

## The Dilemma: Submit or Suffer

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### *Third of six articles*

PARNU, Estonia -- Indrek Kelder, a 27-year-old accountant, thought he was being recruited for tests of "some kind of vitamin." It seemed like a great deal: Free air tickets to Switzerland, two weeks at a comfortable clinic and a cash stipend of several hundred dollars, more than a typical monthly salary in this struggling Baltic nation.

In October 1998 he jetted to Basel, a pristine mountain town of flower boxes and church spires, expecting a transfer to a three-star hotel. Instead he found himself in a sterile clinic filled with beds, where he would be tested for a drug whose risks and purposes he did not understand. He said he wanted to back out, then realized it was dark, the airport was an hour away and he had no obvious alternative.

Eventually he signed a consent form written in German, a language he could not read. When he finally got an English translation, he said, the clinic doctor agreed only to show him a copy. Kelder said he had no idea what tablets he swallowed during the next two weeks. "Maybe it was written between all this mumbo jumbo."

His countryman Irme Petrimae arrived in Basel in January 1999 knowing almost nothing about the drug he was to take, and left after three weeks just as ignorant. "They told me something about skin disease," said the 22-year-old. "All these forms, and we didn't get any copies. I didn't like it, but when we were already there, it was too late to change our minds."

The clinic at which Kelder and Petrimae stayed ultimately shut down after authorities discovered that its operator, Van Tx Research Ltd., had filled many of its beds with people who didn't know they were in experiments, refugees seeking political asylum in Switzerland and drug addicts. It had performed 161 drug trials for some of the world's best-known pharmaceutical companies. A Swiss prosecutor is investigating fraud charges.

The case was "the most unpleasant experience ever in the short history of clinical trials in Estonia," said Alar Irs, an Estonian medical regulator.

The violations uncovered in the Van Tx case point to wider failures with patient consent procedures that some doctors and researchers say will increasingly occur as drug companies stage human tests in far-flung countries using naive, impoverished or uneducated patients.

Participants in human drug experiments are supposed to be fully informed of the risks they face during a test. The principle of "informed consent" lies at the heart of human drug testing contained in guidelines widely endorsed around the world. These rules ban coercion and trickery and give patients the right to withdraw from a test at any time for any reason.

But researchers and doctors say these principles have been breaking down as drug companies enroll thousands of test subjects at a time in Eastern Europe, the former Soviet Union, Africa, China, Latin America and elsewhere.

In some cases, unscrupulous operators just ignore the rules. In other instances the problems are more complex, involving such questions as whether an illiterate Third World villager who knows little about modern medicine can give informed consent in a way comparable to a Western patient.

Visits by Washington Post reporters to foreign test sites, as well as inspections and surveys of drug experiments overseas by various regulators and medical researchers, provided indications of widespread lapses.

A recent survey by two Johns Hopkins University researchers of more than 500 U.S. and foreign investigators found that most thought consent procedures in experiments were mainly used to shield researchers from lawsuits, rather than to protect patients.

Inspections of foreign drug test sites by the Western Institutional Review Board, a for-profit, U.S.-based ethics committee that approves drug research protocols, revealed breakdowns in the process. "Many, many times what we find at the site is a very abbreviated version of [the consent form] we approved," said Angela Bowen, the firm's president.

The Catholic University medical school in Santiago, Chile, surveyed 44 clinical trials in that country four years ago and found "ethical problems" in 20 of them. The most common failing was inadequate consent by test participants -- or no consent at all.

Faced with what seems to be a stark choice between risking an experiment or receiving little or no care, some patients sign consent forms because they don't believe they have an alternative, doctors and researchers said.

A South African medical council surveyed patients and found that 88 percent of women enrolled in one AIDS experiment said they had felt compelled to take part, even though all had signed a consent form saying they had volunteered. Nearly a third said they thought the care they received at the hospital would suffer if they did not participate. Ninety-nine percent of the women believed the hospital would not allow them to quit the study once it began.

The sense among patients of being imprisoned by a medical experiment can sometimes be literal, as a Post reporter discovered while visiting a Hungarian mental ward this spring. An experiment had been conducted there involving aripiprazole, an anti-psychotic drug under development by Bristol-Myers Squibb and Otsuka Pharmaceuticals.

## No One Does It In Practice

For patients confined to the locked psychiatric ward at Kutvolgyi Uti Hospital in Budapest, the drug research underway last year offered a brief taste of freedom. It was a chance to make a phone call during a few minutes on an open ward, and it offered patients the vague hope of being able to go home a few days sooner.

That's why Adam Novak, a 25-year-old bartender suffering from schizophrenia, said he signed up. He said he had been locked up for two weeks at the hospital when his doctor asked if he would be willing to test aripiprazole.

The company said he signed a consent form, which he does not dispute, "but when you are being held like that and in such a state, you are not really able to understand it," said Novak, one of 600 patients worldwide expected to test the drug in that study.

Testing mental patients kept under lock and key would put an American researcher on treacherous ethical ground. "You would try to stay away from that because of the fear the patient would be coerced into consenting and you couldn't be sure the consent was really informed," said Lawrence Gostin, a professor of law and public health at Georgetown University.

But in Budapest, "it is easier to find patients here, yes," said Gabor Faludi, the researcher who signed up Novak. "Patients in Western countries -- and in the United States especially -- have an overdeveloped sense of their rights and a fear of being harmed."

He acknowledged that obtaining informed consent from mental patients is "a hard question. . . . But the reality is that scientific research can only be conducted on these patients when they are in a phase where they are getting worse."

Andrea Borbely, a 35-year-old housecleaner who was confined in the same hospital, said she refused several times to participate. Bristol-Myers said it has no record of Borbely being in a test, but Faludi said he enrolled her after getting consent from her family. Borbely contends her medication was changed, and then changed again when the experiment was over. She said it was done simply "for the sake of the test. That is what makes me angry."

Faludi said Borbely received a standard drug being used as a comparison, and her subsequent medication changes were his attempt to find an effective treatment for her.

A spokeswoman for Bristol-Myers Squibb said approaching acute psychiatric patients for testing in locked wards was standard practice in Hungary.

Medical researchers there have been guided by a formal patient bill of rights since 1998. But while its provisions are "very good, no one does it in practice. It is so new," said Judit Harangozo, a Budapest psychiatrist.

Said Gabor Gombos, president of the Mental Health Interest Forum in Budapest, an embryonic patients' rights organization: "Our experience is that patients don't know they have rights, that they can say 'no' and expect not to suffer consequences."

But researchers such as Gyorgy Boszormenyi Nagy, a physician at Hungary's National Institute of Pulmonary Medicine, complain that patient consent forms developed in the United States are too complex.

"There is too much information on it, too much science, too many medical terms. They should be written plainer," he said, without feeling a need "to give every warning so as to cover every possibility if something goes wrong."

## The Meanings of Consent

The drug companies themselves, rather than the regulators, sometimes determine how much test subjects know about the medicines being tested. Communication among international medical test regulators is poor and sometimes nonexistent. Test participants in one country may unknowingly sign up to test a drug whose side effects already worry regulators in another country.

Two years ago, for example, the American pharmaceutical giant Pfizer Inc. had high hopes for its schizophrenia drug Zeldox, which was predicted to earn Pfizer \$600 million in profits within four years. But the Food and Drug Administration was concerned about indications that the drug affected heart rhythms and issued a "not approvable" letter, meaning Zeldox required more tests on human subjects before it could be approved for sale in the United States.

Pfizer said it did that further testing primarily in the United States, with one test site in South Africa.

Pfizer was also conducting a large number of other clinical trials as part of its ongoing effort to collect safety and efficacy information on Zeldox.

The Post visited one of those trial sites at a Bulgarian mental institution last spring.

A drug information sheet given to patients at the State University Hospital of Neurology and Psychiatry, a crumbling asylum outside Sofia, the capital, made no mention of the FDA's concerns. Luchezar Hranov, who ran the study for Pfizer, also said he did not inform volunteers of the FDA's action.

"I don't believe anyone would care," Hranov said. "The FDA is out of someone's reach. I would have to do an educational course."

The three-page information sheet told patients Zeldox had "been tested in studies involving more than 3,000 patients, and the results of these studies are currently being reviewed by government regulatory authorities in Europe and the United States." The sheet noted that Zeldox appeared "to slightly affect the electrical activity of the heart in some people."

Pfizer neglected to tell Hungarian regulators about the FDA action, as well, said both Janos Borvendeg, medical director at Hungary's National Institute of Pharmacy, and Tamas L. Paal, head of the institute, which is his country's equivalent of the FDA for drugs. Hungary had been one of the test sites for Zeldox in Pfizer's original round of research before the FDA intervention. Under Hungarian regulations, Pfizer was obliged to report the FDA action to Hungarian officials because Zeldox was part of another ongoing trial last year, Paal said.

In July, an FDA advisory committee recommended approval of Zeldox for sale in the United States, and a final decision is pending.

Borvendeg said Hungarian regulators had a right to know about the FDA's concerns. "I will go to the company to ask about this and see whether it was an oversight or whether they were trying to cheat on me," he said. Pfizer responded that it adheres "to the laws of each country in which clinical research is conducted."

Testing drugs on mentally ill patients makes obtaining informed consent especially problematic. In some cases, doctors who have been paid to recruit subjects are the ones judging when a patient is capable of consent. Other times, patients believe that joining a test is the only way to receive quality care.

Doctors said that in the crowded state-run mental institutions of Eastern and Central Europe, agreeing to participate in a clinical trial can vault a patient to the top of a busy doctor's priority list.

"The patients know there is a hierarchy of patients and that the best deal for them is to be in a trial," said Laszlo Lajtavari, a psychiatrist at the Nyiro Gyula Hospital. "If you're not in a trial, you're part of the big group of

people I see and you're not getting as much attention from me. I do not think that would be coercive to get them to say yes, but it is how it is."

Tibor Toth, 58, one of Lajtavari's patients who has been in and out of psychiatric hospitals since 1967, said the doctor's attention was one reason he agreed to take part in a recent drug experiment. "When I got a chance to have tablets and a chance to have continuous monitoring by my doctor, I was happy to take it," Toth said. The consent form he signed was "like a small contract. I had to read it, talk it over with anyone I wanted to, with my family." Toth recalled being told that the only risk in taking either of the drugs in a comparative test would be headaches. "To be honest, I can't remember everything I was told because I was going from one state of illness to another," he said.

In the United States, psychiatric patients could expect more protections, said Ernest D. Prentice, vice chancellor of the University of Nebraska Medical Center and head of its institutional review board. Ethics boards reviewing testing protocols might encourage patients to name a representative to act in their interest or ask that someone from outside the research team be present at all consent discussions. Once a patient regains coherence, researchers might be asked to reaffirm the consent, Prentice said.

Yet, in Eastern Europe, just the words "United States" can be enough on a consent form. Erzsebet Terjek, 45, a Budapest schizophrenia patient who agreed to test a Johnson & Johnson drug called risperidone, said she understood the risks outlined in her consent form but decided to take part because she trusted American products. "I believe they can cure me sooner," she said. "I am honored to be chosen for an American experiment."

Attila Samu, 36, an epileptic who has been part of anti-seizure drug experiments, said he understands the bargain Hungarians make. "I would like to see the day come when Hungarian companies can manufacture drugs like these, so we are not just test subjects," he said. "But for now, I see the new drugs come from America and we're the people who try them out."

## Poverty and Choice

The problem of obtaining informed consent becomes even more severe in very poor countries where patients have no decent health care.

"I'd argue you can't do studies ethically in a country where there is no basic health care," said George J. Annas, head of the health law department at Boston University's School of Public Health. "You can tell a person there that this is research, but they hear they have a chance to get care or else refuse their only good chance at care. How can you put them in that position and then say they are giving informed consent?"

Researchers say it can be especially hard to help Third World patients understand such basic drug-testing practices as the use of placebos -- dummy medicines given to some participants in an experiment.

"This is a concept we have trouble explaining," said Grace Malenga, a medical researcher in Malawi, a small country in southeastern Africa.

Some researchers say shortcuts in obtaining consent are common in developing countries where patients trust doctors to tell them what to do.

To properly obtain informed consent in such settings requires an "enormous effort" by the doctors involved, said Karen Barnes, an infectious disease specialist in Cape Town, South Africa. This is especially true when -- as is often the case -- there is no translation for "placebo" in the indigenous language, forcing researchers to resort to elaborate metaphors and analogies.

Barnes estimated that it requires 45 minutes to counsel each test volunteer in a session that may include not just the participant, but family and local medical workers -- a regimen that hard-pressed doctors are often reluctant to undertake.

Researchers in China, a major site of drug experiments, often skirt international rules about consent, said Sang Guowei, deputy director-general of China's State Drug Administration. "Most medical practitioners are not aware of the necessity and possibility of obtaining the informed consent," he told a pharmaceutical industry conference in San Diego last June. "They say it is too difficult for them. Especially they are worried [that], at any time, the volunteers have the right to withdraw from the study."

Medical experiments staged in authoritarian China -- whose Communist government detains citizens arbitrarily and has uprooted millions from their homes in recent decades -- also raise questions of political coercion.

There, and in other nations governed for decades by dictators and despots, the Western concept of freedom of choice is weak or nonexistent.

"What we have come across in the countries that were part of the former Soviet Union is that there is no concept of consent -- of them giving consent," said Marjorie A. Speers, then a deputy associate director in charge of oversight of international research for the U.S. Centers for Disease Control and Prevention, in 1998 testimony before the National Bioethics Advisory Committee. "It literally freaks out the people who participate in the study, because it raises concerns that there must be something wrong with this if you are asking for my permission to do it."

In countries wracked by recent wars or oppressed by secret police, test subjects are reluctant to sign their names to any document. In such places, medical researchers sometimes accept from test subjects an anonymous "X."

Even in relatively peaceful, stable countries in Asia and Latin America, authoritarian cultural traditions can impede the process. Doctors in Latin America exercise absolute authority with patients and "are basically against informed consent," said Daniel Campos, an Argentine oncologist whose company tries to match drug companies with physicians interested in conducting trials. "Telling patients everything, like you do, that's a real novelty. . . . Patients want doctors who say 'Do this because I say so.' "

## Fiasco in Switzerland

Human drug testing is not unusual in Switzerland, where the pharmaceutical industry is one of the staples of the economy.

That's especially true in Basel, home to two of Switzerland's top three drug-manufacturers, Roche and Novartis. For years, the companies conducted clinical drug trials at their own laboratories, using area residents.

But as costs rose, the Swiss firms -- like their American counterparts -- doled out testing work to contract

research organizations. And regulators soon discovered that in an era of booming human drug tests and free-flowing cash incentives, even wealthy Western countries have difficulty enforcing informed consent.

Prosecutors are investigating whether Switzerland's most aggressive and successful independent research firm, Van Tx, violated the rights of patients and falsified results of drug and urine tests. A lawyer for Cornelis H. Kleinbloesem who headed the now-bankrupt company, said that if abuses occurred, Kleinbloesem was unaware of them.

Kleinbloesem, the former head of clinical trials for Roche, started his operation under the name of Clin-pharma in 1995. It was renamed Van Tx in 1998.

The firm quickly outstripped most of Switzerland's other three dozen drug-testing firms. Jean-Christophe Meroz, a lawyer for the Swiss agency that oversees the pharmaceutical industry, said Van Tx recruited subjects and got trials underway at "record" speed and "met the market needs perfectly." Recalled Markus Steiger, Van Tx's former financial manager: "We had a lot of work. We had no time."

Roche and Novartis were major customers, but Van Tx attracted business from all over the world, landing contracts with at least seven U.S. firms. The company accounted for nearly 30 percent of all of Switzerland's Phase One clinical trials -- the first human testing stage after a drug has been tested on animals and in laboratories -- between 1995 and 1999. It posted roughly \$10 million in revenue annually, according to Hardo Loehr, deputy head of Basel's bankruptcy court.

Although the Swiss had well-established regulations governing drug trials, in practice officials exercised little oversight. Jurg Schifferli, head of the ethics committee that oversaw one of Van Tx's Basel-area clinics, said he made only one visit -- scheduled in advance -- and found all in order. Regulators and researchers operated on a basis of trust, Schifferli said, adding, "Maybe I was naive."

By late 1998, Van Tx had dozens of contracts, but not enough subjects. The firm's answer was to import them from Estonia. Van Tx rounded out the ranks with at least some local drug addicts and refugees seeking asylum, according to Meroz and Conrad Engler, head of Pharma Information, a firm that handles public relations for Swiss pharmaceutical companies.

In the tiny southern Estonian town of Tartu, Van Tx enlisted an elderly lung specialist to drum up subjects. Although Heinart Sillastu would not disclose his compensation, he said Van Tx paid for him to travel "to many places," including France, Hong Kong and, repeatedly, Switzerland.

He, in turn, paid several other Estonian doctors and students at a local university to help him find test subjects. Over a period of eight months, he recruited 177 Estonians.

In a country where the average monthly salary is \$160, Van Tx's promise of \$140 to \$600 in cash, plus a free trip to Switzerland, proved alluring. "I can live for five months on that," said Erik Roop, one participant.

Some subjects met with Sillastu; others said they were simply handed plane tickets by friends and told when to show up at the airport. Some told authorities Sillastu gave them consent forms to sign; others said they saw no papers.

Sillastu said he made it clear to volunteers why they were needed, but left it to Van Tx to provide the full explanation. Later, when stories about the clinic's practices began to surface, he said he became more explicit

with recruits. "In the last groups, when the scandal was already going on, then I gave everybody a description of the trial, and what would be the side effects, and so on," he said. "So that nobody could say they didn't know."

Roop, a 22-year-old student from Estonia's state university in Tartu, said the fact that participants did not understand what they signed was just one of Van Tx's problems.

During his May 1999 stay, he said, subjects switched urine samples to hide alcohol and cigarette use and spent off-hours shoplifting on Basel streets. The nurses were so incompetent, Roop said, he drew his own blood, using the experience with needles he gained during his days as a drug addict.

Most of Van Tx's Estonian recruits were healthy. But Sillastu also rounded up 38 heart patients and four arthritis patients for a more advanced drug trial. For help, he turned to Jaan Lemendik, who heads the outpatient clinic in the sleepy, seaside town of Parnu.

Sillastu says he paid Lemendik "a little bit" and told Lemendik explicitly that the trial involved an experimental drug to prevent blood clotting. Lemendik denied receiving a payment and he knew only the drug was new, not that it was unapproved.

Among Lemendik's recruits was a 57-year-old Estonian businessman suffering from high blood pressure. The doctor gave him and about eight heart patients consent forms written in Estonian. But the businessman, who requested anonymity because he feared he would be denied medical care if Estonian doctors learned he had complained publicly, said he only had time to scan and sign the forms before Lemendik collected them, telling the patients how lucky they were to be chosen.

Lemendik denied this. "I was not trying to lure anyone into this," he said.

After waiting three days in Basel, the businessman was transferred to Van Tx's suburban clinic and quickly figured out he was not at a treatment center when he saw wards full of foreigners. He refused to sign a new consent form and demanded to be allowed to go home. He said he was told to find his own way to the airport. It took the intervention of his lawyer to get him out of the clinic three days later.

"In general, I understand," the businessman said, sitting in a deserted cafe in Parnu on a warm fall day. He rubbed his thumb and index finger together in the universally understood gesture. "It was business."

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