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Cancer patient
Alexander Ershov took
his chances on an
experimental drug.



DRUG TESTING GOES OFFSHORE

Nearly 40% of all clinical trials are now conducted in poorer countries such as Russia and India, where costs are lower and patients more vulnerable. And that's raising **questions about ethics and oversight.**

BY ABRAHMLUSTGARTEN

Sunlight streams through a window of a St. Petersburg hospital, highlighting the gray stubble on Alexander Ershov's chin as he caresses a plum-sized tumor above his collarbone. Two years ago

the 59-year-old metalworker, who had spent more than half his life operating industrial X-ray equipment, was rushed to this same clinic with a tumor in his kidney. The cancerous organ was removed, but Ershov never had a follow-up exam. Not for lack of trying. Once he waited hours at an outpatient clinic before being told the facility's only oncologist was on vacation; another time he was placed on a waiting list and told to check back in a couple of weeks. Last fall Ershov's blood pressure began to rise alarmingly, and the clinic at his factory prescribed drugs for hypertension. Only later, when his condition worsened, did doctors consider his cancer history and allow him back into the St. Petersburg City Clinical Oncology Dispensary.

The cancer had metastasized into his lymph nodes, which had two immediate effects: It turned his voice into a throaty whisper, and it brought his condition to the attention of Dr. Peter Karlov. Karlov was recruiting patients for a clinical trial of an experimental drug, and Ershov fit the parameters of the study. "They told me the treatment was safe," says Ershov. "I trust my doctor completely." Like 90% of Karlov's clinical-trials patients, he signed the consent form on the spot.

For Ershov, a late-stage-cancer patient in a country with a dysfunctional medical system, the chance to get \$800 worth of drugs a month at no cost, reliable access to doctors, and at least the hope of a cure was too good to pass up. He is like thousands of others at hospitals across Russia who are participating in clinical trials of all types, run by almost every major Western pharmaceutical company. The trials have become not a choice but a necessity for patients with few alternatives. And the nation's centralized hospital system makes recruitment for trials quick and easy, which in turn makes them relatively cheap for Western sponsors. Patients can be recruited ten times faster in Russia than in the U.S., doctors say, shaving precious time and millions of dollars off the drug-development cycle.

That also raises concerns about the ethics and oversight of foreign trials as they spread across the globe. From Azerbaijan to Nigeria, pharmaceutical companies are increasingly shifting clinical trials to emerging markets—as much as 40% of all drug trials this year, according to several pharmaceutical executives, up from about 10% in 1999. And they are doing it by outsourcing many of those trials to contract research organizations, which in turn subcon-



THE RECRUITER Dr. Kostenko has enrolled hundreds of St. Petersburg patients in drug trials.

tract the work of finding patients to people like Dr. Karlov. Merck's Vioxx and Zocor were tested in Russia and other developing countries, as were many of Pfizer's billion-dollar drugs, before gaining approval in the U.S. While the vast majority of the trials are conducted without problems, there have been enough instances of ethical abuse and breakdowns in the scientific process to cause concern. A lawsuit still making its way through U.S. courts alleges that Pfizer tested a meningitis drug on Nigerian children in 1996 without their consent, resulting in five deaths. And there have been charges over the years that other trials have endangered patients or have been conducted without proper ethical review (see box, "When Trials Go Bad").

Ward Cates, president of the research arm of nonprofit Family Health International, which runs drug trials in Africa, acknowledges the difficulties of working in emerging markets. "How do you

meet procedures required by the FDA in settings where electricity is going off two hours a day?" he asks. In March he shut down a Nigerian trial for Viread, an anti-retroviral drug made by Gilead Sciences, a California company, amid concerns that the scientific data were not being handled properly and that the drugs could not be stored securely.

"For us to say the sky is falling would be wrong," says Dr. Bernard Schwetz, director of the Office for Human Re-

"It's a deal with benefits for all sides," says St. Petersburg cardiologist Viktor Kostenko.

search Protection, a sister agency of the FDA charged with oversight of trials that receive federal funding. “But with the volume of research that is going on outside the U.S., we are concerned. Are the data derived from ethical conduct and sound scientific designs?”

THE SHIFT OF DRUG TESTING TO poorer countries is largely being driven by economics. An average new drug costs \$900 million to bring to market, and more than half the cost is tied to the four trial phases in which new medicines are tested on humans for safety and efficacy. Recruiting patients is the most expensive part of drug development, accounting for 40% of the trials’ budget, according to published studies.

Working in countries such as Russia, says Pfizer senior vice president Adrian Otte, can cut three to six months off a trial, meaning a drug can get to market that much faster. And the trials are cheaper. GlaxoSmithKline CEO Jean-Paul Garnier says that a third of his company’s trials now take place in low-cost countries, and he aims to hit 50% within two years. Why? Running a trial in the U.S. costs about \$30,000 per patient. He can do it in Romania for \$3,000. “Globalization,” says Garnier, “is the ultimate arbitrage for companies like Glaxo-SmithKline.”

The outsourcing of clinical trials makes sense for other reasons too. The FDA encourages testing on ethnically diverse populations, hoping for more insight into the ways drugs can affect different people. And drug companies are hoping to penetrate new markets. Russia’s drug market is estimated at \$5 billion this year, India’s at \$5.4 billion.

But the shift also represents a move into the shadows of regulatory scrutiny. While FDA rules must be satisfied for any drug to get approval in the U.S., the agency’s oversight of distant trials is tenuous at best. A 2001 FDA inspector general’s report, for example, criticized the agency for not tracking the number of international sites where trials are being conducted, let alone the number of investigators and patients. That report warned the FDA that “it does not have sufficient assurances of human-subject protections in a growing proportion of research.”

The very business model that summons drug companies to those places also risks exploiting the vulnerability of foreign patients—they are eager to sign up because they lack a viable alternative and tend to have blind faith in medicine. “Patients be-

WHEN TRIALS GO BAD

IN 1996, AS BACTERIAL MENINGITIS was sweeping across Nigeria, Pfizer saw an opportunity for research. While aid organizations rushed supplies of an approved meningitis drug to hospitals in the area, the pharmaceutical giant fast-tracked a clinical trial and chartered a DC-9 to transport its labs and doctors to Africa. There, according to a lawsuit filed against the company in federal court in New York City in 2001, Pfizer administered doses of its experimental drug Trovan to children without their parents’ consent. The case also alleges that in order to make Trovan

seem more effective, Pfizer underdosed children in a control group that received an already approved medication, resulting in the deaths of five children and the impairment of 200 others.

Most experts say the Trovan trial was an aberration, but it is also held up as a foreign version of the Tuskegee tragedy—a textbook case of what can go wrong when pharmaceutical companies conduct human research in poor countries with lax oversight. Here’s a quick look at Trovan and other drug trials that have gone bad in recent years.



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TRIAL	Place (Year)	Company	What Went Wrong
Viread (anti-retroviral tested for HIV prevention)	Cambodia, Cameroon, Nigeria, Thailand, Ghana, Malawi (2005)	Gilead Sciences	Activists (like those above in Thailand) allege a placebo design amplified HIV risk to patients. Cambodia suspended its trial.
HVNET012 (mother-child HIV-transmission prevention drug)	Uganda (2002)	Boehringer Ingelheim	The company withdrew its application to the FDA after discrepancies over patient consent and missing reports of adverse reactions.
Nonoxyl 9 (spermicidal gel for HIV prevention)	Ivory Coast (2000)	Columbia Laboratories	Trials were abandoned after treated patients reported a higher rate of infection than the placebo group.
M4N (oral cancer therapy)	India (1999)	Johns Hopkins University	A compound was tested without adequate consent or review. The trial was halted, but the researcher remains employed.
Trovan (meningitis drug)	Nigeria (1996)	Pfizer	Plaintiffs sued in U.S. court, alleging children were tested without consent, but the case was remanded to Nigeria. An appeal is pending.

lieve in doctors more here,” says Dr. Viktor Kostenko, who has been the chief investigator for 11 drug trials in St. Petersburg. “They are ready to give cooperation to see some benefits. It makes recruitment easy.” Ruth Macklin, a bioethicist who works with the World Health Organization, agrees: “People who are not fa-

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miliar with research can mistake guys in white coats giving them injections for their doctors. It takes some sophistication to tell the difference.”

At the same time, disparity in pay scales and lavish compensation—a trials investigator in Russia can make ten times his salary by recruiting his patients into studies—present potential conflicts for doctors. Patients in St. Petersburg told stories about bribing doctors, passing on a few dollars to ensure they would get a repeat visit or admission to a clinic. Even doctors admit the practice is systemic. In some cases the bureaucracy “is flexible and can be moved a little bit,” says Vladimir Filov, director of the experimental-therapy lab at the Petrov Institute of Oncology, where numerous trials have been conducted. But Filov doubts that clinical-trial data have been tampered with in Russia. “Corruption here cannot be connected with intention to deceive,” he says, “but rather with meeting an objective.”

Making the process even more difficult to control is a lack of transparency. Not only are U.S. regulators sometimes in the dark, but the industry is also notoriously tight-lipped about its projects, says David Rothman, director of the Center for the Study of Society and Medicine at Columbia University. Doctors have been sworn to strict confidentiality, and patients don’t want to lose the chance for free treatment by talking. “In some countries you cannot have oversight over every single inch,” says Juntra Karbwang, clinical coordinator for the WHO. “Pharmaceutical companies might have access to these places, but it’s not easy for us to track.”

A FEW MILES FROM DOWNTOWN ST.

Petersburg, where Audis and Hummers cruise past the Hugo Boss store on Nevsky Prospect, an elevator screeches to the top of a Soviet-era apartment building. It is here, in dreary bedrooms like the one belonging to a 74-year-old woman named Dasha, that one can best understand how the drug industry’s need for human subjects intersects with patients’ lives. Dasha (who would not allow her real name to be used) stares out a window at a concrete courtyard and describes the clinical trial she signed onto three years ago. “I was not dying, but I was deteriorating, and I needed real treatment,” she says, explaining that a doctor had misdiagnosed her heart attack as angina. “The doctors are from the previous generation—they are good for nothing. I wanted regular medical care.”

With the help of a friend, Dasha enrolled in a trial for a cholesterol-lowering drug. She received a thorough examination, but as the years passed and it became apparent that her drug was not helping her condition, her quality of care began to fade. Lately she has had to ask for blood tests and for a liver exam that is crucial for patients on anticholesterol medication. With shaky hands she holds out a straw basket with half a dozen medications—a cocktail the doctor has prescribed to compensate for the trial drug’s ineffectiveness. “He is indifferent to what is happening to me now,” Dasha says. “His main task is to fill out papers in accordance with the protocol.”

Nina Rybakova, who lives nearby, is much happier with her experience as a clinical-trial patient. But she, too, was eager to sign up to get free drugs and treatment—in her case for a trial of an anti-osteoporosis therapy after an operation on a herniated disk two years ago. She was given a consent form to read that spelled out

possible risks but says her doctors were overwhelmingly positive. “They told me there will be nothing detrimental to you, just the benefits,” says Rybakova, who is also 74. “I thought, ‘Why not?’”

Whatever the illness, there is a ready pool of patients like Dasha and Nina. Some of their names can be found in a four-inch-thick, leather-bound ledger in the cardiology ward at the nearby St. Petersburg Research Institute for Emergency Medical Care. The hospital is close by the smokestacks of a cement plant and adjacent to a field of muddied construction waste. In a large foyer, patients lie on metal-frame cots below peeling plaster and water-streaked walls. A woman moans in pain. It is here, with the help of the ledger, which contains the names of thousands of patients catalogued by diagnosis, that Dr. Kostenko does his recruiting.

Russia’s centralized health system means that hundreds of patients with similar symptoms are congregated in the same place, like Kostenko’s ward. Many of them are what the industry calls “treatment naive,” meaning they have not built up resistance to new drugs from years of antibiotic treatment, and their diseases are often advanced. They offer a perfect baseline for scientific study.

A drug company might hire Kostenko directly, or he could work for one of the many contract research organizations (CROs) retained

by pharmaceutical companies to conduct local projects. Either way, Kostenko controls access to the patients. The separation is by design: International ethics guidelines prohibit pharmaceutical companies or their contractors from having direct access to patients. Kostenko won’t say exactly how he makes money, but according to Natalie Gershman, CEO of Geny Research, a small Massachusetts CRO that specializes in Russian trials, doctors can be paid more than \$900 for each patient they recruit. Compare that

with the \$200 a month a state-employed doctor gets as a base salary in the city’s outpatient hospitals, and it is clear why many of Russia’s best doctors are migrating to the trials industry. Kostenko recently enrolled 200 heart-attack patients for a drug trial in his ward. Between the database and the financial incentive for doctors to recruit efficiently, things happen fast in Russia.

“It’s a deal with benefits for all sides,” says Kostenko. “For doctors who have financial interests, it’s important for professional growth. And it’s important to patients, because they can receive advanced drugs and get professional examinations free.”

When a trial runs slowly in the West, it is often brought to Russia to make up for lost time. In 1999 the New England Research Institutes, a CRO specializing in public health research, began a multicenter international trial to test the effectiveness of magnesium sulfate on heart-attack patients. After 18 months of recruitment in Canada and the U.S., fewer than 300 patients had been found. The trial was on the verge of collapse when the study’s sponsors contacted a California CRO, Evidence Clinical & Pharmaceutical Research. In little more than a year, Evidence recruited an additional 5,600 patients, mostly in Russia but also in Bulgaria and the former Soviet republic of Georgia. PSI Pharma, the largest CRO operating in Russia, recruited 2,400 patients in just two weeks for a phase 3 trial of a hypertension drug. In that time Belgian investigators enrolled only 20 patients.

Hired as middlemen by the drug companies, the contract research organizations in turn find and pay the doctors, mine for



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patients, and provide local expertise and regulatory experience. As trials have increasingly spread around the globe, the CRO industry, estimated at \$11 billion this year by CenterWatch, a market-research company, has flourished. There are now more than 1,000 CROs, from tiny startups in places like Sofia and Bangalore to publicly held multinationals operating in 80 countries. Quintiles, headquartered in North Carolina, is the largest. This year the company's Eastern Europe division operated trials at 2,500 sites with almost 30,000 patients, according to Heinz Carmen, vice president of Quintiles' operations in the region.

Gershman says it's not uncommon for a drug company to put a trial out to bid among big CROs, which will then outsource it for site management to smaller, more specialized firms like Geny. That can be problematic, says Angela Bowen, CEO of Western Institutional Review Board, a for-profit ethics organization hired by drug companies to ensure that trials meet international standards. In Bowen's experience, the smaller outfits sometimes resist criticizing the doctors they hire because reprimanding them threatens the company's ability to offer doctors and patients to drug companies in the future. "There are these additional forces because of the financial relationship between them and the sponsors," Bowen says. "It sets up a situation that can lead to bad behavior."

That's partly why the WHO and medical organizations in both Europe and the U.S. are racing to keep pace with industry migration and to educate local doctors and CROs about the standards of conduct for medical research that the FDA requires of all trials submitted to it. These internationally accepted guidelines, known as Good Clinical Practice, require the establishment of local review boards; ask government health ministries to ap-

Recruiting patients is the **most expensive** part of drug development—about 40% of a trial's cost.

prove all trials before they begin; warn against excessive payment to doctors; and outline how to obtain informed consent and avoid taking advantage of vulnerable patients. The problem is that the guidelines are just that. Until it's time for final FDA review, a drug company's compliance with international standards remains largely voluntary. A 2002 report published by the U.S. National Bioethics Advisory Commission, created by President Clinton in part to address the globalization of drug trials, found that "ethics-review committees in developing countries were less likely to raise either procedural or substantive issues compared to U.S. boards." Last summer another study published in the *Journal of Medical Ethics* found that a quarter of all trials in developing countries did not receive any local official review. Still, the U.S. approval process places a great burden on local review. "Studies can be conducted before they are submitted to the agency, and of course we have no jurisdiction over them," says David Lepay, director of clinical-practice programs in the office of the FDA commissioner. Lepay says once trial data are submitted to the FDA, they undergo the same rigorous evaluation as data from trials conducted in the U.S. "It's trust and verify—that's what we rely on our inspection program to do."

The FDA requires that international sites be open to spot inspections, but judging by the numbers, those inspections are woefully inadequate. There were more than 500 trials conducted in Russia alone last year at some 3,000 sites. The FDA inspected only about 100 sites around the world in 2004. Investigators like to point out that an FDA inspection has never resulted in rejection of Russian data. And while it's true that most sites meet FDA standards, even those that pass are often deemed in need of improvement. Of the international sites inspected last year, more than 30% were criticized for failure to follow protocol, and one in 12 was cited for failure to report adverse patient reactions.

While the FDA hopes the world's ethical standards will catch up with its regulations, the outsourcing of pharmaceutical trials suggests otherwise. Trials will continue to shift to poorer countries in search of more patients, lower costs, and faster recruitment. Right now Russia is the frontier, but as it gains experience and improves its research standards, costs will inevitably go up. Drug companies are already well established in Poland and the Czech Republic and are looking farther east for new testing grounds. "Eastern Europe has maybe three years," says Ken Getz, founder of the Center for Information and Study on Clinical Research Participation, which monitors drug research. "India has five, and China hasn't even started counting." By then it will be even harder to put the drug-testing genie back in the bottle. ■

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EAGER TO SIGN UP Nina Rybakova says she enrolled in a trial of an anti-osteoporosis drug at a St. Petersburg hospital in order to get free medication and treatment.