National Cancer Advisory Board (NCAB)
Clinical Investigations Subcommittee Meeting

Embassy Suites
4300 Military Road N.W.
Washington, DC
June 21, 2010
6:00 to 7:30 p.m.

SUMMARY

Participants:

Subcommittee Members
Dr. Waun Ki Hong (Subcommittee Chair)
Dr. Judith Kaur
Dr. H. Kim Lyerly

Other Participants
Dr. Jeffrey Abrams (NCI)
Dr. Bruce Chabner (NCAB)
Dr. Deborah Jaffe (NCI)
Dr. Diana Lopez (NCAB)
Dr. Margaret Mooney (NCI)
Dr. Jennifer Pietenpol (NCAB)
Dr. Sheila Prindiville (NCI)
Dr. Carolyn Runowicz (NCAB)
Ms. Mary Spock (The Scientific Consulting Group, Inc., rapporteur)

Dr. Waun Ki Hong, Chair of the Clinical Investigations Subcommittee, welcomed participants, and noted that John Mendelsohn had given an excellent presentation on the Institute of Medicine (IOM) Report on the National Cancer Institute's (NCI) clinical trials program, and announced that Dr. Jeffrey Abrams would discuss the report in his presentation on NCI's clinical trials.

Changing the NCI's Clinical Trials System to Meet the Needs of the 21st Century – Drs. Jeffrey Abrams and Margaret Mooney

Dr. Abrams noted that since the mid- to late-1990s, there have been examinations of the cooperative group clinical trials systems by advisory boards and experts to the NCI. The clinical trials system must change to reflect changes in cancer biology; some improvements are needed, such as increasing the speed and efficiency of trials, and some, such as clinical trial prioritization methods, already have been made. Several new programs relating to data and specimens available for discovery and development are being launched, including patient characterization

centers and a program making resources available to conduct the critical markers for patient selection and stratification or monitoring of therapy in the Phase 3 trials.

High Priority Trials
Dr. Margaret Mooney explained that many factors in the clinical trials system need to be organized and integrated, but one of the most important is the selection, review, and approval of high priority clinical trials. The accrual on cooperative group treatment trials is approximately 25,000 patients per year, and early drug development program adds another 5,000 patients per year.

- Scientific steering committees representing the broad oncology community now prioritize large-scale national clinical trials.
- Steering committee goals include ensuring well-informed evaluation of strategic directions and providing more rapid development of successful new therapies due to a more integrated and efficient prioritization process.
- Approximately 98 trial concepts were evaluated since the inception of the steering committees with an approval rate of 56 to 60 percent.

Dr. Bruce Chabner asked about the average reimbursement per patient in the trials. Dr. Mooney responded that it was set at a base rate of $2 K per patient accrued. Dr. Carolyn Runowicz asked how that figure compared to biotechnology or pharmaceutical company trials. Dr. Chabner responded that reimbursement for a pharmaceutical trial was approximately $10 to $15 K, and the cost per patient is approximately $7 K. Dr. Abrams added that the earlier phase trials paid at a slightly higher rate of $5 to $6 K per patient. The budget for the cooperative group trials overall is approximately $150 million per year, which has been flat for several years. Dr. Abrams explained that the NCI's contribution is $2,000 per case, but often industry partners contribute to that so that total reimbursement is higher. In April 2010, for Phase 2 trials, reimbursement increased to $5 K. The NCI recognizes this as a major problem and is trying to increase the funding. Dr. Runowicz asked whether American Recovery and Reinvestment Act (ARRA) funds could be used to supplement the cooperative group funding, and Dr. Abrams responded that ARRA funds went to areas in which new positions could be created.

Dr. Chabner asked if the Cooperative Group Chairs hold meetings. Dr. Mooney responded that an annual meeting is held every fall with the Cancer Therapy Evaluation Program (CTEP) and that several conference calls were held annually. Dr. Chabner recommended that the Chairs meet to discuss how the system could be run on a flat budget, and asked whether 10 groups were needed and if prioritization was possible with the current number of groups. Dr. Abrams observed that the IOM report was just issued, and that the NCI as an institute had not formulated an answer, but that the steering committees were serious about having only one trial in a disease presentation at a time.

Rapid Protocol Creation
The IOM report explicitly referenced the need to review, develop, and activate trials as rapidly as possible. The Operational Efficiency Working Group (OEWG) came to an agreement on key barriers to timely trial activation and made a commitment to achieve new target timelines. The

group also developed new process maps for trial activation, identified external factors outside of NCI or investigators' control that delay activation, developed recommendations to achieve timelines, and established firm dates to end protocol development if all issues are not resolved.

- The OEWG was established to recommend strategies and implementation plans for reducing the time for activation of Cooperative Group and Cancer Center trials.
- Each of the components (review of the concept, first submission of the protocol, and final protocol revision and activation) was examined with the target of a 50 percent reduction in protocol activation time.
- For phase 3 studies, the target for all three steps is 300 days, and if a Phase 3 trial is not open to patient enrollment within 2 years (18 months for a Phase 2 trial) from when it was initially submitted for review, it will be disapproved.

Dr. Chabner asked why it took 90 days to approve a concept. Dr. Mooney responded that it would take at least 3 weeks for a committee to review the concept; then it returns to the investigator for discussion of revisions. The first 90 days involves the steering committee, the second consists of the group submission of the first version of the protocol, and the last 120 days involves CTEP and everything that must be done to the protocol document, contract negotiations, FDA review, and everything necessary to activate the trial. Dr. Abrams added that the number of revisions needed to be decreased because they take a great deal of time.

Dr. Mooney noted that Phase 2 trials from 2006 to 2008 took less time overall, but showed the same pattern in terms of where time was spent. A 50 percent reduction is the target for the median timelines from review to activation of the trials, with an absolute deadline for activation of 18 months. Dr. Hong asked whether that goal was realistic. Dr. Mooney agreed that some processes need to be re-engineered at CTEP. Dr. Chabner asked if these targets had been compared to industry trials or investigator-initiated trials at Cancer Centers. Dr. Abrams responded that the investigator-initiated trials took a fair amount of time, and that industry trials took from 6 to 12 months. The NCI does not have as much control over everything as industry does, but the timeline goals are aggressive, and would be a major achievement.

Dr. H. Kim Lyerly noted that with a fixed budget, only a certain number of trials can be conducted; sometimes revisions are made because no slot is available for the trial. The expectation with having a steering committee is that if it decides that a trial should go forward, it will go forward without delay. Dr. Chabner commented that it must be asked whether real prioritization is possible with multiple groups with interests in multiple diseases. Dr. Abrams stated that peer review has to come into the equation; NCI does not have to insist that a group can stay alive only because it has a new trial in every disease. Performing well, conducting good data collection, and accruing should be the number one priority.

Dr. Runowicz asked if the steering committees were led by the best people. Dr. Abrams responded that qualified people were chosen. Dr. Hong asked how often the steering committee rotated. Dr. Abrams replied that steering committee members served for set terms. Dr. Runowicz observed that young investigators who want to write the protocols do not have a lot of protected time anymore, which builds in a delay. Dr. Mooney responded that some of the groups are

moving towards having more professional medical writers. Dr. Abrams added that the ARRA funds gave a grant to each group to have new personnel.

Dr. Mooney noted that all treatment trials were tracked as of April 1, 2010, and that the absolute deadlines are being implemented as of January 1, 2011. Initial process improvements include early steps to provide direct, coordinated interactions to resolve issues at the concept and protocol stages, including teleconferences to address major issues. Dr. Abrams commented that in CTEP and the groups, a protocol coordinator manager position now exists to move the protocol along. Dr. Chabner asked why CTEP had to be involved in the last 120 days. Dr. Abrams responded that CTEP helped to get the protocol through the FDA. In addition, but now once the concept is approved, the competitive review process is over and CTEP staff's goal is to activate the protocol as quickly as possible.

Dr. Diana Lopez asked if these cooperative group trials often accrued as 4 patients or less. Dr. Abrams replied that the steering committees should be asking the question whether patients could be enrolled in a particular trial. Dr. Lyerly commented that some trials could not accrue because a newer therapy had been developed. Dr. Hong agreed that questions could become outdated in the time it took to activate a trial, and that 50 percent of trials activated are not completed. He asked whether CTEP had enough manpower and infrastructure to accomplish the stated goals. Dr. Abrams responded that the ARRA funds were helpful with manpower, and once they were no longer available, he hoped CTEP would have sufficient ability to conduct the work. He noted that telephone conferences were going to be used to clarify and decrease revisions.

Central IRB

Dr. Abrams noted that a central IRB (CIRB) was developed in 1999 to streamline or eliminate redundant regulatory procedures. Approximately 350 clinical trial sites have joined, but usage is hindered by lack of national accreditation and concern by some sites about liability despite Office of Human Research Protections (OHRP) support. He noted that CTEP has 2,109 sites, and CIRB has 346 enrolled signatory institutions (representing 700 sites). Forty-two of the 65 Comprehensive Cancer Centers have joined. When a new cooperative clinical trial is approved, it is sent to the coordinating cooperative group and the CIRB. The CIRB will review the study within 3 weeks and the goal is to have initial review approval within 6 weeks.

- A CIRB oversees all adult Phase 3 and pediatric Phase 2 and Phase 3 trials conducted by the NCI Cooperative Groups.
- Currently, accreditation of the NCI CIRB is under way and OHRP clarified in writing on April 30, 2010 that it fully agrees with FDA's position on the benefits of relying on a single central IRB for multicenter research.
- For initial reviews, CIRB affiliation was associated with time savings that translate to a savings of $717 per review.
- The timeline from CIRB receipt to approval has decreased from 157 days in 2007 to 36 days in 2009-2010 by having the principal investigator available via telephone to answer questions.

Dr. Chabner noted that some institutions do not have confidence in the CIRB. Dr. Abrams responded that it the CIRB's reviews are posted, and have received positive feedback.

Central Patient Enrollment
The Cancer Trials Support Unit (CTSU) has centralized administrative and regulatory functions for NCI clinical trials and has expanded access. A centralized CTSU Web Site lists all the cooperative group studies, and Web-based trial registration with real-time site activation and accrual monitoring will be available by the end of 2010.

- More than 45,000 patients were enrolled via CTSU since 2002, and cross-group Phase 3 trial accrual has increased from 20 to 40 percent.
- CTSU has gained the trust of cooperative groups and implemented regulatory support services, the Oncology Patient Enrollment Network (OPEN), customer services including a help desk, reimbursement services and the Web site.

Dr. Chabner commented that the system could be simplified into one or two groups.

Standard Tools for Trial Conduct
A common, comprehensive Clinical Trials Data Management System will begin implementation by end of 2010. The system will include:

- Establishment of standard procedures for data collection using remote data capture;
- A completed set of FDA-grade electronic case report forms using common data elements;
- Implementation of a common electronic protocol authoring tool; and
- Development of a credentialing system for investigators and sites.

Conclusion
The NCI cooperative groups system is more than 50 years old and must evolve to serve 21st century science. Goals are to engage clinical investigators, community physicians, and patients to optimize the size and coordination of NCI's entire clinical trials infrastructure; complete the development of a robust, unifying clinical trials information technology system; harmonize guidelines across the NCI so that they reward the integration of clinical research resources; and confront the need for enhanced support of clinical investigators and clinical investigation sites.

Dr. Hong noted that science is changing on a daily basis, and it may be time to make some radical changes in NCI's clinical trials system. To conduct targeted therapeutic trials, a facility must store biospecimens, which is expensive. How will CTEP address this? Dr. Abrams commented that the patient characterization center and clinical assay development program is determining how to work with people early on in developing markers to have them ready by the time a Phase 3 trial is conducted to select and stratify patients appropriately. Dr. Chabner stated that the Cancer Centers are conducting this work, and have more potential to contribute than cooperative groups. The clinical trials system needs to be redesigned.

Dr. Runowicz observed that cooperative groups can roll out big trials. Dr. Pietenpol suggested that cooperative groups prioritize trials that industry and institutions will not conduct.

Dr. Abrams responded that pediatric tumors and rare tumors and marker trials should be prioritized by cooperative groups.

Dr. Chabner asked if the 10 most important developments in cancer treatment in the past 10 years, how many came from cooperative groups. Dr. Abrams responded that they are listed in the IOM report.

Dr. Lyerly asked where CTEP saw itself with the Agency for Healthcare Research and Quality and the National Institutes of Health teaming up on comparative effectiveness research. Dr. Abrams responded that comparative effectiveness research required that treatments must be available, so many of CTEP's current trials do not meet that definition. Dr. Lyerly asked if anyone from CTEP would be on the technical planning committee. Dr. Abrams replied members of the Division of Cancer Control and Population Sciences represented NCI.

Dr. Chabner commented that the system simply may be out of date. Dr. Hong noted that the most important question is whether there is adequate infrastructure and manpower to achieve CTEP's ambitious goals.

The Subcommittee meeting adjourned at 7:30 p.m.

Dr. Waun Ki Hong	8/16/10	Dr. Jeffrey Abrams	8/17/10
Chair	Date	Executive Secretary	Date