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FORTY YEARS' WAR

Lack of Study Volunteers Hobbles Cancer Fight

By [GINA KOLATA](#)

Not long ago, at a meeting of an advisory group established by Congress to monitor the war on [cancer](#), participants were asked how to speed progress.

“Everyone was talking about expanding the cancer work force and getting people to stop [smoking](#),” said Dr. Scott Ramsey, a cancer researcher and health economist, who was participating in that [January 2008](#) meeting of the President’s Cancer Panel. “Lots of murmurs of approval.”

Then it was his turn.

The biggest barrier, in his opinion, was that almost no adult cancer patients – just 3 percent – participate in studies of cancer treatments, mostly new drugs or drug regimens.

“To me it was obvious,” Dr. Ramsey said. “We can’t improve survival unless we test new treatments against established ones.”

The room fell silent.

“It was one of those embarrassing moments,” said Dr. Ramsey, an associate professor at the Fred Hutchinson Cancer Center in Seattle. He had brought up the subject he said no one wanted to touch.

Forty years after President [Richard M. Nixon](#) declared war on cancer, death rates have barely changed. “Why aren’t we getting cures?” Dr. Ramsey said. “This is one of the biggest reasons.”

Of course, there have been highly successful clinical trials – studies of drugs like Gleevec for [chronic myelogenous leukemia](#) and [estrogen](#)-blocking therapy for [breast cancer](#), and also studies that proved drugs did not work. But the problem is still immense, cancer researchers agree.

There are more than 6,500 cancer clinical trials seeking adult patients, according to clinicaltrials.gov, a trials registry. But many will be abandoned along the way. More than one trial in five sponsored by the [National Cancer Institute](https://www.nationalcancerinstitute.gov/) failed to enroll a single subject, and only half reached the minimum needed for a meaningful result, Dr. Ramsey and his colleague John Scoggins reported in a recent [review in The Oncologist](#).

Even worse, many that do get under way are pretty much useless, even as they suck up the few patients willing to participate. These trials tend to be small ones, at single medical centers. They may be aimed at polishing a doctor's résumé or making a center seem at the vanguard of cancer care. But they are designed only to be "exploratory," meaning that there are too few patients to draw conclusions or that their design is less than rigorous.

"Unfortunately, many patients who are well intentioned are in trials that really don't advance the field very much," said Dr. Richard Schilsky, an oncologist at the [University of Chicago](https://www.msd.uchicago.edu/) and immediate past president of the American Society of Clinical Oncology.

Others studies, by companies, are designed to persuade doctors to use their drugs.

Still others are testing questions like whether it makes a difference to give a drug every nine days or every two weeks. "These are practical real-world questions," Dr. Schilsky said. "But they don't do a great deal to advance the research field. They are not going to provide the next breakthrough."

In any case, the great majority of oncologists just steer clear of studies. They make little or nothing on trials and, in fact, often lose money. These doctors also may discourage patients from going elsewhere to enter a trial: if a patient leaves, the doctor loses business.

One issue is the money lost on [chemotherapy](#), the source of 60 percent to 80 percent of the revenue at oncologists' offices. The doctors buy the drugs and are reimbursed by insurance for slightly more than the drugs' cost. But if patients are in clinical trials, the drugs may be paid for by the federal government or a drug company sponsoring the study — and doctors get nothing.

Then there is the poorly reimbursed hour or so it takes to explain a trial to prospective patients. And, after all that, most patients either turn down the trials or, after further testing, turn out to be unqualified.

That is just the start, cancer specialists say. There is voluminous paperwork. And the risk of legal liability for errors like neglecting to mention a financial interest in the drug being tested, in specimen handling or in billing.

“A lot of doctors say, ‘This is not worth it,’” Dr. Schilsky said.

Reluctant Patients

It is one of the worst times imaginable – a cancer diagnosis, all the terror that goes with it, and then, sitting in a doctor’s office and being asked to make difficult decisions about treatment. Then add questions about joining a trial. Some say it is just too much to think about.

Research starts with so-called Phase 1 trials that test a drug’s safety and the maximum dose patients can tolerate. Although it is possible that some will benefit, most do not because the doses are ineffective or unsafe and few new drugs prove worthwhile.

Then comes Phase 2, further testing of the drug in a small study, and Phase 3, in which patients with a particular cancer that is still treatable are randomly assigned to get the best available current drug or that drug plus the new experimental one.

Most patients are not interested in clinical trials. Some do not want the extra office visits and tests a trial entails and do not want their treatment determined by the flip of a coin. Others fear getting a placebo, even if there isn’t one – placebos are rarely used in United States cancer trials. Others find the whole idea too overwhelming when they are trying to save their lives.

At California Cancer Care, in Greenbrae, north of San Francisco, where Dr. Peter Eisenberg works, the agony of choosing a trial was on display. Although the oncologists there try to offer trials to every patient, last year they enrolled just 43 of about 700 new patients.

The most enthusiastic have lethal [tumors](#) and no effective treatments, Dr. Eisenberg explained. They are like one of his patients, Ken Fye, a retired rheumatologist with [pancreatic cancer](#) who hopes to find a study in which he can enroll. He figures he has little to lose and wants to help science. “It would be obscene if I did not,” he said.

It is not entirely clear why some trials succeed, but researchers say those that do may have some features in common: patients may be like Dr. Fye, with no or few options, so

they are easier to recruit, particularly if the drug promises to make a real difference, not just give them a few days or weeks. Successful trials also typically address an important problem, as opposed to a more marginal one, and involve experienced investigators and patient advocates who push for participation.

But it can be particularly hard to recruit patients whose prognosis is better.

Gael Casner, for instance, turned down a trial that would have required her to see Dr. Eisenberg for weekly infusions of a cancer drug, [Avastin](#), that was being tested. It had helped women with breast cancer that was more advanced than her own.

For Ms. Casner, a 57-year-old college admissions adviser, the prospects, after surgery and chemotherapy, were excellent. “I was thinking, ‘O.K., I hate shots,’” she said. And she has to travel for her job, making it difficult to go in once a week for an infusion.

“If they had said every month, I would do it,” Ms. Casner said. “But every week was a deal breaker. That was why, personally, for me, the trial did not make sense. I was not in a life-threatening situation.”

Then there are the patients for whom there is still a real risk of a recurrence but who are not prepared to cope with a clinical trial on top of everything else. Those are like Dr. Eisenberg’s first patient on one bright June morning, a 74-year-old man accustomed to danger — he flew helicopters for the military — now facing a very different kind of risk for which he felt unprepared.

The man, who asked that his name not be used to protect his privacy, sat grim and ashen in a sunny exam room, his wife at his side, his daughter across from him. He had [colon cancer](#). It had already invaded his lymph nodes and eaten through the wall of his bowel. He had had surgery and now had to decide what, if anything, to do next.

Choice No. 1: no chemotherapy, no further treatment. Thirty-one of 100 patients like him who chose no further treatment were alive and cancer-free for at least five years. But 30 of 100 relapsed, and 39 died of other causes, like a [heart attack](#).

Choice No. 2: the most aggressive chemotherapy, including 48-hour intravenous infusions of a drug with serious side effects. If he chose that regimen, he would have a 43 percent chance of being alive and cancer-free in five years. But he also had a 14 percent chance of relapsing. And he had a 44 percent chance of dying of something else.

The bottom line, Dr. Eisenberg said, is that 11 people of 100 who get this chemotherapy are alive and well because of it. But that also means that almost 9 of 10 who opt for this treatment are not helped – they either relapse or die of other causes within five years.

Choice No. 3: a less aggressive chemotherapy with a smaller improvement in survival rate.

But there was another option. He could join a Phase 3 clinical trial sponsored by a drug company, ImClone. He would be randomly assigned to receive chemotherapy with or without ImClone's drug, [Erbix](#), approved for people with colon cancer more advanced than his. The aim was to find out whether Erbix could also help those with earlier colon cancer.

"The trial may help you or it may hurt you because the drug may make you sick," Dr. Eisenberg said.

"I know this is overwhelming," he added.

"I've been overwhelmed for three months," the man replied.

The 45-minute conversation over, the man, shaken, went home to ponder his options.

A week later he was back. He wanted chemotherapy, but a clinical trial was not for him. He joined the majority of cancer patients, hoping for the best with what is already known.

Reluctant Doctors

For 15 years, Dr. John M. Rainey at Louisiana Oncology Associates in Lafayette did his best to enroll patients in clinical trials. He believed in research and thought doctors like him should do their part. But he finally had to stop. Every study was costing his group a few hundred dollars to \$1,500 and the bureaucratic requirements were getting out of control.

"When we put a pencil to it, it didn't make economic sense," Dr. Rainey said.

First was the institutional review board, the committee that reviews the trial to make sure patients are protected from harm. Every time a study patient had an adverse reaction, every participating medical center had to notify patients and respond to the

review board. Many reactions had nothing to do with the drugs, Dr. Rainey said, and instead were related to the patients' illnesses.

"It became a hassle factor," he said. "We didn't have the manpower." One of the five doctors in the group was spending three to five hours a week filling out forms.

"You could see five or six or seven patients in that time," Dr. Rainey said.

Then there was the unreimbursed or poorly reimbursed time to explain a clinical trial to patients and get consent. Those who agreed would have to come back a second time to start treatment, adding to the patients' costs as well, since most lived 25 to 50 miles away. If they were not in a study, their treatment could start right away.

"We were seeing more and more patients, and time did not allow us to sit down with patients and get them on trials," Dr. Rainey said.

"It just did not make economic sense for us to go in the hole," Dr. Rainey explained.

And that, researchers say, is one reason why progress is so slow.

Only one study in five even publishes its results, Dr. Ramsey and Dr. Scoggins found.

And, of the unpublished studies, "a significant percentage" probably ended uncompleted because they could not recruit enough patients, noted Dr. Gregory A. Curt and Dr. Bruce A. Chabner, editors of the journal *The Oncologist*, in an editorial on Dr. Ramsey's and Dr. Scoggins's paper. "Which potential statistic is the sadder, the low publication rate" or, Drs. Curt and Chabner wrote in *The Oncologist*, the meager number of patients who enroll?

"In truth they both are," the two oncologists continued, "as neither should be true."

A New Approach

Cancer experts offer two answers to the problem of clinical trials: spend more, giving doctors better incentives and perhaps even paying patients, or, with no real prospects for a big infusion of money, use available money and patients more efficiently.

Donald Berry, a statistician at the M.D. Anderson Cancer Center in Houston, wants to use resources more efficiently. To do so, he designed a new sort of study to test experimental drugs for breast cancer.

The study, starting this fall, is a departure from traditional notions of drug testing and cancer treatment.

Participants will be women who are newly diagnosed with breast cancer and at high risk that it will spread in their bodies.

Ordinarily, women with breast cancer have surgery first to remove the tumor in their breast and then have chemotherapy. The problem with removing the tumor right away is that it can take 5 to 10 years to know whether an experimental drug killed any remaining cancer cells. It is easier and much faster to assess an experimental drug's effects on tumors that remain in the body. So in this study, women will get standard chemotherapy and experimental drugs first. Researchers will do MRI scans to see whether the tumors are responding.

Then, six months later, surgeons will remove the tumor or, if the tumor is gone, tissue from where it used to be, to determine how the cancer responded to the drugs.

The idea of leaving a cancer in place for six months can sound shocking, even dangerous. But cancer researchers say it actually makes no difference whether chemotherapy comes before or after surgery.

"If a woman comes in with a large tumor, surgery isn't going to save her life," said Dr. Laura Esserman, a breast surgeon at the University of California, San Francisco, who is principal investigator for the study. Death is caused by cancer that spreads beyond the breast.

"The standard way," Dr. Esserman added, "operate, give a drug, hope for the best, is not going to work if you are trying to drive progress quickly."

Also, this study will analyze the genetic makeup of the patient's tumor and use that information to determine which drugs might be most effective. In most studies researchers have not accounted for genetic differences in tumors.

The study will also ensure that women have a better chance of getting whatever drug seems to be working. As the study goes on, if one drug appears to be working better than

others, researchers will adjust the study so that new participants whose tumors have the same genetic makeup will be more likely to get it.

The aim is to need far fewer women to determine whether a drug works, and to get answers more quickly.

Dr. Berry said that some traditional breast cancer trials are seeking 5,000 or even 10,000 women. It is no surprise, he added, that trials start “limping along” trying to enroll their quotas of patients.

In the new study, the winners of this drug competition will be tested in a definitive Phase 3 study with just 300 patients whose tumors have a similar genetic profile to those of the women who **responded**.

“This is definitely the answer” to the problem of getting enough patients for studies, Dr. Berry said. “We will use patients more wisely.”