NCI’s Clinical Trial System: Efficiencies Grow, Debate Goes On

By Joanne Nicholas

Getting an up-or-down approval for a clinical trial protocol from the National Cancer Institute (NCI) has gotten a lot faster in the last 6 months.

“At first blush, things look much more timely, but it will take at least a year to see if we are meeting our new timelines,” said James H. Doroshow, M.D., director of NCI’s Division of Cancer Treatment and Diagnosis. The targeted time from submission of a study idea to opening the trial to patients for Cooperative Group phase III trials is now 300 days, compared with the 830 days it has taken in the past, said Doroshow.

Doroshow explained that faster turnarounds are the result of efforts to integrate the recommendations of two reports: the April 2010 Institute of Medicine (IOM) report, A National Cancer Clinical Trials System for the 21st Century, and a 2005 report from NCI’s Clinical Trials Working Group, which Doroshow chaired. He said that the IOM recommendations mirrored some of the working group’s findings, so many improvements were already under way.

Reporting at the September meeting of NCI’s Clinical Trials and Translational Research Advisory Committee (CTAC) and in a follow-up phone interview, Doroshow said that what has changed to date is improved efficiency in the clinical trial review process. Early indicators show the NCI Cooperative Groups on track to meet the timeline of 300 days to begin a phase III trial. Using these new standards, “the median time to [clinical trial] activation is on target to meet its goal to cut it in half or by as much as 60%,” he said.

Improvements that have boosted efficiency include the development of standard terms of agreement for research trials (START), which include templates with language for documents that address the responsibility of industry and academic collaborators to use before beginning each trial; the development of a uniform clinical trial data management system, with software that creates standardized research records to simplify data entry for research staff; and the establishment of a website that lists every cancer clinical trial in the country, allowing anyone interested in launching a trial to eliminate redundancy by checking whether one is already under way.

Two of the most successful initiatives have been the streamlining of NCI’s cancer therapy evaluation program (CTEP) and an enhanced and sped-up centralized institutional review board (CIRB).

“Instead of CTEP performing a sequential review, we have short-circuited the entire process,” said Jeffrey S. Abrams, M.D., associate director of CTEP. “We now review the protocol and make changes directly on the document [by] using ‘Track Changes’ and then e-mail it to the investigator. Next, CTEP staff and the investigators have a conference call to resolve all the problems, avoiding repetitive reviews.”

Centralized IRB Gains Ground

The CIRB for adult trials was established in 2001 and the pediatric CIRB in 2004, with the idea of cutting back on duplicate reviews by local IRBs for multisite trials. The central IRBs do not completely bypass local IRBs, but local investigators who want to participate in a multisite trial can go to the CIRB website to download the protocol, the patient consent form, and an already completed application and then submit them to their local IRB. The IRB chair and/or a subcommittee must review the documents for local context concerns, but the full board does not have to meet.

The CIRBs have been slow to reach their potential, but glimmers of hope emerged in a CIRB progress report that NCI’s Jacquelyn Goldberg presented at the CTAC meeting. She said the boards have improved communication with principal investigators and statisticians of group trials through teleconferences and by having them attend CIRB meetings so that “people who can answer their questions are right there.”

Comparing May 2007–April 2008 data with those from May 2009–April 2010 showed that receipt of a proposal to an initial review by CIRB now takes 17 days, down from 29 days in the past. “The time frames plummeted even as the workload increased from 14 to 18 studies,” said Goldberg. Going from receipt to approval took 20.5 days instead of 94 days, and the entire process from CIRB receipt to final approval decreased from 126 days to 43 days.

Several important recommendations from the IOM report remain unresolved, however. These include adequate reimbursement for clinical trials, currently set at $2,000 per patient for Cooperative Group trials, although the NCI’s most recent review found that the actual cost was $6,000 per patient; the need for expanded participation in clinical trials by both patients and community oncologists; improved reimbursement for studies involving imaging and quality-of-life evaluation; and more funding for biomarker-driven trials and other scientific innovations.

Cooperative Group Structure

One of the few contentious topics at the CTAC meeting involved changes to the cooperative group structure. Few took issue with creating efficiencies, for instance by combining statistical operations, as three cooperative groups—the Cancer and Leukemia Group B, North Central Cancer Treatment Group, and American College of Surgeons Oncology Group—recently have.
But opinions differed on how to reorganize and still maintain the sense of community of the individual cooperative groups, which some feel is an important factor.

James L. Abbruzzese, M.D., chair of the department of gastrointestinal medical oncology at the M. D. Anderson Cancer Center in Houston, suggested that those three “very good groups” should merge to “integrate the scientific components of the groups as well as data management.” He argued that the marriage “would create tremendous synergy.”

Jan C. Buckner, M.D., chief of medical oncology at the Mayo Clinic, Rochester, Minn., and cochair of the North Central Cancer Treatment Group, stopped short of calling for a merger but asserted that one group’s strengths “can be made even stronger by some sort of collaborative arrangement.” She said, “There are various complementarities in statistics and [on the] IT and data management side. Obviously, it does make sense to look for complementarities of science as well.”

Sandra Horning, M.D., a senior vice president at Genentech in charge of global clinical research in hematology–oncology and a former president of the American Society of Clinical Oncology, advanced the European model for reorganizing cooperative groups. “Our European colleagues have moved ahead of us. And they moved ahead of us because they are organized around a disease, like [chronic lymphocytic leukemia],” she said. “And they are doing definitive trials that are changing the practice of oncology.” She noted that “this is the way oncology is practiced. It certainly is the way that industry-sponsored trials are run.”

More conservatively, Heidi Nelson, M.D., professor of surgery at the Mayo Clinic and cochair of American College of Surgeons Oncology Group, advocated for groups’ combining statistical functions only. “It’s much easier to look at the pieces. The IT and databases, those are not people,” she said. “Those are functions.” Nelson asserted that the cooperative groups rest heavily on volunteerism. “It’s not just about three people; it’s about hundreds of people who represent thousands of people who work within the groups, and they can’t lose interest along the way.”

Nelson’s sentiments were echoed by Richard L. Schilsky, M.D., at the University
of Chicago Medical Center, who led the Cancer and Leukemia Group B for many years and was a member of the IOM panel on clinical trials. In an interview, he stressed the strong sense of community within the individual cooperative groups. “There are a lot of volunteer efforts to train and lead the next generation of oncologists. There is no other venue where researchers can sit down with the leaders in their field—top oncologists and statisticians—and learn how to design a clinical trial. If these opportunities get lost in a makeover, it would be a huge detriment.”

Schilsky suggested that the “best strategy is to raise the bar and be guided by the peer-review process, which may eliminate those groups that don’t meet these higher standards.”

He added that more direct ways exist to effect IOM’s recommended changes: “The NCI should take over the function of auditing clinical trial sites since many institutions work with several groups. It should take responsibility for drug distribution in trials to eliminate this budgetary issue for groups and, perhaps most importantly, increase funding for operating expenses, which are currently reimbursed below 50% of trial costs.”

There appeared to be a consensus at the CTAC meeting that the IOM report was well done, including some praise from the top. Harold E. Varmus, M.D., newly appointed NCI director, said, “It is necessary to say quite explicitly that this report is quite good and does articulate what is wrong with the clinical trials system.”

Varmus advocated “setting firm temporal standards” that would get the right trials done in the right time. But he said that merely improving efficiency for the NCI is not enough. “The science of oncology has changed, and the needs for certain procedures and strictures have also changed but have not kept up with what I see as change in the way we think about the treatment of cancer,” he said. “There are ongoing reviews and initiatives at the NCI that should address these issues as well.”