

BIG PHARMA'S SHAMEFUL SECRET

Every year, drug companies spend \$14 billion to test experimental substances on humans. Across the U.S., the centers that do the testing—and the regulators who watch them—allow scores of people to be injured or killed.

By David Evans, Michael Smith and Liz Willen

◀ Oscar Cabanerio has been waiting in an experimental drug testing center in Miami since 7:30 a.m. The 41-year-old undocumented immigrant says he's desperate for cash to send his wife and four children in Venezuela. More than 70 people have crowded into reception rooms furnished with rows of attached blue plastic seats. Cabanerio is one of many regulars who gather at SFBC International Inc.'s test center, which, with 675 beds, is the largest for-profit drug testing center in North America.

Most of the people lining up at SFBC to rent their bodies to medical researchers are poor immigrants from Latin

America, drawn to this five-story test center in a converted Holiday Inn motel. Inside, the brown paint and linoleum is gouged and scuffed. A bathroom with chipped white tiles reeks of urine; its floor is covered with muddy footprints and used paper towels. The volunteers, who are supposed to be healthy, wait for the chance to get paid for ingesting chemicals that may make them sick. They are testing the compounds the world's largest pharmaceutical companies hope to develop into best-selling medicines.

Cabanerio, who has a mechanical drafting degree from a technical school, says he left Venezuela because

he lost his job as a union administrator. For him, the visit to SFBC is a last resort. "I'm in a bind," Cabanerio says in Spanish. "I need the money."

Every year, Big Pharma, as the world's largest drugmakers are called, spends \$14 billion to test experimental drugs on humans. In the U.S., 3.7 million people have been human guinea pigs. Few doctors dispute that testing drugs on people is necessary. No amount of experimentation on laboratory rats will reliably show how a chemical will affect people. Helped by human testing, drugmakers have developed antibiotics capable of curing life-threatening infections as well as revolutionary treatments for diseases like cancer and AIDS.

These medical success stories mask a clinical drug trial industry that is poorly regulated, riddled with conflicts of interest—and sometimes deadly. Every year, trial participants are injured or killed. Rules requiring subjects to avoid alcohol and narcotics and to take part in only one study at a time are sometimes ignored by participants, putting themselves at risk and tainting the test data. The consent forms that people in tests sign—some of which say participants may die during the trial—are written in complicated and obscure language. Many drug test participants interviewed say they barely read them.

Ken Goodman, director of the Bioethics Program at the University of Miami, says pharmaceutical companies are shirking their responsibility to safely develop medicines by using poor, desperate people to test experimental drugs. "The setting is jarring," says Goodman, 50, who has a doctorate in philosophy, after spending 90 minutes in the waiting rooms at SFBC's Miami center, which is also the company's headquarters. "It's an eye-opener. Every one of these people should probably raise a red flag. If these human subject recruitment mills are the norm around the country, then our system is in deep trouble."

Pharmaceutical companies distance themselves from the experiments on humans by outsourcing most of their trials to private test centers across the U.S. and around the world, says Daniel Federman, a doctor who is a senior dean of Harvard Medical School in Boston. The chief executive officers of drug companies should be held accountable for any lack of ethics in these tests, he says. "The CEOs of the companies have to be publicly, explicitly and financially responsible for the ethical approach," says Federman, 77, who still sees patients. "It's not possible to insist on ethical standards unless the company providing the money does so."

CEOs of 15 pharmaceutical companies that outsource drug testing to firms including SFBC—among them, Pfizer Inc., the world's largest drugmaker; Merck & Co.; and Johnson & Johnson—declined to comment for this story.

SFBC Chief Executive Arnold Hantman says his center diligently meets all regulations. "We take very seriously our responsibilities to regulatory authorities, trial participants, clients, employees and shareholders," Hantman, 56, says. "We are committed to conducting research that fully complies with industry and regulatory standards."

The pressure pharmaceutical companies face to develop

new drugs has intensified in the past 15 years. Faced with the expiration of patents on best-selling drugs like AstraZeneca Plc's Prilosec, which has helped tens of millions of people with heartburn and ulcers, Big Pharma has been in a frenzied race to find new sources of profit. When the patent for a company's blockbuster drug expires, a lucrative monopoly vanishes. Such drugs typically lose 85 percent of their market share within a year of patent expiration, according to CenterWatch, a Boston-based compiler of clinical trial data.

The U.S. Food and Drug Administration, the principal federal agency charged with policing the safety of human drug testing, has farmed out much of that responsibility to a network of private companies and groups called institutional review boards, or IRBs. The IRBs that oversee drug company trials operate in such secrecy that the names of their members often aren't disclosed to the public. These IRBs are paid by Big Pharma—just like the testing centers they're supposed to be regulating.

The oldest and largest review company is Western IRB, founded in 1977 by Angela Bowen, an endocrinologist. WIRB, an Olympia, Washington-based for-profit company, is responsible for protecting people in 17,000 clinical trials in the U.S. The company oversaw tests in California and Georgia in the 1990s for which doctors were criminally charged and jailed for lying to the FDA and endangering the lives of trial participants. No action was taken against WIRB. Bowen says she didn't see human safety issues in those trials. WIRB aims to visit test sites it monitors once every three years, Bowen says.

The FDA's own enforcement records portray a system of regulation so porous that it has allowed rogue clinicians—some of whom have phony credentials—to continue conducting human drug tests for years, sometimes for decades. The Fabre Research Clinic in Houston, for example, conducted experimental drug tests for two decades even as FDA inspectors documented the clinic had used unlicensed employees and endangered people repeatedly since 1980. In 2002, the FDA linked the clinic's wrongdoing to the death of a test participant.

'The FDA's backbone has been Jell-O,' says Michael Hensley, a former FDA investigator. 'The FDA stopped enforcing the rules years ago.'



Review boards can have blatant conflicts of interest. The one policing the Fabre clinic was founded by Louis Fabre, the same doctor who ran the clinic. Miami-based Southern IRB has overseen testing at SFBC and is owned by Alison Shamblen, 48, wife of E. Cooper Shamblen, 67, SFBC's vice president of clinical operations. Both Shamblens declined to comment.

SFBC's 2005 shareholder proxy, filed with the U.S. Securities and Exchange Commission, lists Lisa Krinsky as its

chairman and a director of medical trials and refers to her 26 times as a doctor. Krinsky, 42, has a degree from Sparta Medical College in St. Lucia in the Caribbean; she is not licensed to practice medicine.

Arthur Caplan, director of the Center for Bioethics at the University of Pennsylvania in Philadelphia, says handing oversight of human drug experiments to private, for-profit companies is a mistake. "This whole world gives me hives, this privatized review process," Caplan, 55, says. "I've never seen an IRB advertise by saying, 'Hire us. We're the most zealous enforcer of regulations you could have.' People say, 'We'll turn it around faster. We're efficient. We know how to get you to your deadlines.'"

The Pharmaceutical Research and Manufacturers of America, a Washington-based trade association and lobbying group, says human drug tests in the U.S. are safe and well monitored. "The vast majority of clinical trials conducted in the United States meet high ethical standards," PhRMA, as the group is known, said in a written response to questions. "The U.S. regulatory system is the world's gold standard, and the Food and Drug Administration has the best product safety record."

Joanne Rhoads, the physician who directs the FDA's Division of Scientific Investigations, says that view isn't realistic. "What the FDA regulations require is not any gold standard for trials," Rhoads, 55, says. The agency doesn't have enough staff to aggressively monitor trials, she says, adding that FDA regulations are a bare minimum and much more oversight is needed. "You cannot rely on the inspection process to get quality into the system," Rhoads says. "I know many people find this not OK, but that's just the truth."

Michael Hensley, a pediatrician who was an FDA investigator from 1977 to '82, says the agency has become less active in clinical trial oversight in recent years. Families of injured or dead trial participants seeking accountability for mistakes have to file lawsuits. "The FDA's backbone has been Jell-O," says Hensley, 60, who's now president of Chapel Hill, North Carolina-based Hensley & Pilc Inc., which advises pharmaceutical companies on FDA compliance. "The folks at the FDA stopped enforcing the rules several years ago."

By law, drug companies must first conduct tests to determine whether potential drugs produce dangerous side effects, such as organ damage, impaired vision or difficulty breathing. The FDA calls them phase I tests. In 1991, 80 percent of industry-sponsored drug trials were conducted by medical faculty at universities, with protection for participants provided by the school's own oversight boards, according to the New England Journal of Medicine. Now, more than 75 percent of all clinical trials paid for by pharmaceutical companies are done in private test centers or doctors' offices, according to CenterWatch.

Some test centers, FDA records show, have used poorly trained and unlicensed clinicians to give participants experimental drugs. The centers—there are about 15,000 in the U.S.—sometimes have incomplete or illegible records. In Cal-

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ifornia and Texas, clinicians have used themselves, staff or family members as drug trial participants.

"Unfortunately, I don't think it's been recognized how important it is that people who actually conduct the trial be trained," Rhoads says. "We oftentimes see people with no qualifications whatsoever, but they'll go to a one-day training course and they call themselves a certified study coordinator." These people often run 90 percent of the study with little involvement by physicians, she says.

Participants in Miami clinical trials talk openly about how they violate SFBC rules intended to protect the integrity of research findings. SFBC prohibits people from taking part in two clinical trials at the same time.

Roberto Alvarez, 36, an Argentine in the U.S. on a visa; Efrain Sosa, 35, a Cuban native; and Marlon Matos, a 27-year-old immigrant from Venezuela, say they've participated in more than one clinical trial in Miami at the same time or gone from one test to another, ignoring required waiting periods. They say they do it for the money, without telling the test centers, and that no one has ever caught them violating the rule.

"We maintain many safeguards to help us ensure that the participants of our clinical trials are not participating simultaneously in multiple clinical trials," SFBC's Hantman says. SFBC fingerprints participants to keep track of their tests at the company, he says. "Unfortunately, there is no clearing house that we're aware of that would allow us to find if they were participating in another trial at the same time," he says.

In April, Alvarez signed up for a 36-day clinical trial at Miami testing company Elite Research Institute for a new sustained-release form of donepezil, an Alzheimer's drug that Tokyo-based Eisai Co. sells in the U.S. with New York-based Pfizer. At the time, Alvarez was in the middle of a 212-day test sponsored by Madison, New Jersey-based Wyeth at SFBC for an experimental muscular dystrophy drug, according to consent forms he signed. "I hop around to get around that," says Alvarez, a part-time construction worker who's wearing a black T-shirt and jeans when he's interviewed in a bagel shop two doors down from SFBC. "They ask, but I just don't tell them. Everybody does that."

Steve Simon, a research biostatistician at Children's Mercy Hospital in Kansas City, Missouri, says that when people participate in more than one clinical trial at a time, it can be harmful to people and research. "When neither researcher knows about the potential interactions with the other trial, that raises concerns about scientific validity," says Simon, who has a Ph.D. in statistical research. "You don't know how these things might interact. It's asking for trouble."

Garry Polsgrove's Last Battle

Garry Polsgrove received two Purple Hearts for his service as a Marine in Vietnam. Three decades after that war ended, Polsgrove, 55, was homeless and unemployed. In order to have a bed and earn some money, he entered an experimental drug test at the Fabre Research Clinic in Houston in April 2002, says his sister, Nancy Gatlin. He was healthy when he signed on for the medical trial, she says.

Polsgrove enrolled in a clinical trial for clozapine, a schizophrenia medication being tested for Miami-based Ivax Corp., the largest U.S. maker of generic drugs. A day after he took the first dose, Polsgrove's heartbeat became irregular, according to a January 2005 letter to Fabre from the U.S. Food and Drug Administration. A few days later, he developed diarrhea. A clinician misdiagnosed his condition as a virus unrelated to the test, the FDA wrote. A week after that, Polsgrove developed low blood pressure that was never explained, evaluated or treated, according to the FDA. The next day, lab tests showed he had life-threatening kidney failure.

Polsgrove died of myocarditis, or swelling of the heart, 22 days after he enrolled in the trial. The FDA waited until January 2005—nearly three years after Polsgrove's death—before telling Louis Fabre, 64, the clinic's owner, that it would move to shut down his testing center.

Fabre had conducted more than 400 clinical trials involving 20,000 people for at least 50 drug companies since 1973. The FDA found human protection failures in six inspections since 1980. The mistakes at the clinic included enrolling people who weren't qualified to be in medical tests, offering what it called free treatment when it was actually testing unapproved drugs, failing to follow drug company-ordered procedures for tests, keeping illegible notes and not promptly reporting serious side effects.

The institutional review board that

was supposed to protect patients from harm was the Human Investigation Committee in Houston. That IRB received an FDA warning letter in 1992 saying it had conflicts of interest: It was run by Fabre himself. Members include his business partner, psychiatrist Stephen Kramer, and his lawyer, Bruce Stefler.

The FDA also said in a January 2005 letter that the consent form Fabre gave Polsgrove "failed to describe clozapine's risk of fatal myocarditis," the disease that killed Polsgrove. Four months before Polsgrove began the experiment, the FDA required a special warning for clozapine about that risk.

Until April 2005, when Fabre closed his trial center, its Web site said he'd tested drugs for leading pharmaceutical companies, including Abbott Park, Illinois-based Abbott Laboratories; New York-based Bristol-Myers Squibb Co.; and New York-based Pfizer Inc., the world's biggest drugmaker.

The FDA wrote in the January letter that Fabre used unlicensed employees to run the Ivax trial, failed to supervise them and then falsified the circumstances of the death. Polsgrove, who was 5 feet 8 inches tall, with brown hair and blue eyes, spent his final days inside the four-bedroom house that was Fabre's clinic.

"It was no issue with the FDA," Ivax spokesman David Malina says. "I think we have no responsibility for the unfortunate thing that happened to this man." He says the FDA approved its version of clozapine after Polsgrove's death. Fabre, who now runs a drug development company, declined to comment. His lawyer, Douglas Farquhar of Washington, wrote in a letter to the FDA that Fabre did nothing wrong.

"The homeless are the perfect people to put in these trials," says Ron Sellers, pastor of the Impact Houston Church of

Christ, who knew Polsgrove. "Even if they die, it's not likely to be investigated too seriously."

Fabre left Polsgrove in the care of John Rodriguez. In its letter to Fabre, the FDA said Rodriguez "is reported to have had medical school training in Mexico; he is neither licensed nor credentialed in the United States."

Six days before Polsgrove joined the Ivax experiment, Andrea Branche, an FDA inspector, visited Fabre and found that clinic records were illegible. Branche reported that Rodriguez had screened subjects, performed physicals and conducted electrocardiograms. Fabre falsely presented Rodriguez as a licensed physician's assistant, and the inspector believed him.

Kramer, 64, says Fabre's IRB held its meetings in restaurants around Houston. Kramer says he offered Rodriguez tips on caring for Polsgrove. "When that patient had trouble, he called me, and we discussed what to do," says Kramer, who blames Fabre's predicament on bad luck. "It's unusual that the patient died, and it was on his watch, so he's screwed."

Shortly after Polsgrove died, Fabre wrote that Polsgrove's low blood pressure wasn't related to the experiment. "This a.m., patient was awake and well at 7:30," Fabre wrote. "We feel that this is not related to medication." The FDA said Fabre's conclusion was contradicted by the high level of clozapine in Polsgrove's blood. Fabre should have suspected Polsgrove's heart irregularity was clozapine related, stopped giving him the drug and provided appropriate medical care, the FDA wrote.

The agency found Fabre failed to properly protect participants during inspections in 1980, '93 and '99 and twice in 2002, yet it never stopped him from doing any of his trials. Fabre was cited again in March 2005. The confidential FDA process of banning a clinician can take years to complete.

Twenty-five years ago, the FDA found that dozens of pages of records were missing for a Fabre test, and investigators questioned whether all of Fabre's patients existed. "They are there, and if some of the data is missing, the patient is still real," Fabre said, according to the inspection report.

Charles Arledge, 50, participated in several of Fabre's trials during 1974. Arledge, now a Houston carpenter, says he helped his girlfriend, a nurse at the clinic, concoct phony paperwork describing nonexistent patients at the clinic. "If you look at this as science, you're in trouble," Arledge says. "This is science fiction."

In 1992, Upjohn Co., now part of Pfizer, investigated Arledge's allegations, finding that Fabre had enrolled himself and employees in his tests.

After the FDA documented Polsgrove's death, Fabre did experiments on humans for Indianapolis, Indiana-based Eli Lilly & Co. and Madison, New Jersey-based Wyeth. Gerald Burr, Wyeth spokesman, says the company halted its trial with Fabre in January after learning of the FDA's action against him. Wyeth found the January FDA letter to Fabre on the Internet, Burr says.

"Lilly was not aware of the seriousness of the FDA's concern with Dr. Fabre in 2002, nor were we aware of the death of the patient in the clozapine trial until February 2005," Eli Lilly spokesman Phil Belt says. Lilly immediately stopped using Fabre's clinic in February, he says.

Gatlin, 61, first saw the FDA findings on her brother's death in August. She says the FDA should have barred Fabre from running experimental tests years ago. "People like this should be stopped," says Gatlin, a retired postal clerk in St. Louis. "They slapped his little hand and let him go on."

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Ernesto Fuentes, Elite's clinical trial director, didn't return calls for comment. Eisai spokeswoman Judee Shuler says Elite did everything it could to ensure participants in the clinical trial weren't in other tests at the same time, including asking subjects verbally if they were. Pfizer spokesman Stephen Lederer says his company had no role in the donepezil tests.

Gerald Burr, a Wyeth spokesman, says the company carefully planned and monitored the clinical trial. The FDA requires pharmaceutical companies to hire monitors to audit clinical trials to ensure patient safety and scientific validity. "Our sponsors visit our facilities frequently to monitor our trials and also routinely audit our work," SFBC's Hantman says.

Pharmaceutical company monitors spend more time scrutinizing data being gathered than watching out for people's safety, Harvard's Federman says. "There are no monitors of monitors," he says. "It's like looking at a dark cloud. There's minimum training. They're relying on people running the trials."

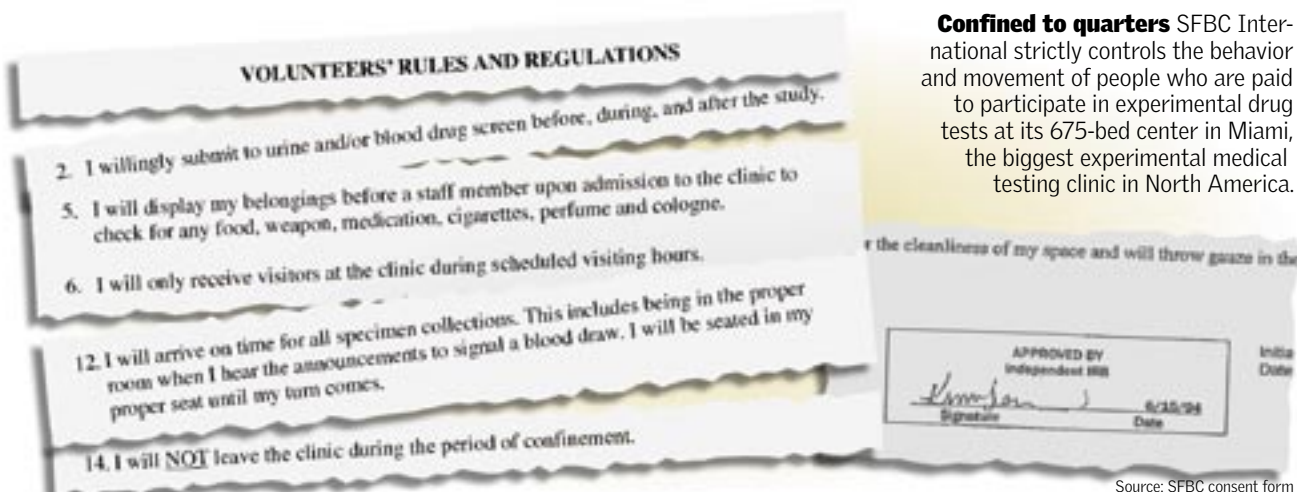
The shortcomings of human drug testing may come to light in the welter of litigation surrounding Vioxx, the blockbuster pain reliever that Whitehouse Station, New Jersey-based Merck pulled off the market last year after its own studies found long-term use posed twice the normal risk of a heart attack. A 2004 study by David Graham, the FDA's associate director for science and medicine, estimated that Vioxx caused as many as 140,000 heart attacks and strokes, killing as many as 55,000 people. On Aug. 19, a Texas jury ordered Merck to pay \$253 million to the widow of a Vioxx user, an amount that will be reduced to \$26 million under state law. The company has been sued by more than 5,000 people who say they were hurt by the drug.

Before Vioxx was approved by the FDA, Merck tested it on thousands of people in early phase I clinical trials across the U.S., including at SFBC's Miami center.

Pharmaceutical companies sponsored 36,839 new clinical trials from 2001 to '04, six times more than in the period from 1981 to '85. The search for the next money-spinning drug is fueling the surge in human testing. Pharmaceutical companies that make 28 top-selling drugs will lose a total of \$50 billion in revenue as their patents expire from 2003 to '08, according to Norwalk, Connecticut-based market research firm BCC Inc. Schering-Plough Corp., for example, suffered a drop in revenue after losing U.S. exclusivity for Claritin, an allergy treatment, in December 2002. The Kenilworth, New Jersey-based company's sales fell 18 percent to \$8.3 billion in 2003 from \$10.2 billion the year before, and the company reported a net loss of \$92 million in 2003 compared with a profit of \$1.97 billion in 2002. Schering-Plough shares averaged \$17.42 in 2003, down from an average price of \$25.99 in 2002.

Schering-Plough has used SFBC for clinical tests, including trials in the past year comparing different forms of Claritin. "We believe that they are at the industry standard, and the appropriate checks and balances are in place," Schering spokeswoman Rosemarie Yancosek says.

As drug companies try to get new drugs to market, time is



Source: SFBC consent form

literally money. They lose as much as \$5 million a day waiting to get approval of new medications, according to CenterWatch. Eighty percent of all experimental drugs tested in humans are never approved by the FDA.

Big Pharma has an insatiable demand for people to be in clinical trials, says Marcia Angell, a doctor who was editor in chief of the *New England Journal of Medicine* from 1999 to

2000. "Human subjects are in very short supply, so it's not surprising that under the growing pressure to find them, there are sometimes terrible ethical violations," says Angell, 66, a Harvard Medical School senior lecturer. "Drug companies may claim innocence, but they need to take responsibility."

In 1978, the National Commission for the Protection of Human Research Subjects, an advisory committee appointed

A Matter of Trust

By the time Bill Hamlet dropped out of a clinical trial of Genentech Inc.'s Raptiva in December 2000, the 58-year-old artist and woodcarver could barely walk or stand. Thick red scabs from a severe outbreak of psoriasis covered his legs, back and torso. Blood stained his sheets and clothing.

Before entering the study, Hamlet says he was in good health. He took the medication methotrexate to control psoriasis and a mild case of psoriatic arthritis, a condition causing inflammation of the skin and joints. In his half year in the trial, Hamlet was first given a placebo, a substance with no active medicine, and then an experimental drug. He says that when he consented to join the test, no one told him his psoriatic arthritis could worsen if he got a placebo.

Hamlet, who lives on 19 wooded

acres in Pittsboro, North Carolina, enrolled in the test, sponsored by South San Francisco, California-based Genentech, at his doctor's suggestion in July

2000. His doctor, Mark Fradin, 45, was the physician running the trial in nearby Chapel Hill. Hamlet says Fradin, a dermatologist, told him the experimental drug was promising and offered fewer side effects than methotrexate. He says he trusted Fradin and signed a consent form. "I always thought he was my buddy," Hamlet says.

In order to begin the Genentech test, Hamlet had to stop taking methotrexate. Within weeks of discontinuing the successful treatment, Hamlet's skin irritation flared up worse than it ever had, he says. "You see how horrible it was," Hamlet says, flipping through a blue binder filled with photographs that chronicle his transformation from robust health to constant pain.

Within a week of beginning the test

with a placebo and 72 days after stopping methotrexate, Hamlet's arms, trunk and legs were covered with scabs and "large encrustations," according to a lawsuit he filed against Genentech, Fradin and Western Institutional Review Board, which was hired by Genentech to ensure that risks didn't exceed benefits.

Genentech and WIRB paid Hamlet an undisclosed amount this year to settle the lawsuit, which was filed in Orange County Superior Court in North Carolina. The defendants neither admitted nor denied wrongdoing. "We reached a confidential settlement, and it's not our policy to comment on the details of a lawsuit," Genentech spokeswoman Tara Cooper says.

Fradin said in a deposition in July 2004 that he didn't know whether Hamlet would be given Raptiva or a placebo during the trial. Fradin said he might have advised Hamlet not to enter the trial if he had known Hamlet might be given a placebo. "If I had known that he would not get any active drug and if

by President Richard Nixon, recommended, in what became known as the Belmont Report, that clinical trial participants be fully informed of risks and sign a consent form. So-called informed consent wasn't required by the FDA until 1981.

Interviews with people in clinical trials and relatives of participants who died in medical experiments across the U.S. suggests that researchers often don't fully explain risks and potential side effects. Bowen, whose Western IRB has overseen trials at SFBC sites, says phase I centers often don't conduct the informed consent process properly. "I'd say it's fairly widespread," she says. "It's a genuine social problem that needs to be dealt with."

Alvarez, the clinical trial participant from Argentina, says he skimmed over the 12-page consent form for a test SFBC managed for KW-6002, an experimental Parkinson's disease drug made by Tokyo-based Kyowa Hakko Kogyo Co., before signing the form on Aug. 30. "The thing I pay most attention to when filling this thing out is this," says Alvarez, flipping through the form, written in Spanish, to a page that describes payment terms. "How much it pays and how long it takes. I don't read them too carefully."

Page eight of the consent form explains that the 57-day test Alvarez has signed up for pays \$4,300, spread out in payments

tied to completion of three 8-night "confinements." During confinements, participants aren't allowed to leave the SFBC building unless they decide to drop out of the trial. They live in 12-foot (3.66-meter) by 24-foot rooms outfitted with three double-decker beds. The center has recreation rooms with televisions, pool tables and video games. The payment schedule provides an incentive for participants to stay the course: About half of the money, or \$2,355, isn't paid until the last week of the eight-week test. The trial, which was scheduled to end on Nov. 2, also includes 12 outpatient visits to test for levels of KW-6002 in subjects' bloodstream.

The consent form says KW-6002 can produce side effects that include heart palpitations, sleep disorders and breathing difficulties. An SFBC employee asked if Alvarez had read the consent form and understood what the test entailed when he signed up, Alvarez says. He told the clinician he had read the form, and the clinician didn't say anything more about risks, he says.

SFBC Executive Medical Director Kenneth Lasseter says the center always explains risks to participants. "We have a whole team of people," he says. "They go over the risks and discomforts and explain them to the subject." Lasseter says he's never before heard that participants said they weren't fully

I had known that he would have a significant flare-up, then I might have counseled him not to do it," Fradin said.

Fradin didn't return calls seeking comment. His lawyer, William Daniell, says Fradin settled Hamlet's suit without paying damages. "He feels the care he provided was entirely appropriate," Daniell says.

WIRB President Angela Bowen says she doesn't think her IRB did anything wrong. "Nor do I think the physician did anything wrong with Hamlet," Bowen says.

Arthur Caplan, director of the Center of Bioethics at the University of Pennsylvania says such explanations make no sense. "It's outrageous to take any patient for whom a therapy is working well and, without that person's full, complete and indisputable knowledge, stick them into a placebo-controlled trial," he says. "The core principle of medical ethics is 'First, do no harm.'"

Within a month of starting the drug experiment, Hamlet developed symptoms of arthritis, medical records show. By December 2000, his condi-

tion was so extreme he needed a cane to walk. During the next six months, Hamlet saw Fradin at least 12 times, according to the suit. Fradin and WIRB never advised him to leave the trial, Hamlet says.

Although Hamlet grew increasingly ill during the trial, he didn't drop out, convinced he was on a placebo and believing he would eventually get Raptiva instead. Hamlet, who had the right to leave the trial at any time, says he suspected he was getting a placebo three weeks into the trial. Because the rules of the trial prohibited clinicians from knowing who got placebos, Hamlet had no way to know if he did. He confirmed his suspicion when he saw his records more than two years later, after filing the lawsuit.

By October 2000, Hamlet was switched from a placebo to the experimental drug, and the psoriasis slowly improved. His arthritis, though, grew worse, his medical records show.

The FDA approved Raptiva for treatment of plaque psoriasis in Octo-

ber 2003. The medication doesn't work to control the arthritic symptoms that were associated with Hamlet's disease, psoriatic arthritis, Genentech said in a March 2004 news release.

Greg Koski, a physician and former head of the federal Office for Human Research Protection, which protects people in federally funded clinical trials, says patients who are being successfully treated shouldn't be taken off medication to try an experimental drug or placebo.

Hamlet's case should be a lesson to the clinical trial community, Koski says. "It's an example of how the system can really fall apart and result in harm to individuals," he says.

On Dec. 21, 2000, Hamlet received his last injection in the trial. He dropped out a week before the trial ended. "I felt like a guinea pig," Hamlet says. "I would say that I got zero medical care during the study. I became the person to observe, not to treat."

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informed of risks in tests. "Everyone who is screened has a one-on-one interview with one of the screening team that goes over the informed consent," he says. "If they are denying that, that's simply a fabrication. They simply are not being truthful."

Informed consent documents routinely fail to explain



'He trusted the system that ultimately failed him,' the daughter of a doctor who died during a clinical trial says.

risks to potential participants, says Laura Dunn, a professor of psychiatry at the University of California, San Diego, who wrote an article on informed consent that appeared this year in the *Journal of the American Medical Association*. "Decades of research show that poor understanding of informed consent documents is widespread," she says.

The title of the KW-6002 consent form says the test is a phase I clinical trial. The document doesn't explain what phase I means, that the purpose is to determine the side effects and safety of an experimental drug. The test, the consent

form says, aims to determine how the active ingredient in KW-6002, istradefylline, is "absorbed, distributed, decomposed and eliminated from the body." Joseph Brindisi, a spokesman for Kyowa's U.S. unit, declined to comment.

It's inevitable that tests that often make healthy people sick rely on the poor, says Greg Koski, who from 2000 to '02, was head of the federal Office for Human Research Protection. A division of the Department of Health and Human Services, the office oversees all federally funded clinical trials; it doesn't review pharmaceutical company-sponsored tests in private centers. "I have little doubt that there is a disproportionate burden of risk that falls on the disadvantaged members of our society," says Koski, 55, who's now a radiologist in Boston.

SFBC Executive Vice President Greg Holmes says money is the main reason people sign up for phase I tests. "Look at the benefits," he says. "There is little benefit other than getting paid. There's no secret there."

SFBC conducted a test in June of a drug that may treat overactive bladders. The test was sponsored by Theravance Inc., a South San Francisco, California-based company that's 21 percent owned by GlaxoSmithKline. The London-based company, the largest drugmaker in Europe, has marketing rights for new Theravance drugs, according to filings with the SEC. "The goal

Death of a Doctor

Scott Scheer wasn't worried about side effects when he agreed to enroll in a federally funded test of different combinations of previously approved blood pressure medications in 1997. At age 57, the radiologist wanted to help medical science, and he assured his wife, Beverly, that some of the best physicians in the Philadelphia suburbs were overseeing the five-year study. "He completely trusted them," Beverly Scheer says.

The consent form Scheer signed before starting the trial at Lankenau Hospital in Wynnewood, Pennsylvania, gave no reason for concern. "Most people who take these drugs do not have any side effects at all," the document said.

Scheer told the hospital his health was "very good," giving it a rating of 90, with 100 the highest, before the

drug trial. He had been taking medication for high blood pressure before the trial and was asked to stop so he could enter the study. He suffered side effects including muscle aches and swollen ankles in the first five months of the trial, medical records show. By July 2001, four years after he entered the trial, Scheer was dead.

In the days before his death, Scheer's family grew alarmed by bruising on his arms, a rash on his feet and overall exhaustion. On July 9, 2001, six days before he died, Scheer visited a hematologist outside Lankenau Hospital. Dr. Edward Stadtmayer diagnosed Scheer with kidney failure and severe anemia that he said was probably caused by hydralazine, one of the drugs in the test.

"Scheer most likely has hydralazine-induced systemic lupus," Stadtmayer,

who met Scheer for the first and only time during that exam, wrote in his patient report. "Drug-induced lupus is a common side effect of hydralazine, occurring in up to 70 percent of patients eventually."

Stadtmayer says he suggested he stop taking hydralazine and tell the nurse in the study.

In a wrongful death lawsuit filed in state court in Philadelphia, Scheer's family says he died as a result of improper monitoring during the clinical trial. The family sued Lankenau Hospital, Drs. James Burke and Michael Duzy and the Main Line Hospitals Institutional Review Board. The suit is pending. Frieda Schmidt, a spokeswoman for Main Line Health, which includes Lankenau Hospital, says she can't comment because of the litigation. George Reichard, chairman of the Main Line Hospitals IRB, which oversees clinical trials at Lankenau, didn't return calls.

The study set out to test different types of drugs used to treat high blood pressure and high cholesterol and

of this study is to determine the highest daily dose of TD-6301 that will not cause an undesired increase in heart rate," the consent form says.

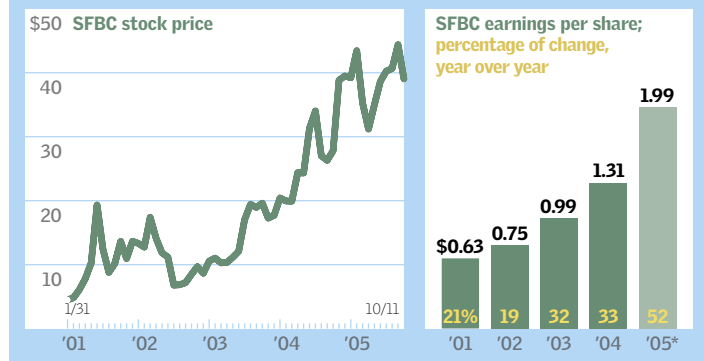
University of Miami bioethicist Goodman says the wording is misleading and confusing. "They're saying it backwards to a population that may not be of the highest education level," he says. The only way to accomplish the intent of the study is to raise the dosage of the experimental drug until heart rates increase, Goodman says. "The real purpose of the study is, 'We're going to make you sick in order to find out at what level you get sick when given this drug,'" Goodman says. "Obviously, they don't want to say that."

SFBC's Lasseter says the wording in that consent could be better. "It's clear to me," he says. "Perhaps it needs to be explained more."

GlaxoSmithKline spokesman Rick Koenig says his company wasn't involved in the clinical trials. He adds that Glaxo-SmithKline has the right, but not the obligation, to develop the Theravance drugs. Theravance spokesman David Brinkley says his company policy is not to comment on specific clinical trials.

Cabanerio, the Venezuelan immigrant, says he reads consent forms and questions doctors and clerks at SFBC closely

Profitable tests SFBC International, based in Miami, has increased earnings by an average of 31 percent a year since 2001.



*Estimate. Sources: Bloomberg, First Call

to weigh the risks against his need for cash for his family. In July, he says, he needed the money so badly he was willing to enroll in a test that could have had fatal results. Cabanerio signed up for a trial that mixed alcohol with an experimental opiate pain reliever called Oros Hydromorphone, made by Alza Corp., a unit of New Brunswick, New Jersey-based Johnson & Johnson. The test paid \$1,800.

Participants who chew Oros tablets, as opposed to swallowing them whole as directed, can overdose, which can cause a heart attack or death, a June 21 consent form in Spanish for

compare them with the benefits of Pfizer Inc.'s Norvasc and other, generic medications. Additional drugs were added if a patient's hypertension wasn't successfully controlled.

The consent form said participants would be asked to see doctors at least every three months during the first year of the study and every four months in subsequent years. Scheer's family says his medical records show that Scheer had almost no care from the hospital and that he wasn't asked to come into the hospital every three to four months. Phone interviews and postcard questionnaires replaced in-person visits, says his older daughter, Kirsten Scheer Bauer, 39. On at least six occasions, a nurse sent drugs to Scheer's home via Federal Express, Bauer says.

For the four years Scheer was in the test, side effects he described were included on his chart at Lankenau Hospital; none were treated by doctors overseeing the trial, his family says. The hospital conducted its own probe after the death and concluded the consent form Scheer had

signed was inadequate. The hospital also found that the doctors running the study, Burke and Duzy, failed to notify the hospital and oversight groups of Scheer's side effects as required by study rules and federal regulations. Burke and Duzy didn't return phone calls seeking comment.

Sometime from July 10 to 13, 2001, Burke learned that Scheer had been diagnosed with severe anemia and kidney failure on July 5, according to minutes of the Main Line Hospitals Office of Regulatory Affairs' Allegations Committee. That group was formed in response to a complaint from Bauer. She also went to the federal Office for Human Research Protection, part of the Department of Health and Human Services. The office had authority to investigate because the study was federally funded.

OHRP investigators found that the hospital had failed to adequately protect Scheer and other patients in the study. "Your father apparently was not told about the risk of hydralazine-induced lupus," says an OHRP letter to Bauer dated Dec. 20, 2002. The office also said the hospital's protection of participants in

the study fell short. "OHRP found that certain unanticipated problems involving risks to subjects or others were not promptly reported to appropriate institutional officials," the letter says.

Bauer says she had to fight to retrieve Scheer's records from the hospital. No one running the test called to follow up after the family called to report Scheer's death, she says. "He trusted the system that ultimately failed him," says Laura Scheer Brooks, 38, Scheer's younger daughter.

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the test says. People also can have allergic reactions to Oros, which, if severe, can be fatal, the form says. "It's not the job I would choose, but financial circumstances require you to do it sometimes," Cabanerio says.

The doctors who examined Cabanerio during the screening process for tests at SFBC asked him to recite a couple of side effects listed on the test's consent form to see if he understood the risks, he says. While being screened for the Oros test, Cabanerio says, a doctor told him there were few risks involved. "He said the strongest reaction would be like a shot of whiskey," Cabanerio says. "He said it would be fun."

The test included four 3-night stays in which some patients were given Oros and up to 40 percent alcohol mixed with orange juice on an empty stomach, according to the 14-page consent form. After Cabanerio and 18 other people began the test on the fourth floor of SFBC's center, one woman fainted, Cabanerio says. Another woman in the test got so drunk after drinking the brew that she began imitating a strip-tease dancer. Cabanerio says he didn't feel bad because he was in a different group of participants that received lower doses of alcohol and were allowed to eat beforehand.

Cabanerio participated in the test in July. That's the same month the FDA asked Purdue Pharma LP, a Stamford, Con-

necticut-based drug company, to withdraw another opiate tested with alcohol at SFBC's Miami center. Purdue withdrew the drug, Palladone, because its time-release mechanism is dissolved by alcohol, which could cause a deadly release of all the opiates at once, according to the FDA. Participants were given naltrexone to block the opiates.

Alza ensures tests of its drugs are safe for participants by following FDA rules and guidelines approved by IRBs, company spokesman Ernie Knewitz says. "Patient safety is the most important element in each clinical study conducted by Alza," Knewitz says.

The Purdue experiment paid volunteers \$2.78 an hour, or \$66.72 per 24-hour day, for the first nine days of confinement. For those who remained, payment jumped to \$333.33 a day for the final three days, with a bonus of \$800 paid following a single follow-up visit.

Such payment backloading is coercive and thus unethical, says Peter Lurie, a physician who is deputy medical director of Public Citizen, a Washington-based group that monitors patient safety issues. "It provides a very powerful incentive for somebody to continue in a study even if they're being made uncomfortable by it," he says.

Purdue's payment schedule complies with guidelines set

The Youngest Victims

Hours before 5-month-old Michael Daddio underwent surgery for a congenital heart defect in November 2001, his parents, Robert and Tracie, got some unexpected news. Instead of the operation the doctors had prepared them for—one they say they were told would have a 90–95 percent success rate—Michael was going to undergo a different procedure. The doctors said the surgery would make his treatment safer and his recovery less painful down the road.

Michael died of heart failure in July 2003, six weeks after his second birthday. His parents didn't find out until after his death that Michael had undergone experimental surgery aimed at preparing him to receive an unapproved medical device.

The couple filed a wrongful death and negligence lawsuit in U.S. District Court in Philadelphia in February. The Daddios allege in their suit that doctors at Alfred I. duPont Hospital for Children in Wilmington, Delaware, ignored federal

regulations requiring that experimentation on humans be approved by the hospital's institutional review board. In surgical experiments, as in testing for new drugs, the U.S. Food and Drug Administration requires that participants or parents be fully informed by doctors of risks and sign consent forms.

The Daddios say in the suit that doctors bypassed the informed consent process entirely. They are among 13 families suing Dr. William Norwood, duPont Hospital and its Nemours Cardiac Center. Seven children died after the experimental surgery, according to civil suits filed by Philadelphia attorney Theresa Blanco.

"There was no institutional review board approval sought or obtained," the suit says. The federal government requires IRBs, which can be private companies or hospital groups, to oversee medical experiments to protect participants.

Tracie Daddio, 36, who does public

relations for a construction company, says she still can't take down Michael's crib or remove his toys from the nursery in her Magnolia, Delaware, home. "To think that something could have possibly been done in a different way and that he could be here today is hard to accept," she says.

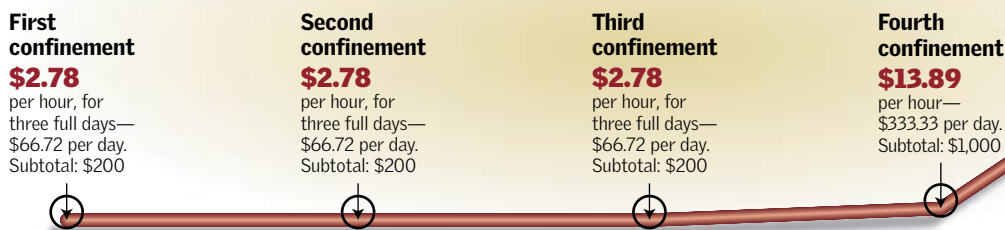
Michael's condition came as a shock to the Daddios because their daughter, Tara, 7, is perfectly healthy. Shortly after Michael was born, doctors told the couple that their son suffered from hypoplastic left heart syndrome, a congenital heart condition affecting one in 5,000 babies. The left side of the heart is underdeveloped and too small to pump blood as needed. Correcting it with customary techniques would require three surgeries. The first stage is known as the Norwood Procedure, named for Michael's doctor, who pioneered the method in 1979.

The Daddios were at first glad that

Endurance test Participants have to stay in drug tests to receive full payment. In Purdue Pharma's trial of pain killer Palladone at SFBC International, participants earn less than Florida's \$6.15 hourly minimum wage in the early stages; 75 percent of the \$2,400 total pay comes after the fourth confinement and the follow-up visit.

Purdue Pharma's Palladone test pay scale (total pay: \$2,400)

Day 53
\$200
per hour,
for four hours.
Subtotal: \$800



Source: Informed consent form from clinical trial at SFBC International, dated April 4, 2005

by the FDA and international regulators, company spokesman James Heins says. He says any experiment dropouts willing to return for the follow-up visit were paid \$800. Heins says anyone who dropped out in the middle of a confinement period without a health reason was considered “noncompliant” and was paid \$25 a day.

Under federal regulations, anyone can drop out of a clinical trial at any time. University of Pennsylvania bioethicist Caplan says it's often not easy to voluntarily leave a test. He says he enrolled himself in a trial in which a clinician inserted a tube down his throat. Caplan says after the procedure started, he told a nurse: “You know, I don't like this. I don't

want to do it anymore.” He says the nurse told him: “You can't do that. You can't stop!” He completed the procedure.

Wyeth sponsored trials at SFBC this year to find out what dosages of an experimental drug to treat muscular dystrophy caused side effects, according to the consent form for the trial. Possible side effects included severe allergic reactions that can cause breathing difficulty, abdominal pain, increased heart rate and death, according to the consent form. Healthy people were paid \$5,500 for staying in the center for 15 nights during a 26-week test. Another version of the test with a 29-night stay in the center paid \$6,900.

John Juarez, who was born in Miami, says the injections

Michael was in the hands of the top specialist in the field. “We totally trusted him,” says Robert Daddio, 37, a Delaware state trooper.

DuPont Hospital and its IRB determined in its own investigation that its doctors had failed to inform the families that their children would get experimental surgery, and the families hadn't signed consent forms, according a report by hospital investigators. The hospital fired Norwood in February 2004. Norwood filed a wrongful termination lawsuit. His lawyer, Victor Battaglia, wrote in the suit against the hospital, “No reason for terminating Norwood existed or was provided.” Norwood and Sara Petrosky, his attorney in lawsuits against him, didn't return calls.

The Daddios say the consent form they signed for Michael's second surgery in 2001 called it an established procedure. “We weren't told it was experimental, and we were never given any facts, any choices

or options,” Tracie Daddio says.

From the time of Michael's second surgery until his death, he suffered complications and spent months in the hospital. When at home, he was often hooked up to an iron lung, a machine that enabled him to breathe.

“Something in my stomach told me something was wrong because, after the surgery, his health just kept going downhill,” Robert Daddio says. “We kept hearing there was a 90–95 percent success rate, that Michael was just going through some rough times, and he'd be fine.”

James Hildebrand, director of clinical research services at Nemours's Department of Biomedical Research, says Norwood should have known better. “The only explanation I can see is poor judgment,” Hildebrand says. “You are world renowned. You have a procedure named after you. You should know the difference between research and practice.”

Mona Barmash, a Pennsylvania mother

who heads the Congenital Heart Information Network, says the case has raised awareness of the meaning of informed consent. All the families were told their children would undergo approved surgery with a high success rate, and none were told their children were participating in experiments, she says. “People were presented with papers in some cases after their kid is wheeled away to surgery, and that's no way to obtain informed consent,” Barmash says.

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of Wyeth's experimental drug felt like a burning electric shock searing his body from within. "It made me feel really weird," says Juarez, 22. In the last few weeks of testing, Juarez developed red hives up and down one arm that wouldn't go away for days, he says. And he started growing hair all over his body, including thick sideburns that he still wears.

Wyeth has documented that an IRB approved the trial, consent was handled properly and the test followed all FDA rules, Wyeth spokesman Burr says. "Wyeth is committed to sponsoring and supporting carefully conducted clinical trials as the fastest and safest way to find treatments that work in people and ways to improve health," he says.

The FDA depends on IRBs to approve and review trials. For drug tests conducted at SFBC in Miami, AstraZeneca, Merck and Purdue have used Southern IRB, the review board owned by Alison Shamblen, the wife of SFBC Vice President Cooper Shamblen.

Purdue, whose Palladone tests were monitored by Southern IRB, didn't know Southern was owned by a relative of an SFBC executive, Heins says. "If Purdue had been aware of the relationship you allege, the company would have looked into the issue before conducting trials at the site," Heins says. "Purdue will address this issue should we decide to work with SFBC in the future."

Merck, which has relied on Southern IRB to monitor tests at SFBC, including an April experiment for a drug to prevent nausea and vomiting, says the company wasn't responsible for using an IRB owned by a relative of an SFBC executive. Merck chose SFBC because for years it had worked with Clinical Pharmacology Associates, which SFBC bought in 2003, Merck spokeswoman Janet Skidmore says. "SFBC selects which institutional review board is most appropriate," she says. "Merck did not choose Southern IRB; SFBC did."

SFBC's Hantman says Alison Shamblen hasn't been affiliated with Southern IRB since early 2005. Rosa Fraga, Southern IRB's chairwoman, says Shamblen still owned the IRB as of Oct. 10. Fraga says Alison Shamblen decided in October to shut Southern IRB after 16 years. Fraga herself will soon open a new company called Southern IRB Services, she says.

The FDA has found "significant objectionable conditions" during three inspections of SFBC since 2000. In 2002, the FDA found SFBC conducted invasive procedures on people without getting proper consent from the participants. In March 2005, the FDA wrote up a significant objectionable conditions finding it hasn't yet made public.

SFBC's Hantman declined to release the report. "We have consistently received positive feedback from the FDA's reviews," he says. SFBC's Lasseter describes the FDA reports as being "like a traffic ticket."

SFBC Chairwoman Krinsky says the company hasn't received a warning letter, which is more serious than a significant objectionable conditions citation, from the FDA in more than 20 years. She says the company has addressed all observations by the agency.

The Human Testing Mill

Roberto Alvarez has just finished eight nights of being confined in the largest center for clinical drug trials in North America, and he's happy to get out.

Alvarez, 36, is being paid \$4,300 to be in a 57-day test of an experimental Parkinson's disease medication, and it's the first time he's been allowed outside SFBC International Inc.'s center in Miami. The building, five stories high and peach colored, is located next to the \$62-a-night Sun 'n Surf motel and a strip club advertising "Full Nudity."

"It can be weird inside, like a jail," says Alvarez, a part-time construction worker from Argentina. He says he goes to SFBC for the money.

One mid-September morning, a squeaky metal side door opens onto a noisy waiting room, where more than a hundred mostly Spanish-speaking volunteers go every weekday to sign up for experimental drug tests that pay as little as \$25 a day and as much as \$6,900 for seven months. People line up at a window as a clerk, also speaking in Spanish, describes tests, emphasizing how much they pay.

"*Aqui hay un estudio que paga \$2,000,*" the clerk says to one man, referring to a test for an experimental schizophrenia medicine. "Here's a study that pays \$2,000."

SFBC Chief Executive Officer Arnold Hantman says

SFBC makes sure people understand tests in which they enroll. Participants are "sequestered" in some trials to ensure they aren't exposed to anything that could affect the validity of data, he says. "We take very seriously compliance with the law and all ethical guidelines," he says.

SFBC has thrived on the \$14 billion pharmaceutical companies spend annually on drug trials. SFBC has sites in the Americas, Europe, Asia and Australia. The company, which was founded in 1984 and went public in 2000, has boosted profit at least 45 percent a year since 2001.

At SFBC's Miami center, people wait to be called by a man who watches them sign documents describing tests. Others sit in a hallway, ready to be examined by a doctor. In a nearby bathroom, an open trash can is stuffed with blood-stained adhesive bandages, the kind used after samples are drawn.

In the center, participants sleep six to a room in double-decker beds. Hantman says SFBC typically occupies 35 percent of the 675 beds in the Miami center. In April 2004, Hantman told investors, "We can use all of the capacity." SFBC tells the Miami County Building Authority the maximum number of participants is 350.

"You get inside and see the density of the people shopping for studies based on convenience and

payments," says University of Miami bioethicist Ken Goodman, 50, who spent 90 minutes in SFBC's waiting rooms in June. "The line between compensation and coercion is a very fine line."

Participants are required to wear purple drawstring pants and T-shirts. Signs in the waiting room ban make-up, face creams and nail clippers. Anyone who shows up late is fined \$20.

Some people try to make extra money by getting around rules banning participation in more than one test at a time. On Jan. 31, Alvarez signed up for a 212-day test for Wyeth's MYO-029, an experimental drug to treat muscular dystrophy.

On April 24, while he says he was enrolled in the trial at

SFBC, Alvarez began another test, at Elite Research Institute in Miami. Tokyo-based Eisai Co. was testing a sustained-release form of Alzheimer's drug donepezil, which it markets in the U.S. with Pfizer Inc. The 36-day test paid \$2,125, according to the 10-page consent form Alvarez signed.

"You get kind of desperate when you're not in a study and start calling around," Alvarez says. "You look at the calendar and figure it out. When you overlap, you find out how to do one at another clinic. It's hard to stop."

Ernesto Fuentes, the doctor who oversaw the test at Elite Research, didn't respond to three phone requests for comment. Eisai spokeswoman Judee Shuler says Elite did all it could to ensure participants in the trials weren't in other tests at the same time, including asking them verbally. Eisai and Elite expect volunteers to be honest, Shuler says. It's almost impossible to detect someone in simultaneous trials if the participant hides the fact, Hantman says.

Marlon Matos, 27, who has been testing drugs since January, has flouted the rules by using phony documents and by enrolling in trials in quick succession, without telling the test centers. On Feb. 2, he went to Miami Research Associates and let a doctor thread a tube known as an endoscope down his throat. His pay: \$50.

That exam was the beginning of a 73-day outpatient test of rifalazil, an antibiotic that Lexington, Massachusetts-based

ActivBiotics Inc. developed to treat the bacteria that causes ulcers, according to a 13-page consent form Matos signed on Jan. 25. Total pay for the test was \$200.

Within a week, Matos needed cash to send to his 6-year-old daughter in Venezuela, so he looked for more tests. He says he went to SFBC to sign up for Wyeth's muscular dystrophy trial and abandoned the daily pill-taking regiment at the Miami Research test. The new test's payout was \$6,900. Matos says he signed the consent form and showed an SFBC clerk his Florida driver's license and a photocopy of a forged Social Security card.

"That's not good," says Joanne Rhoads, the physician who directs the FDA's Division of Scientific Investigations. "Unfortunately, we have no way of knowing who's a professional guinea pig. There's no database to see who's been in another trial."

SFBC Chairwoman Lisa Krinsky says SFBC does all it can to prevent participants from breaking rules and has removed people from tests when they do.

Wyeth spokesman Gerald Burr says the Madison, New Jersey-based company is monitoring the SFBC tests and is confident the center is following correct procedures. "Our clinical monitoring is providing assurance of patient safety," he says.

Greg Koski, a doctor who ran the Office of Human Research Protection at the Department of Health and Human Services from 2000 to '02,

says the integrity of a study is harmed when someone participates in multiple clinical trials in quick succession. Researchers don't know how the different chemicals interact or what side effects the mix may have on a person. "It's a serious concern with respect to the validity of research," Koski says. "That could severely undermine the value of the research as well as result in harm to the participants."

MICHAEL SMITH and DAVID EVANS

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Para Investigacion
Clinica**

**Hombres y Mujeres
Saludables
Edades 18 a 85
Mujeres
Posmenopausicas
Edades 18 a 60**

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completa el estudio
usted sera compen-
sada/o con hasta
\$4500.00
Por su tiempo
como corresponde**

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SFBC International
al 305-895-0234 or
305-247-4441
Entre 7AM-5PM**

Testers wanted This SFBC ad seeks healthy volunteers in Miami.

Digitally re-created by Bloomberg. Source: *Miami Herald*

The phrase *institutional review board* dates back to the time when most boards—like the clinicians they monitored—were part of universities or hospitals. Today, the review industry is dominated by a handful of large, for-profit companies with enormous power. IRBs have the duty to reject or stop a clinical trial if the risks are found to outweigh the benefits. Nobody knows for sure how often trials are stopped since there is no central database that tracks IRB actions.

An institutional review board that has monitored SFBC tests is owned by the wife of SFBC's vice president of clinical operations.



The exact number of IRBs is also a mystery. There are an estimated 3,000–5,000 of them, according to the Government Accountability Office, the investigative arm of Congress. The number is unknown because the companies don't have to register with the FDA. IRB members don't have to be trained or certified.

FDA oversight of IRBs is scarce—and becoming scarcer. The agency conducted 175 inspections of IRBs in the year ended on Sept. 30, down from 327 in the year ended on Sept. 30, 2002, according to FDA records. When the FDA conducts an inspection, it reviews informed consent documents and checks that an IRB has at least one person with a scientific background, one layperson and one community member. The agency reviews the IRB's record keeping to see whether it has maintained proper minutes of meetings. "The regulations for IRBs are fairly loose," the FDA's Rhoads says.

The inadequacy of the IRB system is illustrated by the case of Louis Fabre, the Houston psychiatrist who ran at least 400 clinical trials with 20,000 people for more than 50 drug companies at his Fabre Research Clinic from 1973 to 2005. To monitor those trials, Fabre, 64, used an IRB that he had founded himself. He called it the Human Investigation Committee, and its members included his business partner, psychiatrist Stephen Kramer, 64, and his lawyer, Bruce Steffler, 60.

The Human Investigation Committee allowed Fabre Research Clinic to run tests even as FDA inspectors found conduct that put people at unnecessary risk during six inspections from 1980 to 2005. In 1980, the FDA reported that a woman enrolled in one of Fabre's experimental psychiatric drug tests had killed herself during the study. The FDA wrote that the woman was supposed to be in an inpatient study, and Fabre managed the study instead as an outpatient trial. Fabre was never censured for that incident.

In January 2005, the FDA wrote a letter to Fabre detailing his wrongdoing in connection with the death of Garry Polsgrove, an unemployed and homeless Vietnam veteran, in his clinic in May of that year. Polsgrove, 55, died during a trial for generic schizophrenia drug clozapine that was sponsored by Miami-based Ivax Corp., the largest U.S. maker of generic

drugs. (See "Garry Polsgrove's Last Battle," page 42.)

Fabre left Polsgrove in the care of John Rodriguez, who had no medical credentials, according to the FDA. Just six days before Polsgrove enrolled in the experiment, an FDA inspector visited Fabre's clinic and found that Rodriguez had screened subjects, performed physicals and conducted electrocardiograms. The inspector believed Fabre's false claim that Rodriguez was a licensed physician's assistant, Rhoads says. A call to the Texas Board of Medical Examiners would have revealed that Rodriguez was unlicensed. Rhoads says FDA inspectors don't normally verify medical licenses. "On a routine inspection, it's not likely that they're going to dig because it takes a lot of work to do that," Rhoads says. The agency waited almost three years after Polsgrove's death before it moved to ban Fabre from running trials.

Polsgrove was an ex-Marine who had won two Purple Hearts for his service in Vietnam in 1967. Polsgrove's sister, Nancy Gatlin, who says her brother was healthy before starting the drug trial, says Fabre killed her brother. "He should have been stopped a long time ago," she says. Fabre, who now runs a drug development company in Houston, declined to comment. He denied wrongdoing in a response to the FDA.

The FDA can investigate a trial site at any time. Rhoads says when inspectors review a test center, they follow a checklist. "The bottom line is, the inspections by the FDA field investigators are done by people who are trained in investigation, but they don't always have a tremendous scientific or medical background," Rhoads says. "They're basically doing an audit process."

Unable to oversee human drug testing by itself, the FDA has left much of the job to IRBs. Bowen's Western IRB had \$20 million in revenue in 2004. It has grown at about 20 percent a year for the past decade, she says.

Bowen, 73, who used to be president of a drug company called William P. Poythress Inc. in Richmond, Virginia, says Western is the IRB for more than half of all new drug submissions to the FDA.

Bowen says WIRB is the best in the industry because of the professionalism of her members, their training and expertise and their willingness to turn down drug company tests they don't approve. Harvard's Federman sees WIRB differently. "If you listen to themselves talk about themselves, you get a whitewash," he says.

In the 1990s, WIRB oversaw 23 clinical trials conducted by Robert Fiddes, a Los Angeles doctor who was charged with lying to the FDA. The FDA's investigation found that Fiddes repeatedly fabricated data and improperly included employees and family members in trials. He pleaded guilty in 1997 and was sentenced to 15 months in federal prison. A 1999 FDA inspection report criticized WIRB for its role in the doctor's experiments. "There is a failure to have complete documentation of the board's knowledge, discussion and decisions regarding research activities," FDA investigators wrote of WIRB.

Bowen says WIRB didn't know about Fiddes's fraud. "He fooled everybody," she says. Pharmaceutical companies would

be amazed at how poorly some clinical tests are run, she says. "Some of the companies would be embarrassed if they saw the quality of the people doing research," she says. "I call them clueless."

WIRB's headquarters has 44,000 square feet (4,088 square meters) of office space on an 18-acre (7.28-hectare) campus studded with towering Douglas Fir trees. It has 250 employees, who refer to themselves as "Wirbies." Review board members attend about 40 four-hour meetings each month to approve new experiments and trial recruiting materials, review ongoing tests and examine reports of serious side effects, Bowen says. About 60 items are considered at each meeting, giving members an average of four minutes to discuss each issue. The meetings and their minutes are closed to the public, as are the names of the board's members. "If you were a plaintiffs lawyer, wouldn't you like to have the identities of all the membership?" Bowen asks.

The FDA most recently inspected WIRB in August 2002. The agency found that WIRB's computer system lacked an audit function, meaning data entered could be altered without a record of the changes. The FDA called that a "significant objectionable condition."

In a 1999 inspection, the FDA criticized WIRB's role in the case of Richard Borison, a Georgia doctor convicted in 1998 of stealing more than \$10 million of drug research money in experimental tests and sentenced to 15 years in state prison.

In 1990, Borison, the chairman of the psychiatry department at the Medical College of Georgia in Augusta, hired WIRB to oversee his experiments with psychiatric drugs. During the time WIRB was monitoring him, Borison stole the money provided for clinical trials by Pfizer, Wyeth and Basel, Switzerland-based Novartis AG. As a department chairman, Borison was required by college rules to use the school's IRB. Instead, the doctor used WIRB, located 2,300 miles away, to help conceal his fraud from the school, says George Schuster, chairman of the college's IRB. "Borison bypassed us and went to WIRB," he says. "We didn't know until the whole thing blew up that they were using WIRB. If WIRB had followed its own rules, we'd have notified them it wasn't acceptable. We wouldn't have allowed the fraud to continue."

WIRB's rules required it to notify a school when it was hired to oversee research. Bowen says WIRB didn't inform the Medical College of Georgia because Borison had told WIRB he was a part-time professor. Letters from Borison to WIRB were on the school's letterhead,

'Some companies would be embarrassed if they saw the quality of the people doing research,' the head of the biggest review board says.

listing Borison as chairman of the psychiatry department.

In his indictment, Borison was also accused of endangering the lives of participants by using inadequately trained employees and permitting his signature to be forged on prescriptions. An FDA inspection report of Borison in 1997 also detailed patient protection violations, finding that untrained employees administered experimental drugs, evaluated side effects and decided when to increase dosages. The FDA sent its findings to WIRB, which had allowed Borison's tests to proceed for six years.

Today, seven years after Borison's conviction, Bowen says WIRB did nothing wrong in its oversight of the Georgia tests. "I didn't see that there were patient safety issues," says Bowen, who sat on the panel that oversaw Borison's experiments.

WIRB told its staff to send its research approvals directly to Borison's home and not to the school, according to WIRB documents obtained by state prosecutors. An undated WIRB memo says, "Arrangement with Dr. Borison is to have all correspondence sent to his home address." Bowen says WIRB clients are free to use any address. "We send it to where they ask us to," she says. "We didn't know it was his residence."

Prosecutor David McLaughlin of the Georgia Attorney General's Office in Atlanta says he was astonished by Bowen's attitude about Borison. "I'm a prosecutor, sitting in her office, telling her they did this and that, and she was saying, 'It's not a problem for us,'" he says. "That's just bogus. I had such a bad taste in my mouth when I left." The state brought no charges against WIRB.

Pfizer spokesman Lederer says the results of Borison's research were removed from Pfizer's database and weren't sent to the FDA. Wyeth spokesman Burr declined to comment.

Pressure on profits Companies are rushing to develop new drugs as patents expire. After Schering-Plough lost its U.S. protection for allergy drug Claritin in December 2002, revenue dropped 18 percent and the company reported a loss in 2003.



In addition to monitoring phase I trials, the stage at which pharmaceutical companies test people for possible side effects, WIRB plays a leading role in supervising phase II and III trials. In a phase II test, clinicians experiment with various doses of a medicine to test effectiveness. In phase III, they aim to collect enough data on larger groups of patients to demonstrate that the substance works well enough to be approved by the FDA. In all phases, clinicians monitor for side effects.



'The problem is a system in which businesses have control over the evaluation of their own products,' Harvard's Marcia Angell says.

In 2000, Bill Hamlet, a 58-year-old artist and woodcarver in Pittsboro, North Carolina, entered a phase III clinical trial for a proposed psoriasis treatment made by Genentech Inc. Hamlet enrolled on the recommendation of his physician, Mark Fradin, 45, a doctor running the test.

Hamlet says the medication he was taking before the test, methotrexate, successfully controlled his psoriatic arthritis, a condition causing inflammation of the skin and joints. When Hamlet began the drug experiment, his doctor instructed him to stop taking methotrexate. He became sick after going off the medication. During the trial, he spent weeks in bed because he was barely able to walk. Hamlet was left with permanent knee damage, his medical records show. (See "A Matter of Trust," page 44.)

"It was like a train wreck," Hamlet says, recalling the pain and discomfort that became part of his life for six months.

"My whole persona was taken away in one fell swoop by a medical trial." When the test began, Hamlet wasn't told by his doctor that he might be given a placebo, a substance with no active medicine, he says. Nor was he told three months later that he had been switched to the experimental drug. By design, many drug trials don't allow participants or clinicians to know who is getting placebos at the time of the tests.

Hamlet sued Genentech, Fradin and WIRB, which was overseeing protection for participants in the clinical trial. All three settled the lawsuit this year without disclosing terms. Genentech spokeswoman Tara Cooper says the company can't comment because the settlement has a secrecy agreement. Bowen says that clinicians and WIRB did nothing wrong in the Hamlet trial. Fradin's lawyer, William Daniell, says the doctor did nothing improper.

In 2001, WIRB was hired by Johns Hopkins School of Medicine in Baltimore to help review research at the school after a clinical trial participant died in 2001. Minutes of WIRB meetings from the first quarter of 2004, which are available at the medical school because a Maryland law requires such minutes to be public, show shortcomings in WIRB's own review of research. A recruiting script for participants was approved by a WIRB panel even after a doctor on that panel said she didn't understand it. She abstained from the vote. The board also complained that it took seven weeks for WIRB's staff to inform the board of the death of five people in a clinical trial. WIRB deleted some details and all names from the minutes provided for review by Bloomberg News.

For the Johns Hopkins review, WIRB's nine-member panels often met with just five members present, the minutes show. Alternate members made up the majority of WIRB boards 20 times from Jan. 1, 2004, to March 31, 2004. Twice in three months, all of the members were alternates.

Consequences In exchange for getting paid for trials for experimental substances, healthy participants risk debilitating side effects and even death. The following warnings about potential side effects are listed on consent forms for these substances.



In 2003, the Hopkins minutes show, WIRB required a clinical trial sponsor to make changes in the recruiting materials for a trial in order to better protect participants in the experiments. The sponsor, whose name was deleted from the minutes by WIRB, asked WIRB to reconsider its decision. On Feb. 26, 2004, the same WIRB panel, acting with four alternates and one of its regular members present, reversed its decision and allowed the company to keep its original proposed language.

"That was worrisome," Bowen says, after being informed of what had happened. "I wish somebody had caught it sooner." Daniel Ford, vice

dean for research at Johns Hopkins School of Medicine, says the reversal by WIRB concerns him. "It's possible you could have manipulation," he says, "One of the big things WIRB sells is speedy review." Ford says WIRB provides high-quality service.



'Patient safety should never be sacrificed for short-term profit by a company,' Republican U.S. Senator Charles Grassley says.

The University of Pennsylvania's Caplan disagrees. He says WIRB has failed to protect participants in clinical trials. "It appears they have basically reneged on their obligation toward subject protection and have become complicit in protecting the interests of their sponsors because it serves an important business interest," he says. "That's just what you fear from commercial IRBs. They've had conflicts of interest since the beginning."

In a 2002 Seton Hall Law Review article, WIRB's director of regulatory affairs wrote that there's an inherent conflict within independent IRBs because their fees come from the same pharmaceutical companies whose trials they're asked to monitor. "The conflict of interest faced by independent IRBs is real and substantial," David Forster wrote. "Independent IRBs are paid by sponsors and investigators to protect subjects who are participating in research conducted by those sponsors and investigators."

There aren't any federal rules requiring for-profit IRBs, which are often located thousands of miles away from trial sites, to visit or inspect the test center at any time.

Nobody has ever studied the effectiveness of IRBs or tracked how many people are injured or killed each year while participating in clinical trials, says Harvard's Federman, who chaired a national committee on clinical trial safety in 2003. "An intelligent person would assume we know this," Federman says. "We don't know the number of persons harmed in clinical trials each year and are missing a registry of all subjects that participate in trials."

Angell, the former editor of the *New England Journal of Medicine*, says the protection of people in clinical trials shouldn't be left to companies funded by the pharmaceutical industry. "The fundamental problem is a system in which investor-owned businesses have control over the evaluation of their own products," she says. "Oversight of clinical trials is too important to leave in the hands of drug companies and their agents."

Government agencies have repeatedly warned about inadequate protections for people in trials. "Pressures to recruit

subjects can lead researchers and IRBs to overlook deficiencies in efforts to inform subjects of potential risks," the GAO cautioned 10 years ago. In 2000, the inspector general of the Department of Health and Human Services wrote, "In a highly competitive marketplace, with few rules or guidelines governing recruitment, there is a very real danger of a race to the bottom."

In 2002, after three people died in clinical trials at medical schools, bills were introduced in both houses of Congress to strengthen protections for people in drug tests. The bills, sponsored by Democratic Senator Ted Kennedy of Massachusetts and Democratic Representative Diana DeGette of Colorado, stalled in committee and never made it to the floor for a vote. "I hope Congress will act," Kennedy says. "Recent failures of the current system have given new urgency to the need to guarantee the safety of clinical research and prevent similar tragedies in the future. We need to protect research participants."

Testing companies must fully inform people of risks in clinical trials, says Senator Charles Grassley, a Republican from Iowa. "The burden is on the research companies to go out of their way to make sure study participants are fully informed when consent is given," Grassley says. "Patient safety should never be sacrificed for short-term profit by a corporation."

The National Bioethics Advisory Commission, a presidential panel created in 1995 by executive order of President Bill Clinton, issued human protection recommendations in 2001. That panel folded in 2001, and President George W. Bush replaced it with the President's Council on Bioethics, which has issued reports on ethical issues of human cloning and stem cell research.

"Business has taken a much higher profile at the FDA because of the current administration," says Mary Faith Marshall, associate dean for social medicine and medical humanities at the University of Minnesota Medical School in Minneapolis. "There's a much friendlier attitude toward Big Pharma and less emphasis on human subject protection."

"The FDA is an independent agency," White House spokesman Trent Duffy says. "It has maintained its independence. President Bush supports a strong FDA that protects American consumers."

Solutions Doctors who served on federal panels recommend the following protections for people who participate in experimental medical tests.

- **Set up one U.S. panel to oversee all medical experiments**
- **Tape-record or videotape consent discussions**
- **Set up a compensation system for research-related injury**
- **Train institutional review board members in research ethics**

Source: National Bioethics Advisory Commission, 2001

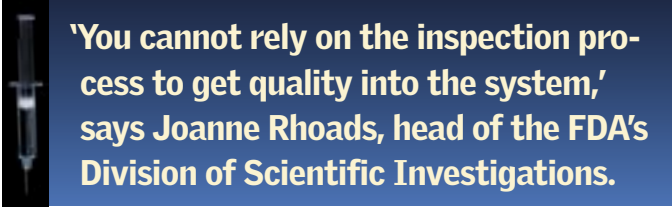
Harvard's Federman says politics is at issue. "This type of inquiry is not a high profile for the current administration," he says. "This is not a government that particularly looks at big business. Pharmaceutical companies have a huge lobbying operation."

PhRMA, which represents more than 40 drug companies, spent more than \$16 million last year on lobbying, a 12.5 percent increase from the year before. PhRMA hired 136 lobbyists in 2004, according to Public Citizen. PhRMA declined to comment about its

lobbying activities. “PhRMA and its member companies are certainly willing to review proposals that could make a good safety record even better,” the group says.

One way pharmaceutical companies could improve safeguards for clinical trial participants is by checking to see whether the people running the tests are actually licensed as doctors. In Jupiter, Florida, a drug testing center called the Drug Study Institute lists its director of clinical research as Melody Sanger, who’s identified as a primary care physician. Florida state records show Sanger, 50, isn’t a licensed doctor. She’s licensed only as a registered nurse, according to the Florida Department of Health. The company Web site says she has run trials for AstraZeneca, Merck, Novartis and Pfizer.

Sanger never misrepresented her credentials to Merck, company spokeswoman Skidmore says. AstraZeneca spokeswoman Carla Burigatto says the Drug Study Institute did good-quality work, adding that Sanger didn’t serve as a doctor on trials for the company. Sanger declined to comment.



'You cannot rely on the inspection process to get quality into the system,' says Joanne Rhoads, head of the FDA's Division of Scientific Investigations.

SFBC describes Chairwoman Krinsky as a medical doctor in SEC filings and company literature. She’s never been licensed to practice medicine in the U.S., SFBC’s Hantman says. Krinsky’s laboratory technician license in Florida expired in 1998. Krinsky is in charge of SFBC’s phase I clinical trials. Hantman says Krinsky is a company executive who doesn’t run any clinical trials. “She is not required to be licensed in Florida,” he says. Hantman says the SFBC center has five physicians, as well as nurses and emergency personnel.

Harvard’s Federman is concerned that SFBC refers to Krinsky as a doctor without disclosing she’s not licensed. “It’s misleading in that most, perhaps almost all, readers would assume she is a licensed and fully trained physician,” he says.

Hantman is SFBC’s treasurer as well as its CEO. Company SEC filings say he’s a certified public accountant. Hantman’s Florida CPA license expired in 1989, public records show. Hantman says he’s been a lifetime member of the American Institute of Certified Public Accountants, a trade organization.

In Houston, the Fabre clinic used Rodriguez to give experimental drugs to people and make medical decisions during tests. The FDA found that Rodriguez had neither a medical license nor any clinical credentials in the U.S.

There are better ways to do research, says Koski, the physician who headed the federal agency for human protection for two years. Koski says a single U.S. panel should oversee all experimental tests. The National Bioethics Advisory Commission suggested that informed consent discussions between researchers and participants be audio- or videotaped to ensure they’re done right. The commission also recommended a system to compensate people for research-related injuries and said all IRBs should have to register with the federal government. In addition, it said all IRB members should be trained in research ethics.

Mark Yessian, who oversaw investigative reports on IRBs over the past decade as Boston’s regional inspector general for the Department of Health and Human Services, says changes are needed. “The drug industry is trying to bring products to market,” says Yessian, who retired in October. “We don’t want to suffocate that, but we need to do it in a more balanced way to give subjects confidence that there are people looking out for their interests.”

Koski says the mission won’t be easy. “It’s not really a ‘few bad apples’ problem,” he says. “We need to create a system that grows better apples.” ♦

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