CARDIOLOGIST BART DENYS SAYS THAT IF you want to understand why testing new medical treatments can be so discouraging and so expensive these days, just leaf through the proposed clinical trials that pour into his office. Pharmaceutical and medical-device companies seek him out in Thibodaux, Louisiana, because he’s an experienced clinical researcher who works for a private institute with access to more than 30,000 patients.

The companies need help from those patients to run trials on everything from experimental heart drugs to better implants—and to win government approval to sell their products. They are willing to pay physicians and subjects to participate. But the process “can be very frustrating,” says Denys, who has done clinical studies for more than 20 years and is now director of clinical research for the Cardiovascular Institute of the South, a large private practice.

Many trials, for instance, require Denys to wrangle piles of paperwork and guide patients through a maze of lengthy consent forms. Some come with enrollment criteria that are so stringent it’s nearly impossible for him to find subjects who qualify. Others require volunteers to undergo dozens of time-consuming and sometimes painful medical procedures. Then there are the occasional studies that Denys dismisses as “hidden marketing campaigns,” trials that appear designed more to promote the use of a product than to answer important questions.

The take-home message for U.S. biomedical researchers? “The system isn’t working,” Denys says. “We’re wasting too much time and money on trials that are poorly designed and difficult to execute. They take too long. They produce trivial information and not enough important treatments. They don’t ask relevant scientific questions. Clinical trials are broken, just broken.”

A harsh diagnosis, but one shared to varying degrees by many in American industry, government, and academia. Over the past few decades, these experts say the cost of testing a new drug in the United States has skyrocketed to nearly $400 million on average, even as the number of major new treatments emerging from the pipeline has fallen. And that’s just part of the $1.2 billion some experts estimate it now costs to bring a new drug to market. The jump partly reflects efforts to make testing safer, more rigorous, and less vulnerable to fraud, analysts say. But studies have also grown more complex because researchers are testing more sophisticated therapies. Also to blame are poor corporate planning and regulatory chaos.

Analysts fear the trend is imperiling drug development by alienating research foot soldiers such as Denys and driving clinical science out of the United States to nations with laxer rules. “Parts of the system are starting to collapse, and that doesn’t inspire confidence,” says Kevin Schulman, who studies the economics of clinical trials at Duke University in Durham, North Carolina. “We could wake up one day and discover that investors don’t want to put money into drug R&D in the U.S.”

Still, clinical research insiders say it’s not too late to fix the problems. Academic centers and government agencies, including the U.S. Food and Drug Administration (FDA), have launched initiatives aimed at improving the efficiency of the thousands of trials begun each year. Sponsors are already trying simpler
Clinical blizzard. Cardiologist Bart Denys says it’s getting harder than ever to conduct clinical trials in the United States, partly due to growing record-keeping requirements.

designs and automated record-keeping. Some companies even want to scrap the traditional three-phase approach to trials.

“No question, these are challenging times, but this is an amazingly resourceful and innovative enterprise,” says Kenneth Getz, a prominent clinical research analyst at the Tufts Center for the Study of Drug Development in Boston. “Time and time again, the pharmaceutical industry has shown it’s not going to let itself disappear.”

Rising expectations

Many of the 60,000-plus clinical trials registered by the National Institutes of Health on its ClinicalTrials.gov Web site (see p. 217) follow a familiar but not formally required three-step process. Phase I trials typically test for safety in a few dozen volunteers. Phase II studies expand the testing to several hundred subjects, usually with the target condition, to gather more data on safety and preliminary evidence on whether the treatment actually works. If phase II is successful, phase III trials enroll thousands or even tens of thousands of patients at dozens of sites around the nation—and increasingly around the world—to measure effectiveness, with researchers watching closely for side effects.

In the past, industry conducted most of this work at university medical centers, which had plenty of patients and physicians interested in research. In the past decade, however, many factors, including cost concerns, have prompted trial sponsors to work more with private doctors such as Denys. “Just 15, 20 years ago, most trials were pretty straightforward,” he says. “I could find 500 patients to enroll in a phase III drug trial without much problem.” The paperwork was pretty brief, and the data on a single subject might fill just a single page. “Not anymore,” Denys says in a wistful tone. “It’s gotten a lot more complicated.”

Several recent studies suggest he’s right. A team led by Getz, for instance, has been combing through a massive trove of trial data compiled by Medidata Solutions Worldwide, a New York City–based company that consults on clinical research. After looking at protocols for more than 10,000 trials approved between 1999 and 2005, the researchers concluded that studies now require more time and effort than ever from doctors such as Denys.

One time sink, Getz concludes in a study published in the May issue of *Regulatory Affairs Journal Pharma*, is the growing number of enrollment criteria. A patient might have to be within a certain body weight or age range, for instance, or not taking certain other medications. Between 1999 and 2005, the median number of criteria in a typical trial jumped dramatically, from 31 to 49. In part, this reflects an industrywide shift to more nuanced drugs focused on more complex diseases, Getz believes, and greater industry attention to specific demographic groups. “That’s not necessarily a bad thing,” he says. “But the end result is that it is getting a lot harder to find patients you can ‘rule in’ to a trial.”

At the same time, the study found that patients who do enroll in trials can count on being poked and prodded more than ever. In 1999, the typical study involved 96 total procedures, such as blood tests or electrocardiograms. By 2005, the list had grown more than 50%, to 158.

That trend is being driven by both scientific and regulatory factors, Getz and other researchers say. In part, trial designers are taking advantage of a host of new
Clinical Trials and Tribulations

Say it’s late 2001, and you want to compare several drug-based treatments for heart disease in a double-blind, phase III trial enrolling 14,500 patients. Get ready to spend at least $102 million to $207 million, according to a 2005 study led by medical professor Eric Eisenstein of Duke University in Durham, North Carolina. Six veteran pharmaceutical executives developed those estimates, and Eisenstein says it would probably cost more today. About two-thirds of the cost is in monitoring visits to sites and management.

The Trial
Subjects: 14,500
Trial sites: 800
Length: 46 to 71 months
Pages per final patient report: 22 to 134
Monitoring visits per site: 6 to 18

Big-Ticket items:
Site and subject payments: $34 to $102 million (48%)
Site management: $31 to $53 million (30%)
Data management: $11 to $21 million (11%)
Safety reviews: $0 to $9 million (3%)

Total: $102 to $207 million

$ Economy option
Limit trial to 60-page reports and 10 monitoring visits.
Total: $140 million

$ Supersaver
Limit trial to 10-page reports and four monitoring visits.
Total: $85 million

Kaitin, head of the Tufts center, among the problems: Delays reduce the value of intellectual property, which has a limited life; give competitors an edge in the race to the market; and increase borrowing costs. Overall, Tufts researchers estimate that “time costs” now account for roughly half of the cost of getting a new drug approved in the United States.

Complexity also drives up the cost of scrubbing data. Sponsors employ a small army of monitors who visit trial sites and examine and correct faulty databases—sometimes at costs of up to $350 per data point, according to industry veterans. “Just sticking another procedure on the form might not seem like much, but it can have big downstream ripple effects,” says Califf.

One strategy trial sponsors are using to reduce costs is to enlist the help of experienced investigators such as Denys, who have access to large pools of patients. Such veterans are in short supply, says Christine Pierce of RxTrials, an Ellicott City, Maryland–based clinical research company that has run hundreds of trials. “Most physicians are simply not involved” in research, she says, noting surveys that suggest less than 15% of U.S. doctors participate in clinical studies, and those that do typically drop out after just a few years. “They find out it’s burdensome, difficult, and not particularly lucrative,” she says.

As a result, many trials rely on neophyte clinicians who, despite their best intentions, have difficulty recruiting even a few patients. Indeed, some companies now assume that up to a quarter of the “sites” in a study—anything from a fully equipped academic medical center to a solo doctor’s office or temporary storefront—will never enroll a single patient. Those false starts “get very expensive very quickly,” says Pierce, noting that it can cost $20,000 to qualify a site for a trial.

Slimming down
Those numbers are one reason drug- and devicemakers are increasingly moving trials out of the United States to China, India, and Eastern Europe (see p. 214). “They believe they can enroll more patients faster and that the subjects will stay in the trials,” says Califf. But he says companies won’t completely abandon U.S. trials any time soon, if only because FDA is unlikely to approve treatments for use here unless they’ve been tested on at least some Americans. So “there’s a lot of interest in figuring out some new ways of doing this,” he says.

Technologies, including high-tech scanners and sensitive genetic tests, that can give them a better idea of how an experimental treatment is working. But analysts say they are also ordering up needless procedures in order to be ready for questions from regulators. “Nobody ever looks at a lot of this data. It’s totally wasted,” says Robert Califf, vice chancellor for clinical research at Duke. “They just want to have it because they perceive it might come in handy if something comes up.”

Ironically, however, Tufts researchers say the extra work isn’t producing higher payments to doctors and patients. They say these fees, which can amount to several thousand dollars per subject for the doctor and hundreds of dollars for the patient, have been flat or declining over the past decade.

“You’re beginning to see this huge mismatch: The clinical researcher and patients are being asked to do more for less,” says Medidata’s Ed Seguine, who worked with Tufts on the study.

Battalions of checkers
The slumping fees, however, don’t mean trials are getting cheaper. Other studies are finding that growing complexity is having a profound impact on bottom-line costs, sometimes in hidden ways.

Difficulties in enrolling patients, for instance, mean that trials often take far longer than planned. The Tufts analysis found that trial length rose by 70% between 1999 and 2006, to an average of 780 days. “Delays are costly because time is literally money in this industry,” says Kenneth
He hopes that at least some of those solutions will come from the new Clinical Trials Transformation Initiative, begun last year by Duke and FDA. Among its targets: Finding ways to standardize and automate paperwork, identify and accredit experienced clinical researchers and sites, reduce monitoring overhead, and clarify what kinds of data are essential for regulators. “The clinical research enterprise needs to evolve,” Janet Woodcock, FDA’s deputy commissioner, said in unveiling the initiative last November. “It needs to be much more streamlined and efficient.”

Those goals also underpin another, longer running FDA effort, called the Critical Path Initiative. Since 2004, the agency has been trying to tackle a host of trial-related issues, including how best to deal with incomplete trial data and how to promote innovative, “adaptive” trial designs. Such studies allow investigators to peek at trial data before the study is formally over, potentially allowing them to shorten trial times or make mid-course corrections.

Many companies aren’t waiting, however. “I’m seeing all kinds of experiments,” says Getz of Tufts. At pharma giant Wyeth, for instance, executives are moving to replace the traditional three-phase trial process with an approach called “Learn and Confirm.” Based on ideas promoted by the late biomedical researcher Lewis Sheiner, it splits the testing process into two phases overseen by different teams of researchers. The learn team leads the equivalent of phase I and II studies, while a confirm team tries to finish the process. Wyeth executives hope the competitive reviews will lead to leaner, meaner trial designs and fewer wasteful late-stage trials driven by researchers unwilling to kill off pet projects.

Other companies are selling off in-house research units and turning to outside contract research organizations in a bid to cut management costs, which often account for more than half a study’s price tag. Studies suggest it’s an area ripe for cost-cutting (see graphic, p. 212). They’re also hiring what one industry insider calls “site whisperers,” consultants who use massive databases and extensive personal knowledge to identify physicians and sites likely to produce patients and high-quality data.

Companies are also hiring consultants to analyze trial complexity. Seguine, for instance, tells how he showed a company that one of its trials was about three times more complex than the standard. “Complexity isn’t necessarily good or bad,” he says. “But you need to consider it.”

In Louisiana, that’s just the kind of advice Bart Denys wishes more trial sponsors were getting. “Some of the studies I see are so complicated I wouldn’t be able to enroll a single patient,” he says, much less concisely explain the risks or study design. Others, he adds, push the boundaries of what’s ethically acceptable. He refuses, for instance, to participate in what he believes are “seeding studies” designed to acquaint doctors with a product (see sidebar, below). And he also dislikes studies that may provide little benefit, and possibly great misery, for volunteers. “I saw one recently that would have required me to inject a placebo into a patient more than 100 times in just a few weeks. I mean, who is designing these things? It’s pretty obvious they don’t see patients.”

Still, Denys says he’s “hanging in with clinical research because it is intrinsic to how I practice medicine—I want to answer questions.” The question now is whether that kind of curiosity will, in the long run, be enough to sustain clinical research in the United States.

—DAVID MALAKOFF

David Malakoff is a writer in Alexandria, Virginia.

Allegations of Waste: The ‘Seeding’ Study

In March 1999, 600 doctors began enrolling more than 5500 arthritis patients in a short clinical trial aimed at comparing the gastrointestinal safety of the new Merck painkiller Vioxx with an existing treatment. But internal company documents suggest the trial had little to do with science and much to do with marketing, according to a recent analysis. Merck denies the charge, but the study has focused new attention on so-called seeding trials aimed at promoting new treatments.

The documents were obtained during the discovery process by attorneys suing Merck over Vioxx’s safety. They suggest that Merck’s marketing division “designed and executed” the 1999 ADVANTAGE trial, which at least one top company scientist criticized as “intellectually redundant” and “wasteful,” physician Harlan Krumholz of Yale School of Medicine and three colleagues reported in the 19 August issue of the Annals of Internal Medicine. The four authors, who are paid consultants to attorneys suing Merck, also claim that Merck employees routinely referred to ADVANTAGE as a seeding trial, “but let’s not call it that in our internal documents,” one wrote in an e-mail, according to the Annals article. The company’s goal, the authors conclude, was to lure leading physicians into the habit of prescribing Vioxx in the months leading up to its U.S. Food and Drug Administration’s approval of the drug—although the purpose of the trial was not made clear to patients or doctors.

Although seeding trials may be a longtime open secret in the industry, the authors write that the Merck documents “provide the first strong documentary evidence” of the practice.

Merck has vigorously defended ADVANTAGE. “The primary intent of the study was to answer scientific questions of importance to primary care physicians,” Jonathan M. Edelman, executive director of Merck’s Global Center for Scientific Affairs, wrote in an open letter. Merck’s business interests “were clearly understood” by independent reviewers who approved the trial, he added. And the Annals itself, he notes, published ADVANTAGE’s results in 2003 because editors thought the findings were useful.

Annals Editor Harold Sox, however, now says the journal would not have published the results had it known of the trial’s apparent purpose. “Deception is the key to a successful seeding trial,” Sox and Journal of the American Medical Association Deputy Editor Drummond Rennie conclude in a recent editorial, adding that it’s up to reviewers, doctors, and even patients to ask questions that might reveal when promotion is masquerading as research.

—D.M