Next Steps in Clinical Trial Redesign

By Joanne Nicholas

The National Cancer Institute recently gave a vote of confidence that will accelerate the reform of its clinical trial system, to incorporate increasing understanding of the biology of cancer. This need is one that cancer groups in both Europe and the U.S. are seeking to fill.

On Nov. 7, the NCI’s Board of Scientific Advisors agreed to issue a Request for Applications to reconfigure the NCI/National Institutes of Health external peer review of the clinical trial system and provide support for a standing, publicly funded, integrated clinical trial network.

“So far, we are on track. They have approved of the approach we have suggested,” said Jeffrey Abrams, M.D., NCI acting director for clinical research. “This has been the culmination of a 2-year effort that has been a very inclusive process with extensive stakeholder review and input.”

IOM and ASCO Input

Among the main proponents of the NCI’s initiative, the American Society of Clinical Oncology (ASCO) and the Institute of Medicine’s (IOM) National Cancer Policy Forum have also been its closest monitors. Last March, they organized a joint workshop with NCI and stakeholders in the cooperative group system to examine NCI’s efforts to implement the recommendations of the April 2010 IOM consensus report, Implementing a National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative System. In July 2011, they issued a public summary. The IOM and ASCO plan a second workshop for this year.

“At the implementation meeting, I was impressed with how the NCI responded. There is a newfound cooperation,” said
Roy Herbst, M.D., Ph.D., chief of medical oncology at Yale Cancer Center in New Haven and a member of the IOM committee that organized the workshop. “Clearly, the NCI has taken the IOM’s recommendations to heart and is trying to streamline the process and promote more innovative trial design.”

Herbst said “everything came together at the same time,” crediting not only the IOM report’s highlighting important changes needed to infrastructure and resources but also NCI’s own review of cooperative groups and policies begun by former director John Niederhuber, M.D., with making the NCI more willing to implement changes. Also, ASCO, academic medical centers, industry, private practitioners, and patient advocates have been willing to work with them. “All forces are now pulling in the same direction,” he said.

In November, ASCO published its own report, Accelerating Progress Against Cancer: ASCO’s Blueprint for Transforming Clinical and Translational Cancer Research, which made recommendations on how to reflect the new era of molecularly targeted therapies with smarter, faster clinical trials.

According to George W. Sledge Jr., M.D., the immediate past president of ASCO and co-leader of the Breast Cancer Program at Indiana University’s Simon Cancer Center in Indianapolis, “ASCO’s stance is that an overhaul is needed to several aspects of the clinical trials system. We are collaborating with the NCI, but our feeling is this is not solely an NCI issue. There are other players in this particular game. He points to changes needed to informed consent (Office for Human Research Protections), Medicare (Centers for Medicare and Medicaid Services), and regulatory issues (U.S. Food and Drug Administration) as examples of agencies responsible for aspects of the clinical trial system that are not in NCI’s purview. “ASCO and the IOM can do things the NCI cannot, including advocating for more research dollars,” explained Sledge.

**Improvements on the Way**

“One big improvement for the overall system’s efficiency is the adoption of a common electronic data-management system that will standardize data entry forms across all 2,000 NCI-sponsored trial sites,” said Abrams. “Regardless of what group someone is working with, it will all be consistent and data management will be done in the same way. The new system is much easier for researchers and nurses in the field, will reduce costs, and will cut down on record-keeping errors and omissions. In fact, one U.S. Cooperative Group has already set up trials successfully on the new system, and we hope to have all groups using it by next year.”

Funding for trials remains a work in progress. The IOM recommended an increase of $2,000 per patient enrolled in a clinical trial, above the current base payment of $2,000 per patient. According to an ASCO study of group sites from 2009, NCI’s low reimbursement rates discourage sites from participating in clinical trials. NCI has now increased the rate to $5,000 for phase II trials. “Going forward, our plan is to develop a funding system that will increase reimbursement for all trials (phase II and III) to $4,000 per patient for “high performance” academic and community sites that contribute large numbers of patients,” said Abrams. “These sites incur additional costs due to higher patient accrual and need to be compensated for their large patient follow-up burden.” He warned that reimbursement ultimately depends on the NIH budget. “If our funding goes down, we would be forced to reduce the number of patients in clinical trials if we wanted to offer the higher per-patient payments,” said Abrams.

**Securing Patient Consent**

Overhauling patient consent procedures poses another challenge to reforming clinical trials. For the first time in 20 years, the U.S. Department of Health and Human Services is looking into how to update regulations governing informed consent and institutional review boards in federally funded research. Meanwhile, the cancer clinical trial community is reviewing its own patient consent forms. NCI is working to shorten its current template down to six pages.

Roscoe F. Morton, M.D., of Medical Oncology and Hematology Associates in Des Moines, Iowa, and chair of ASCO’s Quality Oncology Practice Initiative, agrees that long consent forms have discouraged patients from participating in clinical trials. “If you hand a patient a 15-plus-page consent form that takes time to review, it becomes a barrier to the patient’s entry into a clinical trial and you take time out from your other patients.” Morton suggests “a commonality of informed-consent documents would make it easier for both patients and oncologists to participate in clinical trials. Academic and community physicians need to be brought together in this process to make it more efficient and valuable to the patients.”

The European Society for Medical Oncology also noted the challenge of patient recruitment in the era of personalized medicine in cancer research and development. Although the “approach has the potential to lower the failure rates of investigational drugs by testing them only in individuals most likely to benefit,” researchers must screen a much larger pool of potential participants “to stratify patients by the characteristics of their disease” and then into subtypes found in a few individuals. “Researchers and patient advocates are trying to make it easier to
find eligible volunteers. They need to develop appropriate patient-consent forms.”

**Concerns Remain**

Speaking as a clinical investigator, Sledge voiced concern that NCI will not be able to offer adequate funding to succeed. “There is no question that we are in the midst of a true scientific and genomic revolution that will change the way we do clinical trials,” he said. “We need funding for much greater access to tissues and functional imaging to do real-time analysis to slot patients to the appropriate drugs. The current system is not that system.” Sledge warns that if NCI doesn’t improve trial design and reimbursement, researchers could take advantage of increased funding from other sources for trials around the country: “If the result is that in the future, we are enrolling significantly smaller numbers of patients into NCI-funded trials, then it is possible that the NCI will become irrelevant to the clinical trial process as a whole, which I think would be a sad thing.”

Herbst agrees on the importance of having a large, national clinical trial system in place and supports funding “fewer but more innovative trials.” He echoes Sledge’s emphasis on the importance of molecular testing of patients. “Among the challenges to setting up something new, we must find a way to collect tissue and DNA specimens from the patients.” Herbst, who was the principal investigator for the innovative BATTLE trial (one of the first to use biomarkers to identify patients with non-small-cell lung cancer most likely to benefit from a specific agent), believes that “industry will ultimately support the cost of tissue collection if investigators can prove it will assist the drug to be developed quickly.”

Sandria J. Horning, M.D., senior vice president and global head of clinical hematology-oncology at Genentech and past member of NCI’s Clinical Trial Advisory Council, agrees with Herbst. “It is absolutely critical for every site and every investigator to have what is needed when it comes to funding,” she said. “All key elements of a clinical trial need to be included in the contract between the investigators and sponsor. If additional biospecimens are integral to a trial, then their acquisition should be in the contract.” Horning mentioned trastuzumab (Herceptin) and vemurafenib (Zelboraf) as examples of their successful treatments that target specific molecular characteristics where identifying patients’ biomarkers was a required part of their clinical trials.

One issue expected to be more contentious than it has actually been was reducing the number of cooperative groups from 11 to five. “The currently funded cooperative groups are largely in agreement with our recommendations and have voluntarily moved on their own to consolidate,” said Abrams, who explained that plans are already well under way to have 10 adult groups combined into four, with one pediatric group.

According to Horning, it is too early to know whether the group restructure will succeed. She lauds the relationship Genentech has established with NCI’s cooperative groups. “They are filled with highly trained experts who understand that high-quality information acceptable to health authorities is needed at the conclusion of trials conducted for registration purposes.” Horning notes that other configurations are available to improve the speed and efficiency of clinical trials.

“In Europe, groups tend to organize according to cancer types. These collections of experts can quickly enroll patients on trials they consider scientifically important.” Horning pointed to the work of “the very effective German Chronic Lymphocytic Leukemia group, whose trial led to a new indication for rituximab (Rituxan).” For its part, however, the European Society for Medical Oncology is also looking toward reforms: Last October, a presentation at its annual meeting was titled “Translational Research: How To Test Drugs in the Clinical Trials Appropriately.”

Some experts remain skeptical of the consolidation. Sledge believes a more functional reorganization that goes beyond just a merger of the groups and includes adequate funding is necessary for the cooperative groups to do the “types of translational research they should be a gold mine for.” Although acknowledging that 11 groups may have been too many, he adds, “You can’t merge your way to success.” He feels training the next generation of scientists was an important benefit of the former system that should be maintained. “It should be required as part of the funding process to bring to bring midlevel investigators into the mix, and there needs to be a mechanism to teach researchers how to run large, phase III clinical trials,” said Sledge.

“There is no question that for the past 50 years, the cooperative groups have represented the DNA of the clinical trials’ research in the United States. Their discoveries have had a huge impact on my patients. You would hate to lose that,” he said.