

MINIMAL RISK WITH DENNIS SWANSON

BY DAVID R. ELTZ

THE SECOND IN A SERIES



Lucky for Pitt, Dennis Swanson finds regulations governing human subject research—the same regulations that are likely to drive investigators to shake their fists at the ceiling—*interesting*.

# TRIAL RUNS II

Inside the cylinder, sweat beaded on Dennis Swanson's brow. His pulse quickened. His breathing hitched. Swanson, then the inquisitive director of radiology pharmacy services at Henry Ford Hospital in Detroit, was losing control.

A researcher who'd been testing diagnostic imaging agents for a decade, Swanson was evaluating whether a certain drug combined with magnetic resonance imaging (MRI) could be used to study four pea-sized nodules in the neck that regulate the body's calcium levels, the parathyroid glands. He had volunteered to crawl into the MRI himself, figuring, *What was the risk?* Soon, Swanson was tuning out the MRI's annoying banging and clanging sound only to realize that he was lodged inside something that resembled a coffin. It wasn't long before the constricting panic of claustrophobia wrapped around him.

PORTRAITS | TOM ALTANY



"They had to pull me out," Swanson says, some 20 years later.

Once outside the tube, he recovered and thought his way around the paralyzing feeling. Swanson theorized that he could tolerate the MRI's confines if he kept his brain occupied. So, he slipped back inside, taped a magazine article where he could comfortably see it while lying in the machine's bore, and, for the next two hours, read whenever fear slithered in. His psychological experiment worked; the scientific one did not.

Today, Swanson, director of the University of Pittsburgh Institutional Review Board (IRB) office—the IRB is the oversight body that approves or rejects every formal plan for human subject research at Pitt—forgets what the article was about. It is the claustrophobia he remembers. "It was interesting," he says, pointing out the merits of distracting the mind from fear. He says that again—*It was interesting*—about his brazen act of sailing recently in the Caribbean during a squall, warning himself he might fall off and drown but just the same hanging off the stern to keep the sails from tangling.

Swanson drives his lumbering black Dodge van down a Pennsylvania highway at the 65-mile-per-hour limit. (Okay, maybe just a bit faster.) At 55, he bears a striking resemblance to Jerry Garcia, a slight paunch beneath his navy-blue suit coat, metal-framed glasses riding high on his bearded face, a mane of white hair brushing his collar. (A three-foot-tall pencil sketch of the late Grateful Dead musician hangs in Swanson's office.)

In an hour he'll tell researchers at Pitt's Bradford campus about human subject research and federal regulations and IRBs and research conduct and compliance. He'll watch some, say, social work pros who are conducting sensitive questionnaires, raise their hands with questions, a bit hesitantly, because, well, they don't know all of the rules. That's okay; he wants to help. He finds the regulations—regulations that often drive investigators to shake their fists at the ceiling—*interesting*.

Swanson refers to himself as a child of the '60s: "I like to question federal authorities," he says, eyes on the road. "There's nothing I like better than to quote a federal agency's regulations back to them when they tell me I can't do something."

"I do that a lot. I think we need to question their interpretations of the regulations often. Because, frankly, they aren't the people out doing the research."



Donna Medich

## PHANTOMS WHO KEEP DATA STRAIGHT

In 2000, Donna Medich got a phantom in the mail. In Medich's world, a phantom is a clear rectangular box containing a synthetic lumbar spine surrounded by liquid. She ran 10 scans of the phantom on her densitometer, measuring the bone mineral density (BMD) of the artificial vertebrae. Then, she sent the phantom, along with the results, to a central data collection site for a study that tests the use of parathyroid hormone for osteoporosis treatment. Once the central site got the phantom back from Medich, it mailed it off again. Eventually, the phantom was sent to more than 100 study sites, including some outside the United States. This allowed the central facility to compare phantom readings and adjust data if needed—ensuring that differences are not merely due to equipment aberrations.

Medich, a radiologic technologist, gets phantoms in the mail several times a year. They are used for quality control in several of the 11 trials for which she collects data. Her job is running BMD scans and body composition scans (which measure the percentage of body fat) for the 11 trials. Nine of the studies focus on osteoporosis. (Susan Greenspan, professor of medicine, is the principal investigator for eight of these.) Two trials, headed by David E. Kelley, professor of medicine, focus on diabetes.

"For a lot of the studies, it comes down to the BMD numbers that you get [in determining] whether a therapy works or not," says Medich. In the world of Medich and other technologists who support clinical trials at Pitt, accuracy and precision are everything. —DH

Swanson never was *radical*. Sure, he visited the scene at Haight-Ashbury in 1971, on break from a meeting of pharmacists in San Francisco, but by then the scene had become irrelevant. The most radical thing he has done, from his perspective, was to become the first member of his family to leave Iowa for good.

In 1975, Swanson quit his job, sold the

house, and packed his wife, kids, cat, dog, and all worldly possessions into his station wagon. The wagon headed west so that Swanson could earn a master's in nuclear pharmacy from the University of Southern California (USC). Having been reared in Iowa, educated in Iowa (graduating in 1971 with a bachelor's in pharmacy from the University of Iowa), and in the process of raising a family in Iowa, Swanson never planned to leave

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Iowa. But the lack of variety in being a community pharmacist in Burlington (population 27,500), at the same pharmacy for which he'd delivered prescriptions as a teenager, had grown tiresome. When the local Veterans Administration hospital offered to pick up tuition at USC, Swanson "escaped" into nuclear pharmacy as the field was just taking off.

"It was a minimal risk to do something different," he says in the parlance of his current position.

Whatever risks there were soon paid off. A year later, master's in hand, Swanson landed a faculty appointment at the University of Michigan Medical Center. In six months, he was the center's director of nuclear pharmacy, developing new radioactive drugs for diagnostic imaging.

Pharmacists often say they have the most regulated profession in the world, with oversight from the likes of state pharmacy boards, the federal Drug Enforcement Administration, and the Food and Drug Administration (FDA). Nuclear pharmacists, you can imagine, are regulated even more. At Michigan, Swanson's work necessitated he interact with regulatory agencies. He wrote his team's IRB applications for approval to conduct human subject research. He submitted applications to the FDA for approval to test investigational drugs. He studied the rules of the Nuclear Regulatory Commission.

In the '70s, Swanson came face-to-face with federal investigators. Michigan was one of several sites in a study of a new agent for imaging the flow of bile through the liver, gall bladder, and intestine. It was (and still is) typical, upon asking the FDA to approve a drug, for some of the trial sites to be audited. The FDA picked Swanson's site. Auditors discovered "documentation issues" in the research. In other words, when Swanson's team inadvertently wrote down data incorrectly, they would cover it with typewriter correction fluid and jot the new value over top—a no-no. Per FDA rules, investigators were supposed to cross out the old value, enter the new one, and initial it. Luckily, the auditors pointed out the deficiency without issuing penalties.

Swanson notes that neither he nor the physicians he was partnering with were familiar with the requirement—touching on an ongoing problem with such research. People who become clinical researchers do so because they

have an interest in science, in solving the riddles of the body, in helping people. Often they're not trained in the details and seeming vagaries of regulations. (They also have plenty else on their plates, between performing research, seeing patients, teaching, preparing grants, writing articles for publication in peer-reviewed journals, managing research data and staffs, and other administrative duties.) Pitt has made it a priority to alleviate the pressure on investigators, recently creating a master's in clinical research program and establishing the Office of Clinical Research to manage educational efforts and help investigators navigate the regulatory process. The University also has made it mandatory for clinical research faculty to certify in research practice fundamentals.

Swanson filed away the lesson—to learn the regulations before something intractable happened—and continued his research.

His Michigan team developed two radioactive imaging agents. One is still used today to find pheochromocytomas, tumors particularly adept at hiding—even from CT scans. The incidence of such tumors was so low that no pharmaceutical company would carry the agents; so Swanson distributed the drugs to nuclear pharmacies around the country. As such, the university was required to register with the federal government as a "manufacturer," and Swanson added another body of regulations to his understanding. Later he would help Michigan set up a positron emission tomography (PET) laboratory before moving on to Henry Ford Hospital.

In 1988, Randy Juhl, who'd been dean of the School of Pharmacy at Pitt for two years, recruited his old friend and colleague. The two had known each other in school at Iowa and had golfed together since. Juhl, still dean today, brought in Swanson as his assistant dean for a variety of special projects.

Word about Swanson's knowledge spread. He was drafted into the Department of Radiology in the early 1990s to help Pitt set up a PET center and to get federal approval for using radioactive agents in humans. (While at Henry Ford Hospital, Swanson chaired a group that wrote the PET standards that Congress incorporated in the Food and Drug Modernization Act of 1997.)

## THE HUMAN FACTOR

It takes a lot of people to make a clinical trial happen. What follows is a list of those involved in the Pitt segment of a multicenter Phase I clinical trial, led by Ramesh K. Ramanathan, director of the University's Gastrointestinal Cancer Center, for the new cancer drug Gleevec. The other nine sites in this study have similar staffing requirements.

**Volunteer patients:** 7

**Primary investigator:** 1

**Coinvestigators:** 7

**Institutional Review Board (IRB) committee (which checks the primary investigator's protocol for ethical efficacy to protect the rights of all trial participants):**

**1 committee, 18 members**

**IRB office staff:** 11

**University of Pittsburgh Cancer Institute (UPCI) protocol review committees (which approve the protocol for scientific relevancy):** 2 committees, 15 members each

**UPCI regulatory staff (maintains files of correspondence with all regulatory agencies granting approval of the study):** 9

**General Clinical Research Center (GCRC)—where blood samples and data are gathered from trial participants—review committee:** 16 members

**GCRC staff—**

**nurses:** 12

**clinical technicians:** 6

**administrative staff:** 3

**dietary staff:** 3

**UPCI clinical coordinator:** 1

**UPCI clinic nurse:** 1

**UPCI investigational drug pharmacist (who prepares Gleevec):** 1

**UPCI outpatient pharmacists (who dispense the Gleevec and provide patient education):** 3

**Data manager:** 1

**Phlebotomist:** 1

This particular trial requires the participation of patient volunteers whose health is often very fragile. Sadly, Leslie Levendosky, profiled in our last issue, was not physically able to continue with the Gleevec study. —DRE



By 1996, when Pitt wanted to expand the size of its IRB and create a director's position, Swanson was the logical choice. The nuclear pharmacist is perfect because he strikes a balance between, says Juhl, "the rigidity of federal regulations and the free-flowing characteristics of biomedical research." He knows what researchers do, what they're up against, and how to get them through it while maintaining the integrity of clinical research at Pitt.

**I**t wasn't until the 1970s that the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research recommended that academic research centers establish IRBs. And not until the late '70s were researchers required to obtain written "informed consent" from a patient participating in federally funded experimental therapy (see "Bond of Trust"). Before then, clinical trials were guarded by ethical codes established at individual institutions as well as some nonbinding federal guidelines. Still, sometimes patients received pills yet were told nothing about them. During the early days of the Cold War, researchers working for our own government conducted radiation experiments on citizens, primarily soldiers in the US military, again without their consent.

Even today, IRBs don't always catch every potential problem. This was dramatically demonstrated at the medical research powerhouse Johns Hopkins University last summer. On June 2, 2001, a volunteer in a clinical trial at Hopkins died after inhaling a chemical that caused her lungs to fail. Ellen Roche was 24. She also was healthy when she enrolled in the trial. Investigators had given her the drug hexamethonium hoping to understand what happens during an asthma attack. After Roche's death, the federal government shut down some 2,800 human subject tests at the university for four days. For four days bills weren't paid, some therapies were halted, and a family waited to learn why they'd lost their daughter.

The story of what went wrong long before Roche took the drug emerged after an internal audit by the university and external investigations by the FDA and Office for Human Research Protections. Researchers allegedly had failed to properly warn volunteers of the risks involved, the Hopkins panel reported. What's more, federal investigators charged, the researchers didn't read far enough into the history of the drug; peer-reviewed research from the 1950s—not included in the protocol the



Julie Wagner (left) with Jodi Ribich

## FINDING VOLUNTEERS IN HAYSTACKS

They needed 73 women to participate in a clinical trial, and it was the job of Jodi Ribich and her colleagues to find them. Ribich, nurse coordinator for an ongoing study at Pitt's Osteoporosis Prevention and Treatment Center, and company sent brochures to every woman older than 55 in greater Pittsburgh. They advertised in the Sunday paper. They took an ultrasound machine to local supermarkets, offering free screenings. They visited health fairs. Every Friday for a year, the study's primary investigator, Susan Greenspan, and her team brainstormed about finding more volunteers—all methods which would be approved by Pitt's Institutional Review Board (IRB). They went to the trouble of purchasing small incentives—jar grippers and magnetized memo boards for refrigerators—to give volunteers when they came in for a series of visits, such as an initial screening and a three-month checkup, with Ribich and Julie Wagner, Greenspan's physician assistant. Later, they simplified their incentive system, offering trial volunteers \$5 gift certificates from a local supermarket for each visit. But this required them to resubmit the research protocol to the IRB *all over again* for approval. In the end, though, the best incentive for volunteers turned out to be the altruistic one—the opportunity to contribute to a better understanding of how to prevent and treat a debilitating disease. —DRE

IRB approved—suggests that hexamethonium could cause respiratory problems. Moreover, the FDA accused the IRB of not forwarding questions from some board members to the trial researchers, and concluded that, overall, Hopkins' IRB process was so overwhelmed that research protocols often were reviewed by only one IRB member. The finding sent shivers through the academic medical community, which holds Hopkins in such high regard. (November brought more concern. That

month, Hopkins disciplined a faculty investigator who was conducting a clinical study in India, charging that the researcher did not seek university or government approval before testing a chemical derived from the creosote bush on the oral cancers of 26 people. The investigator countered that she was never told she needed university approval to conduct a trial in India.)

A clinical trial's investigators have a responsibility to keep their trials safe and ethical. Investigators are required to search scientific writ-

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ings well enough to determine whether there are risks to the subjects' health, to inform volunteers of those risks, and to report any occurrence of "adverse effects" to the IRB as soon as possible. At the same time, the IRB is accountable should anything go wrong. At Pitt, the IRB committees protect the welfare of those enrolled in roughly 3,000 human subject investigations under way at any given time. "When something bad happens . . . the federal agencies hold the institution accountable, because it's the institution that's a recipient of the federal grant money [funding the study]," says Swanson.

Hopkins' immediate response to Roche's death was to double its number of IRB committees to six.

Swanson said he was already thinking about boosting Pitt's number of committees prior to the incident. He had done so in 1996, when he came on board as director of the IRB office. Within Swanson's first year on the job, the number of IRB committees at Pitt went from one to four, each comprising some 20 people ranging from research faculty members to everyday citizens (who are especially valuable for making informed consent documents understandable for the average research participant). That accelerated expansion reflected the University's mushrooming research enterprise.

It's a good bet, Swanson says, that Pitt's IRB will add several more committees this year—in part to avoid having to battle anything like what Hopkins just endured.

**P**assing through the IRB office each week are something like 35 new research protocols, 40 studies back to the IRB for review after one year, 20 protocols from investigators petitioning to add changes, and 20 coming back after changes have been added. Really, Swanson's job is straightforward: Interpret incredibly complex, constantly changing regulations written by people who don't do clinical research, and make sure they're followed by people who do often incredibly complex research but who don't necessarily know those regulations. Not a match made in heaven. Were he a marriage counselor working under such conditions, the outcomes might not be as solid—knock on wood—as they've been at Pitt. The secret?

Swanson, current IRB chair Philip Troen, and the IRB are always looking ahead. They watch for coming changes, notes Swanson, before problems occur.

Despite this success, perhaps because of it, the research community sometimes refers to the IRB as the Dark Side, a frustrating fact of Swanson's work. But the frustration cuts both ways. Investigators tend to see the IRB as interfering with their research. When the IRB sends a protocol back to an investigator with questions about medical jargon in the summary, a researcher might say, "Who are you? You don't understand this disease!" notes Clifford Schold, head of Pitt's Office of Clinical Research. Such dissatisfaction among some faculty exists, he adds, because their business is science—not regulations.

That said, Schold, whose office helps investigators to write protocols that pass muster with the IRB, praises Swanson and his office. "I can tell you I've been at two other major academic institutions, and this is by far the best IRB I've ever seen.

"This is the most efficient and the most attentive."

The regulations aren't going away, Swanson says. Biomedical and surgical device research will continue to increase. The regulations will grow accordingly. To handle the glut, he would like the oversight structure at Pitt to become a "one-stop shopping office." (What he'd also like to do someday is open a bar, but that's another story.) Today, one research protocol might need approval from three different University offices other than the IRB—perhaps the Radiation Safety Committee, the Investigational Drug Service, and the General Clinical Research Center—with none of those offices necessarily working in sync. Swanson believes an investigator should be able to hand a protocol to a research ana-

lyst, who then sends it simultaneously to all those offices.

"That's where I really think we need to get to if we're going to continue being a major research player down the line," he says. "If we keep building our own bureaucracy [to meet federal regulatory measures], it's going to reach a point where investigators aren't going to comply with all the things we put in front of them, or it's going to be so difficult to comply they're never going to get their research done."

There is no such model in the country, but to suggest that much to Swanson would be like telling former National Football League commissioner Pete Rozelle that Super Bowls will never make money. And after all, this is a minimal risk opportunity. ■

*This is the second of a two-part series on people who play often unsung roles in advancing new therapies.*

## BOND OF TRUST

"Informed consent" is the bond of trust between a clinical investigator and a patient volunteer. In each clinical trial, participants are required to sign an informed consent document, which states clearly, in common language, the purpose of the research, what will be asked of and done to the patient, and what potential risks could endanger the patient's health. The document must first pass muster with an Institutional Review Board (IRB). The IRB, under the guidance of the federal Office for Human Research Protections, takes even greater care to ensure that studies involving children, prisoners, and people with cognitive impairments are held to the highest ethical standards of consent. For instance, the federal government asks IRBs to consider that people with cognitive impairments who are institutionalized—because of their complete dependence upon that institution—might be vulnerable to requests for their "cooperation" in studies, for fear of being denied services or privileges.

Informed consent is more than a piece of paper. It is a process through which the research volunteer can ask the doctor about the research. The doctor, in turn, has an obligation to make sure the patient understands, say, in a Phase I cancer drug trial, that it is designed to test dosage levels and determine possible side effects, not necessarily to cure that person's disease. Pitt's new Office of Clinical Research was created to help investigators write such documents—and navigate the rest of the complex world of clinical research. Without informed consent, when research is conducted on people unknowingly or when a treatment is altered without a patient's consent, human subjects feel betrayed, as if they were guinea pigs, says Clifford Schold, assistant vice chancellor for clinical research and director of the new office.

More fundamentally, as Schold says, "It's the right thing to do." —DRE