacavir.

ACTG 359

Participants: None active; three inmates had been active participants in the penal system.

Length of study: 24 to 48 weeks; trial has closed.

The aim: To study the activity of the soft gelatin capsule saquinavir in combination with Ritonavir or Nelfinavir and combinations of delavirdine and/or adefovir in HIV-infected subjects with prior indinavir use and viral loads of >2000 and <200,000 copies of HIV RNA/ml.

Drugs involved: saquinavir; Ritonavir; Nelfinavir; delavirdine; adefovir.

NZTA 4002

Participants: None active; two inmates had been active participants in the penal system.

Length of study: 96 weeks from the time first subject enrolled; trial has closed.

The aim: A comparison of a four-drug regimen with a three-drug regimen in antiretroviral-naive HIV-infected subjects.

Drugs involved: 141W94 (amprenavir); abacavir (1592U89); Combivir; Nelfinavir.

M/3331/0074

Participants: None active; one inmates had been an active participant but he was lost to the study when he transferred out of state.

Length of study: 24 to 96 weeks.

The aim: An open-label randomized study of delavirdine in triple- and four-drug combinations with Zidovudine, Lamivudine and indinavir in HIV-infected individuals.

Drugs involved: delavirdine; Zidovudine; Lamivudine; and indinavir.

Source: Florida Department of Corrections

GRAPHIC: COLOR PHOTO; COLOR PHOTO, PAM ROYAL, (3); COLOR PHOTO, Associated Press file photo; COLOR MAP; BLACK AND WHITE PHOTO, PAM ROYAL, (3); Dr. David L. Thomas; Several times a day, inmates at the South Unit line up at a window to receive their medications from nurse Ernestine Forbes.; Yakab Dennis; Julius Samuel joined a study because he wanted access to drug combinations not available at his other prison.; (1990) Dr. Margaret Fischl a pioneering AIDS researcher shown speaking at the Sixth International Conference on AIDS in San Francisco.

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