

# Latin America Is Ripe For Trials, and Fraud

By Karen DeYoung and Deborah Nelson  
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## *Fifth of six articles*

BUENOS AIRES – Luis Antonio Corgiolu had just returned home from teaching his morning class at a technical school when he felt sharp pains in his chest. His wife insisted on calling an ambulance, and the paramedics who rushed him to the hospital suspected a heart attack.

Emergency room doctors diagnosed "unstable angina," a less serious restriction of blood flow to his heart. Corgiolu protested that he was feeling much better, but doctors admitted him overnight.

The 67-year-old father of three grown sons died the next afternoon. A hole in his aorta, the heart's main artery, had caused his original pain, the doctors at Pedro Mallo Naval Hospital told his bewildered family. Doctors had tried to repair the hole with emergency surgery. But his blood flowed out like water from a pump, the doctors said, and there was little they could do. Corgiolu bled to death.

The family tried for weeks to find out how a man who was living, talking normally, and being treated for one diagnosis, could die the next day from something entirely different. No one from the hospital provided what they considered a satisfactory answer.

"We buried him," recalled 27-year-old Javier, the middle son. "And we started learning to accept it."

But Argentine prosecutors believe Corgiolu's death was murder. After more than two years of investigation, they say they are preparing to allege in court that doctors fraudulently enrolled Corgiolu – and many others – in a drug experiment being conducted at the hospital, illegally injecting them with an experimental medicine.

Many health professionals and government officials in Latin America see the Naval Hospital case as a warning. Western drug companies increasingly view the region as a major source of subjects for drug experiments, and as the number of clinical trials has boomed, the frantic pace has threatened to outstrip efforts by local regulators to establish effective oversight.

Executives at Aventis Pharma, the company whose drug was being tested at the Naval Hospital, say the case was an aberration. They cite the experiment's eventual shutdown as proof that the company's monitoring systems work, backed up by effective oversight by government regulators. "The fact that the problems were detected and brought to the attention of the Argentine authorities and the [Food and Drug Administration] demonstrates that the supervisory and quality assurance systems work effectively," the company said in a written statement.

The Naval Hospital, which conducted its own investigation of the case, concluded it had been defrauded by the doctors in question and fired them, a spokeswoman said.

Latin American governments are in fact making a major push to establish systems to control drug tests and comply with international standards, and have passed laws to protect patients. Private programs have been set

up to train medical staff in the complicated procedures and record-keeping required by U.S. authorities for new drugs destined for the American market.

But the regulators are pressured by the drug companies themselves. "Every barrier to their wish to speed things up is seen as a bureaucratic hindrance," said Fernando Lolas, head of bioethics for the Pan American Health Organization, which works with Latin American governments to improve testing standards. "When I talk to [company] executives, I tell them that in the long run, it's worth it to be more ethical from the beginning, rather than risk that some human rights group will point out" their lapses.

## The Signature Problem

It was nearly six months after Corgiolu's death in December 1997, that an unexpected, late-night telephone call brought his wife and sons from their Buenos Aires suburb of Olivos to the prosecutor's office downtown. Prosecutor Lucio Herrera "asked us to tell them the story of what happened to my father," 21-year-old Guillermo recalled, and then showed them a medical file.

"There was a piece of paper with my father's name, and his ID number," Guillermo remembered. "There was a signature at the bottom, 'Luis Antonio Corgiolu.' They asked us if it was his. We all looked at it, and said no."

The paper was an informed consent document, giving doctors at the hospital permission to inject Corgiolu with an experimental drug called cariporide as part of a worldwide, FDA-approved clinical trial. The drug's manufacturer, Hoechst Marion Roussel, now part of Aventis, hoped cariporide would protect the heart from further damage after episodes of angina, artery-clearing angioplasty or bypass surgery.

Among the side effects listed on the form that his family says Corgiolu never saw nor signed, was increased blood pressure. After his angina diagnosis and admission to the hospital, Corgiolu received three intravenous doses of the drug, along with a blood thinner, according to hospital records. While the best of diagnosticians can mistake a rare and often fatal aortic dissection for comparatively common angina, said one American cardiologist uninvolved in the trial, administering such treatment to a man with a hole in his main artery would be "basically like shooting him."

Corgiolu was one of 137 patients given cariporide at the Naval Hospital during late 1997 and early 1998. Prosecutors believe that none of them consented to the treatment. After finding and interviewing nearly all of the patients or their families, they determined that signatures on at least 80 consent documents were forged. Of those who actually signed the paper, prosecutors said, not one said they knew what they were signing.

But the forged consents were only the most glaring example of the fraud prosecutors allege. Electrocardiograms didn't belong to the patients in whose files they were found. Data was changed in medical records to make patients' conditions fit within the study's parameters. And some key documentation disappeared shortly after the investigation began, the prosecutors say.

Thirteen patients died in the eight months before the trial was finally shut down – most of them apparently in the normal course of serious cardiac conditions. But prosecutors say they believe that at least three deaths, including Corgiolu's, were murder. They say they are ready to seek indictments on charges ranging from fraud to homicide against the four-doctor team involved in the study.

Heading the list of defendants, they say, will be cardiologist Luis Garre, the team leader within the hospital coronary care unit, whom Hoechst had agreed to pay \$2,700 for each trial patient enrolled.

Herrera and the Corgiolu family say that Garre's eagerness to enroll as many patients as possible led directly to the misdiagnosis and delay in treating his actual condition, administration of the drugs that made it worse, and Corgiolu's death. Garre did not respond to several requests, through his lawyer, for an interview for this report. In a deposition, he said he could not be held liable for Corgiolu's death, because a subordinate had enrolled Corgiolu in the trial and ordered administration of the drug.

As it turned out, the experimental drug, even when used correctly, was a bust. At a meeting of the American College of Cardiology held in Frankfurt in September 1999, Hoechst announced disappointing results for the worldwide cariporide trial. The test, nicknamed GUARDIAN, involved more than 11,500 patients at nearly 400 study sites in 23 countries. Although the drug was found to be safe in patients with the targeted conditions, cariporide did not significantly reduce the risk of death or new heart attacks. The company decided not to file an FDA application for U.S. marketing approval.

No one at the presentation in Germany mentioned Garre or the Naval Hospital, and he and his 137 patients played only a small part in the overall trial. The hospital was one of 26 study sites in Argentina alone, and no serious problems were found at the others.

But inside Latin America's drug-testing community, there are few who do not flinch at the mention of Garre's name.

"We spoke to him personally, and he recognizes he did wrong," said Gustavo Kaltwasser, a Chilean infectious disease specialist who serves as Latin American representative for the Western Institutional Review Board, a for-profit, U.S.-based ethics committee that approves drug research protocols. "But it's one thing to do something wrong, and another to kill people. I guess the law has to decide."

## Latin Fever

Drug companies are continuing to expand rapidly in Latin America. "This year, the American public cannot seem to get enough of Latin American music and culture," noted an upbeat assessment in last May's issue of *CenterWatch*, a monthly publication on clinical trials. "That same fever may soon be coming to the clinical trials industry. . . . A valuable untapped opportunity is waiting."

The fever is already rising. In Argentina alone, more than 200 clinical trials were begun last year, more than double the number in 1995. Most estimates put the number of ongoing trials in Brazil at near 1,000, a five-year increase of 200 percent. During the first eight months of 2000, the government of tiny Costa Rica, with 3.6 million people, received 42 new trial applications from U.S. and European companies. [See related story.]

"We're colonizing a region for clinical trials," declared Juan Pablo Guzman, who has worked on clinical trials in Latin America for Searle and Pharmacia, at June's annual meeting of the Drug Information Association in San Diego. "We have to believe there is gold at the end of the journey."

The industry's El Dorado is Latin America's 450 million people, most of them accessible in large cities, many of them conveniently plagued with the same First World ailments – heart disease, arthritis, cancer, infections ranging from HIV to earaches – as their neighbors to the north. Although the region already constitutes the world's third-largest pharmaceutical market, behind the United States and Western Europe, many Latin Americans are still in "treatment-naive" condition, coveted by the companies because their bodies have not been adulterated by other drugs that might interfere with the effects of an experimental treatment.

As in other Third World regions, "patients have a strong motivation to participate" in drug tests, said Argentine oncologist Daniel Campos, whose new company here, Salud Uno, matches drug companies with specialist physician networks interested in conducting trials. "These are mostly people who are born, live and die in the same place. It's free diagnosis and treatment."

Huge numbers of patients can be recruited quickly at hundreds of "multicenter" sites in several countries at once. There is also a seasonal advantage, because most of Latin America lies in the Southern Hemisphere. Ailments that predominate in summer can be studied here during the Northern Hemisphere winter, and vice versa.

The region offers a number of university-based research establishments and modern health care facilities, particularly in larger, more sophisticated countries such as Mexico, Brazil, Argentina and Chile. Some countries have government health insurance programs, and many physicians are U.S.-trained and keep up contacts with their American mentors.

These contacts help U.S. specialists subcontract experiments to places where a particular disease is more prevalent. George McCracken of the University of Texas Southwestern Medical Center, a recognized leader in meningitis research, said he would prefer to do all his studies at his home base in the United States. "But it's impossible to do that for meningitis," he said. "In 1980, we would have had 150-200 patients" for a trial. "Now, we might have 30, of whom 25 are pretreated [with on-the-market antibiotics] and not very suitable for study."

When AstraZeneca applied in 1996 for FDA approval of meropenem, a new antibiotic for treatment of acute bacterial meningitis, it listed McCracken as the principal investigator for a trial involving 94 pediatric patients. But "because there were so few meningitis cases in Texas," the FDA noted in an inspection report, "a decision was made to enroll all the children" at the National Children's Hospital in Costa Rica, where they were under the care of Carla Odio, a former McCracken student. McCracken, the FDA said, was "kept informed of the study progress." But he never saw any of the patients.

"If you're going to do multicenter studies, you have no choice" but to subcontract, McCracken said. "The advantages from my standpoint [of conducting trials in Latin America] are that the investigators we use are very well trained. Several of them were trained by me."

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Cost is also a factor. While some Latin American investigators demand per-patient payments comparable to their First World counterparts – Garre's \$2,700 per patient was only slightly lower than Hoechst paid for GUARDIAN patients in Canada, according to internal company documents – hospital and other per-patient costs are considerably less.

Physician-investigators also can help market a drug after approval. Argentine regulators acknowledge that some doctors here are routinely paid by pharmaceutical companies every time they prescribe that company's drug. "Lots of doctors' money comes from that," said Campos.

Despite their eagerness to expand in Latin America, the drug companies themselves report persistent problems getting Latin American physicians to adhere to complicated FDA requirements and record-keeping for new drug investigations. Whether from a misplaced desire to please their drug company patrons, or differing reporting standards, company representatives complain, many Latin doctors are reluctant to advise drug-makers of "adverse events" involving trial patients, whether it's a sneeze or a fever or death.

"They don't know what to consider an adverse event," said Jose Alberto Ardon, medical director of Pfizer Inc.'s Central American operations. "Sometimes they'll just say, 'Oh, this person has a headache, and we know that with this disease or product lots of people get headaches, so it's not important to write it down.'"

These lapses not only violate FDA procedures, they sometimes can have potentially dangerous consequences. In 1996, FDA inspectors visiting two Sao Paulo clinics, where 966 HIV-positive Brazilians were participating in a protease inhibitor study for Merck & Co., found doctors had failed to report potentially life-threatening renal complications in some subjects. Based on results from simultaneous trials in Western Europe and the United States, such complications were determined to be a serious side effect. The drug, called Crixivan, won FDA approval with agreement to label it with warnings of possible kidney stones and other renal problems.

As in the rest of the developing world, Latin America offers opportunities to experiment with treatments that might be considered questionable, or even unethical, in the United States.

At an FDA advisory committee meeting in Gaithersburg two summers ago, participants bemoaned the difficulty of persuading U.S. pediatricians to stick needles into the ears of children with acute ear infections to assess experimental antibiotics. Drug companies were concerned, said one physician, "that if you want these studies done, we are going to have to go overseas, we are going to have to go to Central America, wherever, where it is easier to get patients." Not only were American doctors leery of the painful procedure, participants agreed, most American parents simply wouldn't subject their children to it.

Many Latin American governments have declared their commitment to Good Clinical Practice, the guidelines for trials adopted by the International Conference on Harmonization to which the United States, Western Europe and Japan adhere. Among them are the establishment of Independent Review Boards, committees that guarantee trial protocols and procedures comply with ethical and legal standards. But agreeing to the rules is not always the same as implementing them.

"We Latin Americans . . . like laws and regulations," Western's Kaltwasser said. "We put a lot of effort into them, but we never carry them out."

## Irregularities Emerge

Virtually every major U.S. and Western European drug company now maintains a network of offices across Latin America. Following closely behind have been the Contract Research Organizations, or CROs, the subcontractors who manage and monitor the trials. Theoretically, the companies, the CROs, the ethics committees and the various governments provide several layers of insurance against bad trials. With so many people watching, how could a study go wrong?

ANMAT, Argentina's government entity for approving and monitoring trials, is widely considered the best organization of its type in Latin America, with 30 physician-inspectors who rigorously review clinical trials. Yet the GUARDIAN trial continued at the Naval Hospital in Buenos Aires – with no valid consent forms, faked patient records and suspicious deaths, according to prosecutors – for eight months before the alleged frauds were discovered.

Sheer numbers compound the challenge faced by regulators. GUARDIAN had 26 separate trial sites in Argentina, and was only one of hundreds of studies going on at the time in the country. With so many sites to keep track of, perhaps Garre seemed to require less supervision than most; he had participated in international trials before and was "a recognized cardiologist at a leading hospital in Buenos Aires," the Aventis statement said.

It was Hoechst (now Aventis) that chose Garre as a site investigator. In an August 1996 letter to Quintiles Transnational, the North Carolina-based CRO it hired to manage the study, Hoechst noted that Garre could be counted upon to recruit patients quickly. "According to Dr. Garre's estimates," wrote Silvia Zieher, Hoechst's medical manager for the trials in Argentina, as many as 120 cardiac patients a month passed through the Naval Hospital.

"It seems important to note that Dr. Garre can get authorization from the Naval [ethics] committee . . . really quickly," Zieher noted. "The committee meets every 15 days, and he tells me we don't need to have the protocol in Spanish."

A report filed by Quintiles to Hoechst in December 1996, after it had inspected and approved Garre's operation, estimated he would recruit at least 24 patients at a rate of one to two per month over an 18-month period. But before enrollment was half over, Garre had signed up more than five times that many.

The "high enrollment rate" prompted concern, Aventis said in its written response, and the company audited Garre's operation in March 1998.

Hoechst asked Quintiles to investigate a "document discrepancy" it uncovered, but the CRO "determined this did not indicate evidence of fraud," it said in a written response to Post questions.

It was during a subsequent, unrelated visit two months later, both companies said, that "Quintiles detected serious ECG [electrocardiogram] irregularities." Among them, sources involved in the trial said, was the apparent duplication of electrocardiograms – identical printouts were found in the files of a number of patients. Based on this and other "potentially fraudulent activities at Dr. Garre's site," Quintiles alerted Hoechst, which reported the matter to the hospital. Argentine authorities were also notified, and began a criminal investigation.

In June, 1998 Garre's participation in GUARDIAN was terminated. Although no longer at the hospital, he remains active in his private medical practice.

Hoechst was first drawn to Garre because he had served as principal investigator in previous clinical trials. Two studies in which he participated, both studying the anti-coagulant drug enoxaparin, were for Rhone-Poulenc Rorer, the French pharmaceutical company that merged with Hoechst last year to form Aventis Pharma, whose drug development center is in Bridgewater, N.J.

In light of the GUARDIAN problems, Aventis said, it has reviewed Garre's earlier data and has thrown out his results in one of the enoxaparin trials, called TIMI 11B. Prosecutors said they are investigating possible consent form forgeries in that study.

Neither Aventis nor Quintiles believes the Garre case points to any larger flaws in the clinical trials system. "The vast majority of physicians who participate in clinical trials worldwide conduct the studies ethically and with integrity to bring new drug therapies to patients," Quintiles said in a written statement. "However, the system can be hurt by physicians who, through their misconduct, intentionally defraud innocent parties."

But some of those in the field are not so sure. "Garre was very well respected in cardiology," said Sergio Rosengarten, Sao Paulo-based medical vice president for Aventis's Latin America operations. "He belonged to a well-recognized hospital, with a well-recognized cardiology division. We had never had any previous bad experience with him."

"It can happen again," Rosengarten said. "You never know."

## Acceleration and Errors

"They explained everything to me," 14-year-old Nohelia Gonzalez told a visitor to her tiny bedroom last September, a month before her death from advanced bone cancer.

Surrounded by stuffed animals and Ricky Martin posters, Nohelia was an emaciated bundle of nonstop teenage chatter. The doctors "told me that I was going to be the first" child in Costa Rica to try a new kind of delivery of a pain-killing drug that was approved only for adult use, she said. "They told me I would be in the hospital three or four days to see how I would react, to see if it would make me sleepy. . . . They told me I could drop out whenever I wanted."

The drug was called fentanyl. Janssen Research Foundation, a division of Johnson & Johnson, had developed a way to deliver it through an adhesive patch changed every three days and obtained FDA approval to test it for safety and effectiveness in children. When she signed up for the study in June, no one told Nohelia or her parents that it would cure her cancer. But they said it might eliminate both her pain, and the fog induced by the constant doses of morphine she had been taking.

And it did. During the relatively brief period she participated in the fentanyl patch trial, Gerardo and Sonia Gonzalez said, they had their daughter back. After months of semi-consciousness, Nohelia was alert and happy. She played with her sister's baby and watched her favorite soap operas. Girlfriends who had stopped coming by gathered again in her room, giggling and gossiping and listening to music.

Nohelia's treatment produced the mutual advantage between drug companies and Third World patients that international pharmaceutical companies say they seek. Not only did a middle-class Costa Rican girl have access to a treatment that was otherwise unavailable, her trial participation came with free, near-constant attention from her country's best medical professionals.

The lengthy consent form her parents signed explained risks and possible side effects. After the 15-day trial was finished, Janssen supplied Nohelia with fentanyl patches and continued to check on her progress, until she died.

There are many Nohelia Gonzalez's in Latin America and throughout the Third World – patients treated by caring, conscientious physicians in apparently well-run trials of drugs that offer promise to them and others. Both the pharmaceutical companies and the physician-investigators are pleased to produce them on request.

What's hard to know with precision is how many Luis Antonio Corgiolus there are. "The horror stories," as Lolás, of the Pan American Health Organization calls them, rarely surface unless they are among the very few foreign trials inspected by the FDA or by domestic authorities, or result in criminal investigation.

Some Latin American physicians say they resent suggestions that they are not capable of the high quality research demanded by the FDA and Western European drug monitors.

"Research done in developing countries is not all banana research," said Chilean infectious disease specialist and clinical trial veteran Miguel O'Ryan. "A lot of people are putting a lot of effort into having standards that are as high, or even higher" than those in the United States and Western Europe.

But O'Ryan is one of many who express concern that pressure from the pharmaceutical industry to produce fast, high-volume results – and a willingness to pay for quantity over quality – will ultimately discourage the development of serious science in Latin America. "I really worry about the strategy of the companies of looking for hundreds of sites to get things really fast," O'Ryan said. "I think studies can get out of hand, and it's hard to get meaningful data, comparable data from so many sites. . . . The bad thing is that it's killing our interest as people who want to promote good clinical research in developing countries."

"I think that when there is competition," O'Ryan said, "then there is the possibility, if you're doing it for the money, maybe to do it a little bit on the edge."

Campos, the Argentine oncologist, agreed. "This acceleration is going to cause errors; a point comes when a physician has reached capacity. The frauds will become more sophisticated than the FDA can figure out. The auditors looking for fraud look for certain patterns, and the more Latin Americans get investigated, the more clever Latin American doctors will become about fraud."

"Imagine if Garre had just been smart enough to shuffle the ECGs so it wasn't so obvious?" Campos said. "Let us be careful. But on the other hand, the industry is pushing, pushing."

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