**PUBLIC VS. PRIVATE?**

Cooperative Groups Say NCI Trials Funding Inadequate; Some Turn to Industry

By Charlie Schmidt

Clinical trials sponsored by the National Cancer Institute have played an immense role in the fight against cancer. While industry-sponsored trials focus chiefly on new-drug development, NCI’s trials tackle a broader social agenda, fueled by cancer prevention, quality-of-life issues for patients, and the competing benefits of different treatments or treatment combinations. Much of NCI’s research into the biology of cancer laid the groundwork for drug development by the pharmaceutical industry.

Now, financial shortfalls threaten NCI’s clinical trials programs. Several universities have already said they will not participate in NCI trials unless they find supplemental funding because the money provided does not cover their costs. Because of this shortfall, more universities are turning toward industry-funded trials, which are less likely to tackle basic cancer questions.

“Cancer centers increasingly can’t afford to do public research [funded by the NCI], and that forces investigators towards drug company studies; these decisions are now being made on economic grounds,” says Larry Baker, D.O., chair of the Southwest Oncology Group.

NCI-funded clinical trials are coordinated by two key areas: the cooperative groups program, which administers clinical trials focused on cancer treatment, and the community clinical oncology program, which administers trials focused on cancer prevention and control. NCI pays for all publicly funded trials coordinated by either program with a $2,000 reimbursement for each participating patient, which is supposed to cover all costs for the duration of the trial.

To calculate total funding for a given trial, investigators multiply the number of patients by the $2,000 reimbursement. The resulting value represents the bulk of what NCI will pay for a trial, including long-term follow-up. Faced with a stagnant budget, NCI hasn’t raised the reimbursement rate for 7 years, while median costs per subject have reached $6,000 and beyond, according to the Lewin Group, a health care consulting firm in Falls Church, Va. That means NCI funding covers at best a third of what the trial actually costs. To perform NCI trials, investigators require supplemental funds from hospitals, philanthropies, and other sources. Industry trials, meanwhile, pay at least $9,000 per patient and often more, the Lewin Group reports.

### A Competing Agenda

Because of this shortfall, some cash-strapped investigators have already begun to select industry studies over their publicly funded counterparts, a trend that will probably continue, says Robert Comis, M.D., president and chairman of the Coalition of Cancer Cooperative Groups, an organization that represents the cooperative groups.

Industry studies account for a growing share of clinical trials research, Comis says. “A lot of the publicly funded work we do looks for new ways to use existing medicines, and that’s not the kind of thing that drives the pharmaceutical industry,” Comis says. “The same goes for rare cancers—industry’s not as motivated to focus on them. With the erosion of the public system, you’re likely to see a tremendous impact on the next levels of treatment for cancer patients.”

Several NCI-funded investigators interviewed for this article acknowledge that budget pressures have made industry trials more compelling. Most were reluctant to say so on record, however, to avoid jeopardizing their relationships with NCI.

Still, recent incidents show that budget pressures have put NCI trials at a competitive disadvantage. The University of Michigan Comprehensive Cancer Center, for example, recently refused to open a trial by the American College of Surgeons Oncology Group unless the group could provide its own supplemental funding. And citing fiscal policy, the University of California at Los Angeles no longer participates in NCI trials coordinated by the Southwest Oncology Group, according to an anonymous source. UCLA officials refused to comment.

Results from an investigation by the Coalition of Cancer Cooperative Groups, released in September 2006, found that the modest growth in clinical trial activity from 2004 to 2005 was due mainly to an expansion of industry studies in academic settings. Also, administrators at most research sites contacted said budget concerns had forced them to consider performing more industry-sponsored trials.

“We’ve seen a significant shift to pharmaceutical trials in the last year, which we attribute to public funding shortfalls,” says Marge Good, the administrative director of the Wichita Community Clinical Oncology Group.
Program, which coordinates cancer trials at six research bases throughout the United States. “It seems like access to money has really begun to drive the agenda, and I worry about the consequences.”

Funding shortfalls also raise concerns over quality assurance in publicly funded trials, Baker says. Recently, the U.S. Food and Drug Administration proposed that trial investigators perform additional, independent audits of radiology reports, which are crucial to patient enrollment and monitoring. NCI recognizes the need to comply with FDA regulations, Baker says, and that creates a quandary: Where will the funds to pay for these additional audits come from?

Chronic Shortages
The growing crisis emerged from chronic funding shortages at the NCI that date back several years. In 2001, Congress gave the NCI 91% of its budget request, and that percentage has dwindled every year since. In 2006, the amount awarded was $4.79 billion, just 78% of the budget request, and an amount roughly equal to the NCI’s budget in 2004. Considering that medical inflation is approximately 7% annually, the budget’s purchasing power has fallen steadily. During the first months of 2007, the president proposed cutting NCI’s budget by 10%, provoking a media outcry and a highly secretive round of negotiations to settle the budget that as of press time hadn’t been resolved. Chairs of the cooperative groups, meanwhile, were told to prepare for cuts and the likelihood that NCI trials would be reduced by 3,000 patients.

While budget shortages have produced across-the-board effects, they appear to be most acute among the NCI’s cooperative groups and member sites, says Heidi Nelson, M.D., cochair of American College of Surgeons Oncology Group and a professor of surgery at the Mayo Clinic. Community researchers—who provide up to 80% of patients for cooperative group trials—tend to be hardest hit.

“We have to pay nurses and coordinators, abstract data from medical records, collect specimens, infuse treatments, and record outcomes,” says Nelson. “It’s important to emphasize how important we believe the [public studies] are. There are many studies that have been done by Cooperative Group specialists that by their very nature would not have been done by the for-profit sector.”

NCI Clinical Trials Primer
The National Cancer Institute’s clinical trials are coordinated through two key research centers: the cooperative groups program and the community clinical oncology program.

Cooperative Groups
The 10 cooperative groups are funded primarily through the division of cancer treatment and diagnosis. That division funds only treatment trials, which include studies of new drugs and vaccines, new surgical and radiation approaches, and combinations of all these approaches in patients with a variety of cancers.

The 10 cooperative groups focus on different aspects of cancer research for NCI alone. Several cover a broad spectrum of activities in cancer research, including the Eastern Cooperative Oncology Group, the Southwest Oncology Group, the Cancer and Leukemia Group B, the National Surgical Adjuvant Breast and Bowel Project, and the North Central Cancer Treatment Group. Other groups are more specialized. The Children’s Oncology Group focuses only on pediatric cancers, and the Gynecologic Oncology Group focuses only on cancer in women. Still other groups focus on different medical specialties, including the American College of Radiology Imaging Network, the Radiation Therapy Oncology Groups, and the American College of Surgeons Oncology Group.

Each cooperative group has its own members, which can include hospitals, group practices, and academic cancer centers. Members conduct clinical trials that are designed by their parent cooperative groups, while the groups themselves manage and analyze data from the trials and coordinate funding, according to NCI’s standard reimbursement of $2,000 per patient. The group trials, especially phase III trials, have in recent years been made more widely available to sites that are not members of specific groups via the NCI’s cancer trials support unit.

While the cooperative groups will sometimes seek out supplemental funding, NCI strictly controls funding sources for their trials. Individual sites will sometimes get their own supplemental funding.

Community Clinical Oncology
The community clinical oncology program gets its funding from the division of cancer prevention (DCP), which supports clinical trials devoted only to cancer prevention and control. Clinical trials funded by the program are coordinated by research bases, either NCI-designated cancer centers or cooperative groups that design cancer prevention and control trials with a community focus. There are currently 14 research bases, including eight cooperative groups. DCP also supplies funding to individual sites, which can include hospitals, private practices, and academic cancer centers.

The trials themselves are created by the research bases but must be approved by the DCP. In recent years, community oncology groups have been allowed to participate in cooperative group treatment studies, with DCP overseeing their funding. In this way, NCI has used the community oncology program to broaden the scientific focus of the cooperative groups to include symptom management, quality of life, and cancer prevention.
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manage toxicity and clinical needs, coordinate with institutional review boards, and do up to 10 years of follow-up,” says Patra Grevstad, manager of clinical research at the Swedish Cancer Institute, a community treatment and research facility at the Swedish Medical Center in Seattle. “The [institutional review board] burden in particular has quadrupled in the last 10 years, and the funding we get from NCI doesn’t come near to what’s needed.”

Many research groups get substantial supplemental funding through philanthropies and, ironically, from leftover dollars supplied by industry for pharmaceutical trials. Sometimes residual industry funds have become key sources of revenue for public trial research. However, Good points out that if private research pays more, it also costs more—the auditing is more comprehensive and the paperwork more burdensome. “You don’t always come out ahead,” she says. “Industry studies take a lot of staff time, and a whole lot more work goes into them.”

Meanwhile, affiliated hospitals under financial siege from factors such as the Medicare Modernization Act, which vastly increased prescription drug prices, have reduced their normal levels of support, Comis says.

“The infrastructure that supports these trials is like an organism, and it’s being pressed from all sides,” he explains.

James Doroshow, M.D., director of the division of cancer treatment and diagnosis at NCI, says he’s aware that pharmaceutical research tempts investigators who face shrinking funds. NCI is now developing guidelines for how to pursue supplemental resources, he says.

“It’s important to emphasize how important we believe the [public studies] are,” Doroshow says. “There are many studies that have been done by cooperative group specialists that by their very nature would not have been done by the for-profit sector.”

Robert Catalano, Pharm.D., vice president for regulatory affairs with the Coalition for Cooperative Groups, says that two publicly funded trials illustrate that view. The first, E499, compared a standard chemotherapy regimen of carboplatin and paclitaxel to the same regimen plus bevacizumab (Avastin) in patients with advanced nonsmall-cell lung cancer. The second, E2100, compared a standard chemotherapy regimen with paclitaxel to the same drug plus bevacizumab in patients with advanced breast cancer. In keeping with standard procedure, the trials were funded by NCI through a cooperative research and development agreement with the pharmaceutical company, which supplied the drugs for clinical studies. Both studies were developed by the Eastern Cooperative Oncology Group, approved and sponsored by NCI, and conducted by the cooperative group’s own member research sites.

Both trials showed that adding bevacizumab to standard treatments produced benefits. But according to Catalano, the drug’s producer—Genentech—didn’t undertake those trials because bevacizumab was already approved for a different indication: bowel cancer. With that approval secured, Genentech had moved on to other candidate drugs in its pipeline. Through the agreement with NCI, pharmaceutical companies have access to the clinical trial data, which allows them to negotiate with the FDA regarding potential new approvals for marketing applications. In these cases, both studies were submitted by Genentech to the FDA for approval as new uses for bevacizumab.

A New Era?

Bucking under financial pressure, the cooperative groups have begun to eliminate some trials while making other painful cuts. Studies directed toward rare cancers—including sarcoma, some childhood tumors, and head-and-neck cancers—are particularly vulnerable, Nelson says. What’s more, groups that were unable to wait for final decisions on the 2007 budget made sacrifices, assuming that the cuts would go forward. The Southwest Oncology Group, for instance, halted all trials devoted to head-and-neck cancers and sarcoma in December 2006.

With the public system in growing disarray, pharmaceutical companies have found approaching community centers for trial accrual an easy task. “We don’t go to them, they come to us,” Good says. A key concern, she emphasizes, is that investigators who become accustomed to industry financing may be reluctant to go back to lower-paying public research. And that would exacerbate a potential shift from the public’s agenda on cancer toward industry’s more commercial interests, she says.

How the situation will unfold is unclear. Will NCI’s role as a clinical trials leader be diminished in the future? That’s a question worth pondering, Nelson says. Both public and private research is crucial, but overall progress depends on their being in the right balance. Pharmaceutical companies want to know if their drugs and devices are safe and effective, while public researchers want to know how the range of available therapies can be combined to provide optimal care.

“There’s nothing wrong with industry research; it’s just not enough,” Nelson says.

“In and of itself, industry would have never brought us to where we are today. The trials culture cultivated by NCI unites advances so they can fit into the broader biology of the disease. There could be huge limitations in letting industry be the gatekeeper.”

(C) Oxford University Press 2007. DOI: 10.1093/jnci/djk227

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