Proposed New Clinical Trial System at NCI Gets Mixed Reviews

By Joanne Nicholas

When oncology community leaders got their first look at the National Cancer Institute’s proposal for renovating its clinical trial system, they found some fundamental changes. NCI’s system is based largely on the long-established clinical trial cooperative groups, and many leaders in those groups hoped the proposals would include more funding and less regulation, as recommended in an Institute of Medicine (IOM) report last spring.

But the proposed new system, which includes major changes to infrastructure, goes beyond that report, including major changes to infrastructure. The 10 cooperative groups would be consolidated into five: the existing Children’s Oncology Group plus four adult multispecialty, national groups. That means the nine existing adult groups will have to merge or reconfigure their structures by November 2012, the deadline for grant proposals in the new system. Groups will have to submit proposals in response to a request for applications, now being developed. Applications will go through a formal review process, also under development. All five groups will then undergo a competitive review at the same time, every 5 years, to determine merit-based funding.

“We are looking for a way to provide an infrastructure that is able to take advantage of scientific opportunities across the board,” said James Doroshow, M.D., director of NCI’s treatment division. Doroshow discussed the new system at the December meeting of the Cancer Treatment Advisory Committee (CTAC). “I hope to have four harmonized operations centers and four data management centers instead of nine, four diseasespecific committees for each malignancy instead of eight in some cases.” The new system would also establish three human tissue banks instead of nine.

Doroshow acknowledged that the proposed changes, although responding to the IOM report, went well beyond it. “There are several members of CTAC who were part of the IOM committee, which gives us a unique perspective for understanding the background of their recommendations,” said Doroshow. “We want to implement a comprehensive approach to change that acknowledges the IOM recommendations but fundamentally alters current incentives at all levels to...
catalyze the formation of a highly integrated national clinical trials network.”

“This will not save money,” he added. “We need to find the dollars to provide the resources for this transition but not disrupt ongoing trials.”

In an interview, Doroshow said that a new system was necessary to replace the current groups. While praising their accomplishments over the past 55 years, he believes the mergers will “facilitate a highly integrated group structure that will be more efficient and better able to perform a few big trials every year in common diseases. We will also incentivize the groups to study rarer cancers like sarcoma and head-and-neck cancers.”

“I am a strong supporter of practice-changing studies that would not be well supported in a commercial environment,” he said. “I want to take the best ideas from across the entire oncology community to do optimum national clinical trials using the molecular tools we have now, to reconfigure incentives so science drives the trials. To do this, we need to get input from many communities.”

One change will be in the peer-review system for the groups, which will place more emphasis on the scientific importance of trials. According to NCI’s presentation of the new system to cooperative group leaders on Nov. 29, “current incentives must be refocused away from ‘credit’ to the group for leading a trial,” and “steering committees must focus exclusively on developing trials that will address the most important scientific question in a timely way.”

NCI director Harold Varmus, M.D., also emphasized the scientific importance of trials under the new system. “Most important from my perspective, in this era of molecularly informed therapeutics, the trials are hopefully going to be more amenable to a strong science base,” he said at the National Cancer Advisory Board in December.

Doroshow told CTAC members that he would put the reorganization on their March agenda, promising “to modify what we are thinking based on your feedback.”

That feedback may call for a less radical overhaul of the system, judging from recent interviews with cooperative group leaders.

Back to IOM?

“I think we have to take a step back to the IOM report,” said Richard L. Schilsky, M.D., professor of medicine at the University of Chicago, past chairman of the Cancer and Leukemia Group B (CALGB), and a member of the IOM Clinical Trials Committee. “It does not call for eliminating the cooperative groups but [rather] consolidating their activities and improving common practices,” he said in an interview. “The groups are terribly overregulated, which contributes to delays. The groups are all volunteer armies except for a small staff. Does this particular plan lead to future efficiency in launching and completing trials that are important to practicing oncologists and their patients? Time will tell.”

Robert Comis, M.D., chair of the Eastern Cooperative Oncology Group (ECOG) and president of the Coalition of Cancer Cooperative Groups, voiced concern that the strengths of the current system not be discarded. “ECOG, SWOG [Southwestern Oncology Group], and CALGB are multimodality groups that study the broad spectrum of solid tumors and hematologic malignancies in adults without a primary focus on a given disease,” he said by e-mail. “Taken together, the entire system as it exists today provides great depth and breadth. However the reconfiguration into ‘no more than four’ adult groups occurs, we need to maintain the breadth and strength of what currently exists and ensure that there is some synergy with the reconfiguration, so that taken together we are at least as strong as we were, and ideally, better prepared to do the more cutting-edge genetic research in the future.”

Laurence H. Baker, D.O., chair of SWOG and professor of internal medicine and pharmacology at the University of Michigan in Ann Arbor, has been encouraging other cooperative groups—which, he points out, invented the practice of medicine as opposed to how many were published in Blood or the New England Journal of Medicine. The difference is clinically meaningful, such as an increase in survival. Those are the challenges we put forward as a group. SWOG is the first among the 10 NCI cooperative groups to embrace—and to be funded for—comparative-effectiveness research as part of our mission,” said Baker, who recently received a renewal of SWOG’s operating grants for 6 years.

The Funding Issue

The proposed reorganization does not address the funding problem, which drew
particularly strong reactions from the group leaders interviewed. Both the IOM report and an American Society of Clinical Oncology survey, which was published online the same day in *Journal of Oncology Practice*, urged full funding for NCI’s clinical trials. The survey authors concluded that NCI’s low reimbursement per patient negatively affects participation in federally funded clinical trials. Industry-sponsored trials typically pay more per patient than does NCI.

Doroshow acknowledged that the proposed system “must create incentives and rewards” for the work investigators do, but he said NCI’s trial budget will not increase overall. “As a nation in a difficult economic situation, where money is not going to be readily available, we must do the smartest trials, and the NCI has to carefully figure out how to prioritize not [only] in a particular disease but in everything we do.”

One area the NCI has already invested in is a standard data management system that will provide a software package for use by all cooperative groups at no cost. “Whether it is gynecologic oncology or CALGB or radiation oncology, any trial carried out by the clinical trials network will also use the same IT infrastructure,” Doroshow said. “It is very costly and will take 2–3 years to get the new clinical trials data management system online, but NCI will provide unlimited licenses in perpetuity for the cooperative groups for this new software.” He said the software would probably be “more efficient; decrease errors; increase productivity; be cost effective; and hopefully, the ability to use this [software] package will help with accrual.” As
the first NIH component to adopt it, NCI could become a model for the others if the software also helps investigators collaborate with each other as well as with pharmaceutical companies and the Food and Drug Administration, he said.

But ECOG’s Comis argues strongly for spending more money on case reimbursement as well as infrastructure. He said that the entire cooperative group effort is approximately a $360 million one, with about $190 million coming from NCI, $116 million through institutional (both academic and community) support of accrual costs and pro-bono investigator time, and almost $60 million from industry and philanthropic support generated by the groups. The groups, cancer centers, and community practices “basically kick in a dollar for every dollar the NCI spends,” he said. “One of the most egregious deficiencies is in the case reimbursement area, which must be fixed.”

Baker agrees that the lack of adequate NCI funding will be a problem. “The NCI needs to change the Cancer Therapy Evaluation Program’s [funding mechanism for cooperative groups] to attract cancer centers to participate in NCI trials,” he said. “In my judgment, we have forced the centers to go with drug companies when we can do studies drug companies wouldn’t dare to do.”

Schilsky too stressed the need for more funding. “Without more money, the clinical trials system won’t be significantly improved. We will have to downsize the number of patients enrolled and have fewer studies.”

Schilsky said NCI acknowledges that for what a pharmaceutical company pays for one trial—about $150 million—the NCI sponsors hundreds of phase II and III trials. “They want to have 100% control but pay less than 50% of the budget,” he said.

While NCI continues to work out the details of the new system, members of the cooperative groups appear to want to be partners or at least advisers to the process. At the December CTAC meeting, many asked questions and offered suggestions on how to build in efficiencies and eliminate the problems of the current system without losing its benefits.

“We have all embraced the principles of the IOM report and are eager to see the broad array of issues appropriately addressed to ensure our continued leadership role in the world,” said Comis. “We are seeing other countries’ cooperative group systems overtaking our own and industry performing worldwide studies. We can’t have the next 5 years consumed by administrative details while the rest of the world moves ahead with the science.”

More information on the proposed restructuring is available online at http://transformingtrials.cancer.gov.