DEPARTMENT OF HEALTH AND HUMAN SERVICES
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NATIONAL CANCER INSTITUTE
12th CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE MEETING

Summary of Meeting
December 15, 2010

Building 31 C, Conference Room 10
National Institutes of Health
Bethesda, Maryland

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
BETHESDA, MARYLAND
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The 12th meeting of the Clinical Trials and Translational Research Advisory Committee of the National Cancer Institute was convened on Wednesday, December 15, 2010, at 9:00 a.m. in Conference Room 10, C-Wing, 6th floor, Building 31 on the National Institutes of Health main campus in Bethesda, MD. Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis, NCI, presided, as acting chair, during the meeting. The meeting was adjourned at 4:00 p.m.

Chair
Harold E. Varmus (absent)

CTAC Members
James L. Abbruzzese
Peter C. Adamson
Susan G. Arbuck*
Monica Bertagnolli*
Deborah W. Bruner
Curt I. Civin
Kenneth H. Cowan
Everett Dodson
Olivera Finn
Stephen S. Grubbs
Sandra J. Horning (absent)
K. Gabriel Leung
Scott M. Lippman (absent)
Nancy P. Mendenhall (absent)
Lisa A. Newman (absent)*
David R. Parkinson
Edith A. Perez
Nancy Roach
Daniel J. Sargent (absent)
Richard L. Schilsky
Mitchell Schnall
Peter G. Shields*
Joel E. Tepper
James L. Wade, III

***Ex Officio* Members**
James H. Doroshow, NCI, Acting Chair
Paulette S. Gray, NCI
Rosemarie Hakim, CMS (absent)
Lee Helman, NCI
Michael J. Kelley, VA
Richard Pazdur, FDA (absent)
John F. Potter, DOD
Alan Rabson, NCI (absent)

Executive Secretary
Sheila A. Prindiville, NCI

*Ad hoc Members

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WEDNESDAY, DECEMBER 15, 2010

I. CALL TO ORDER, OPENING REMARKS, AND NCI UPDATE—DR. JAMES DOROSHOW

Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), called to order the 12th Clinical Trials and Translational Research Advisory Committee (CTAC) meeting. Dr. Doroshow then reviewed the confidentiality and conflict-of-interest practices required of Committee members during their deliberations. Members of the public were welcomed and invited to submit comments related to items discussed during the meeting in writing to Dr. Sheila A. Prindiville, Director, NCI Coordinating Center for Clinical Trials (CCCT), within 10 days of the meeting. Any written statements by members of the public will be given careful consideration and attention. Dr. Doroshow reminded members that the meeting was being videocast by the National Institutes of Health (NIH) VideoCasting and PodCasting Web site: http://videocast.nih.gov/.

Motion. A motion was made to approve the minutes of the September 21, 2010, CTAC meeting. The motion was seconded, and the minutes were approved unanimously.

Dr. Doroshow stated than an extramural Chair would be confirmed at the next scheduled CTAC meeting on March 3, 2011. He welcomed new CTAC members Drs. Susan Arbuck, Monica Bertagnolli, Lisa Newman, and Peter Shields. Dr. Doroshow thanked departing member Mr. Gabriel Leung, President of OSI Pharmaceuticals, for participating in the CTAC.

NCI Update. NCI has initiated an award that will allow individuals to dedicate 5 to 10 percent of their time to clinical research. Eleven awards were given in 2009 and 12 were given in 2010. A year from now, the first group of awardees will be invited to speak to CTAC about how this award has helped them further clinical and translational research. The awards are restricted to investigators at NCI Cancer Centers. Each Cancer Center director is allowed to nominate one candidate; each institution may hold only one of these awards at a time.

A feasibility study on the evaluation of NCI's entire clinical trials program was conducted a couple of years ago. Dr. Doroshow presented the results of that study to CTAC. The Evaluation Working Group met recently to come up with a clear set of proposals to evaluate whether they could refine the effectiveness of the NCI Clinical Trials Program and assist CTAC in understanding the performance and impact of the initiatives that were started on the basis of the Clinical Trials Working Group (CTWG). There needs to be a way to look at what is ongoing in order to make midcourse corrections, not only for CTWG initiatives, but also for other aspects of the clinical trials system that need to undergo substantial changes. The Working Group is in the midst of developing a timeline for implementing the components of the evaluation plan. This new effort is going to be led by Dr. Peter Adamson, Chief of Clinical Pharmacology and Therapeutics, Children's Hospital of Philadelphia, University of Pennsylvania, and Dr. Daniel Sargent, Director of Cancer Center Statistics, Mayo Clinic Comprehensive Cancer Center.

Dr. Doroshow stated that the NIH has started a partnership with the Lasker Foundation to develop a series of awards for investigators interested in clinical and translational research. The award would support 5-7 years of research at the NIH Clinical Center and up to an additional 5 years if and when awardees transition to leadership positions or their own laboratories outside the NIH.

A request for applications (RFA) for Special Translational Research Acceleration Project (STRAP) awards supplements was issued last summer. The applications were reviewed by a group of

extramural and intramural investigators and evaluated based on scientific merit and potential to accelerate translation into the clinic. Two supplement projects were funded. The Memorial Sloan-Kettering project allows a multi-institutional cellular therapy to go forward. Andrew Raubitschek's project deals with state-of-the-art delivery of molecular antibodies. The two awardees will be invited to speak about their projects at the next CTAC meeting.

Dr. Doroshow noted that a Translational Science Meeting (TSM), http://ncitranslates.nci.nih.gov, was not held in 2010. The next TSM, which will have a different format from the previous meetings, will be held in July 2011 and chaired by Drs. Jennifer Grandis and Jim Griffin. The focus of the meeting will be translating the enormous amount of information coming from The Cancer Genome Atlas (TCGA) and the NCI proteomics projects and improving the interaction of scientists involved in those projects with clinical and translational scientists. The meeting will be an important venue not only for Specialized Programs of Research Excellence (SPORE) investigators but also for investigators from across the spectrum of translational medicine. The program committee is composed of extramural and intramural senior investigators.

II. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations, NCI, reported on the status of appropriations and gave an overview of the 112th Congress.

Fiscal Year (FY) 2011 Appropriations Activities. The Federal Government is operating under a Continuing Resolution (CR) that expires on December 18, 2010. The CR keeps funding flat at the FY 2010 level. On December 8, the House passed a year-long CR that would continue to provide funding at the FY 2010 level; this CR is currently awaiting Senate action. The year-long CR would allow the NIH Office of the Director (OD) to spend $25 million to establish the Cures Acceleration Network (CAN).

The Senate is working on an Omnibus Appropriation Bill, which would include funding levels from the Senate bill that was introduced in the House in the summer ($5.256 billion allocated to NCI). If passed in the Senate, the Omnibus Bill could be substituted for the House-passed CR and voted on by the House. Another funding option is that a different CR could be introduced that would extend until late January or early February. This would allow the new 112th Congress to set funding levels.

112th Congress—Outlook. Congressional elections were held on November 2. In the House, Republicans took over the majority status—242 Republicans and 192 Democrats. There is currently one vacancy and a special election will be held to fill the empty seat. Due to the change in majority status, each Congressional Committee will have a new chair. There are 53 Democrats and 47 Republicans in the Senate; consequently, the ratio of Committee seats will change slightly.

Some Committee chair appointments were recently announced. The House Appropriations Committee will be chaired by Congressman Harold Rogers of Kentucky and the ranking member will be Congressman Norman Dicks from Washington. The House Energy and Commerce Committee will be chaired by Congressman Fred Upton of Michigan, who appointed Congressman Joe Pitts from Pennsylvania as Chair of the Health Subcommittee. Other Committee assignments and Subcommittee leadership will be appointed in January.

Priorities for the 112th Congress include resolving Appropriations, increasing emphasis on oversight, and implementing, or blocking implementation of, the Affordable Care Act. There were no other specific health-related issues identified by either the Republicans or Democrats as priorities moving forward.

III. NATIONAL LUNG SCREENING TRIAL (NLST)—DR. CHRISTINE BERG

Dr. Christine Berg, Chief, Early Detection Research Group, Division of Cancer Prevention, NCI, reported on the status of the National Lung Screening Trial, which she oversees with Dr. Denise Aberle, American College of Radiology Imaging Network (ACRIN). ACRIN is run through a Cooperative Agreement. NLST is a multidisciplinary effort, with radiologists, pulmonologists, oncologists, medical physicists, radiologic technologists, and medical record abstractors on staff. The NLST Data and Safety Monitoring Board (DSMB) recommended to NCI that the initial trial results be made public. Therefore, initial trial results have been published online on cancer.gov. *Radiology* and the *Journal of the National Cancer Institute* have manuscripts on the trial design and demographics online and free of charge.

NLST compares low-dose helical computed tomography (CT) scan with chest x-ray to determine which has the lowest mortality from lung cancer screening in high-risk participants. A cohort of 53,454 asymptomatic current or former smokers (30 packs per year), 55 to 74 years old, was chosen. Former smokers must have quit in the preceding 15 years and had no prior lung cancer diagnosis or evidence of other cancer. The participants were randomized to either a CT or chest x-ray arm, with stratification for age, gender, and screening center. Enrollment began in September 2002 and ended in spring 2004. Baseline screening was conducted after informed consent was obtained. Two subsequent rounds of screening were completed by mid-2006. Screening exam compliance was excellent, with 91.2 percent of participants returning for the third annual screen.

NLST enrolled approximately 59 percent men and 41 percent women. African Americans and Hispanics comprised 4.4 and 1.7 percent of the subjects, respectively. Though slightly younger than the demographic, NLST subjects were comparable with U.S. Census subjects who met NLST criteria.

A positive screen was defined as a nodule greater than or equal to 4 millimeters, one dimension, or any other findings potentially related to lung cancer. These positive screens did not include other significant abnormalities such as aortic aneurysm, esophageal carcinoma, or coronary artery calcifications, all of which were reported separately. The protocol for evaluation was designed by NLST's radiologists and was similar to the Fleischner Society Guidelines for Management of Small Lung Nodules. Diagnostic evaluations were not mandated in a particular fixed format and varied based on the individual's health status, health care provider, region of the country, etc.

Dr. Berg presented preliminary results. For the first round of screening, the positivity rates (both true and false positives) were 27.3 percent for low-dose helical CT and 9.2 percent for chest x-ray; the second round saw 27.9 percent for low-dose helical CT and 6.2 percent for chest x-ray. During the third round of screening, the screen positivity rates decreased to 16.8 percent and 5.0 percent, respectively, due to stable abnormalities; if an abnormality was stable in size and homogeneity over the course of three rounds, it was deemed not suspicious for lung cancer. The overall positivity rates were 24.2 percent in low-dose helical CT and 6.9 percent in chest x-ray.

Twenty-five percent positivity is an issue; a bigger issue is that 96 percent of that 25 percent is made up of false positives. The actual rates of lung cancer detected with low-dose helical CT in rounds one, two, and three were 4 percent, 2 percent, and 5 percent, respectively; the actual rates in chest x-ray were 6 percent, 4 percent, and 7 percent, respectively. Interestingly, the number of lung cancers detected in the third round of low-dose helical CT was actually higher than that detected in the second round.

In 144,000 person-years of follow-up, there were 354 lung cancer deaths in the CT arm; this includes all lung cancers (interim, cancers after screening), not just those detected by low-dose helical CT. The chest x-ray arm saw 442 total lung cancer deaths, which represents lung cancer mortality per 100,000 participants of 245, compared with 308 in the low-dose CT arm; there was a reduction in lung cancer mortality of 20.3 percent. NLST is the first prospective randomized study ever conducted for lung cancer that documents a mortality reduction from a screening intervention. The *p* value is highly significant at 0.0041, and Dr. Berg and her colleagues adjusted for the several interim analyses that were conducted.

Dr. Berg also compared the mortality rate in the chest x-ray arm to an age-matched population within the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and found essentially no difference between the chest x-ray arm and the PLCO community care arm. In this high-risk population, there seems to be no benefit of chest x-ray in reducing lung cancer mortality. Thus, the benefit seen in NLST must be due to the use of low-dose helical CT.

All-cause mortality was a secondary endpoint in the trial. There were 1,996 deaths in the chest x-ray arm and 1,870 deaths in the CT arm, for a statistically significant reduction of 6.9 percent. Twenty-five percent of all deaths in NLST were from lung cancer. Of the 126 excess deaths in the x-ray arm, 56 percent were from lung cancer. Additional analysis has not yet been conducted on the other 44 percent, but Dr. Berg and her colleagues are working to discover whether something other than random chance can account for the reduction in deaths.

At 7 years, there is approximately 98 percent overall survival free of lung cancer death in the chest x-ray arm, versus 98.6 percent in the helical CT arm; the difference is not large but is statistically significant. All-cause mortality is also lower in the CT arm than in the chest x-ray arm. Some of this difference is due to lung cancer. If lung cancer case survival is plotted as years from randomization, the lung cancer case survival in the low-dose helical CT arm is approximately 58 percent, versus approximately 32 percent in the chest x-ray arm.

The investigators thought it critically important to monitor dose administration closely during the study. A panel of medical physicists helped the radiologist develop the CT technique chart. The study began with four channel scanners; sites were allowed to replace their equipment as new models were released. Each CT had to meet certain acceptance-testing criteria and be approved by the medical physicists before being brought online for the low-dose CT protocol. A quality assurance/quality control program was in place for both physics doses and image quality. Eighteen standardized parameters were used for each machine to ensure that the image parameters resulted in a low-dose image.

An active medical physics group has calculated average doses for the two arms and converted those doses into the whole-body effective dose, which is a standard for assessing impact in terms of long-term radiation carcinogenesis. Using other data sources and approaches, they plan to estimate the long-term risks for low-dose CT.

A number of ongoing substudies have been developed by ACRIN. One substudy is using serial specimen collection for validation of biomarkers in a subset of 10,260 people, examining plasma/buffy coat, sputum, and urine, and resected lung cancer specimens; the specimens are currently at the University of California, Los Angeles, and will be made available to the research community through proposals. An ongoing quality-of-life analysis is looking at the differential impact of screening on quality-of-life measures and anxiety. A formal cost-effectiveness analysis is being conducted in conjunction with RAND to examine the entire impact of the burden of the screening program. Another analysis is exploring the effects of screening on smoking behaviors and beliefs in both the short and long term; 48 percent of the current smokers in the study were reminded to quit each time they came in for screening.

A number of collaborative studies also have been initiated. Dr. Stephen Lam in Vancouver, Canada, is examining low-dose CT with fluorescent bronchoscopy using a Tammemagi risk model; the risk model will be published in the *Journal of the National Cancer Institute.* Dr. Berg, Amy Berrington de Gonzalez (Radiation Epidemiology Branch), and several medical physicists will be conducting a radiation risk assessment. An individual-level meta-analysis is planned with several ongoing European studies, including NELSON and the Danish CT study. In collaboration with colleagues in the Cancer Information Surveillance Network, NLST investigators will be developing a modeling effort for using this technique more broadly. NLST is also working with a number of groups on computer-aided detection/diagnosis. Three lung cancer early detection marker validation studies—two planned and one proposed—will be examining samples from the PLCO biorepository; if promising validated biomarkers are found, the investigators can study the performance of the markers in the low-dose helical CT group with the ACRIN biospecimen repository.

Dr. Peter Bach conducted an analysis of National Health and Nutrition Examination Survey (NHANES) data to explore estimates of the population that could be eligible for low-dose CT screening. Approximately 7,425,000 people match the NLST criteria; at $300 to $1,000 per CT, the cost is high. Using slightly broader criteria, the number jumps to 13,500,000 people, including more men than women and more current smokers than former smokers.

Dr. Berg suggested several topics for discussion, including potential tobacco cessation messages and efforts; primary and secondary chemoprevention; identification of risk cohorts that are best suited to low-dose CT screening; programmatic venues for screening; evaluation of screening frequencies and intervals; and optimization of diagnostic algorithms for positive screens to minimize the cost of follow-up evaluations. In terms of molecular biomarkers, there should be more work to better identify individuals who could be screened and how aggressively positive screens should be evaluated; evaluation of molecular characteristics of screen-detected tumors; identification of prognostic/predictive markers for targeted therapies; faster development and evaluation of targeted therapies; and examination of the role of focused radiation (e.g., Cyberknife).

Questions and Discussion

Dr. Adamson asked whether there are examples of other tests that have been widely adopted that have a 95 to 98 percent false-positive rate. Dr. Mitchell Schnall, Matthew J. Wilson Professor of Radiology at the University of Pennsylvania School of Medicine, responded that it depends on how one defines "false positive." Some definitions may include nodules that are not necessarily suspicious enough to recommend biopsy but are not normal.

Dr. Adamson also wondered, considering that the reported effect is dwarfed by the effect of stopping smoking, how many people would have to quit smoking to achieve the same effect. Dr. Berg stated that half of the participants are former smokers. Quitting smoking reduces overall mortality risk by 50 percent over the first year; smoking cessation reduces mortality more than low-dose CT. It does not reduce lung cancer mortality in the short term, however; evidence shows that people who quit smoking have a higher risk of lung cancer over the short term. Dr. Pam McMann's (Massachusetts General Hospital Institute for Technology Assessment) models show that only 10 to 15 percent of the population must quit smoking to achieve an overall mortality reduction similar to that observed with low-dose helical CT.

Dr. Adamson noted possible unintended consequences of the research; smokers' motivation to quit may be negatively impacted if they think that a CT scan will reduce their chances of lung cancer death. Dr. Berg responded that this issue was raised during development of the study concept. At that time, it was decided that the risk was worth taking; these were still important questions to answer, as there were already programs starting up across the country to conduct CT scans without definitive evidence as to its effectiveness.

Dr. Richard Schilsky, Associate Dean for Clinical Research at the University of Chicago Pritzker School of Medicine, suggested that the follow-on studies would likely need to be prioritized; studies to help determine screening endpoints and who should be screened are the most important, because the false-positive rate is high. This implies that either the patient population was not of sufficiently high risk or that the 4-millimeter endpoint is insensitive. More research should be done to optimize the endpoint such that radiographic findings can be more specific to lung cancer.

Ms. Nancy Roach, Consumer Advocate at C3: Colorectal Cancer Coalition, noted that it might be beneficial to focus on people who have quit smoking rather than current smokers; it seems problematic to screen people who are not committed to quitting. Dr. Berg agreed that tobacco cessation is key. An interesting approach would be to require serum cotinine levels to document having quit smoking.

Dr. James Abbruzzese, Chairman of the Department of Gastrointestinal Medical Oncology at the University of Texas M.D. Anderson Cancer Center, asked whether there are morbidity data related to follow-up and biopsy/evaluation of nodules. Dr. Berg responded that she will be reporting that information with detail in the final manuscript. The DSMB carefully assessed adverse events during the screening rounds; information about the number of biopsies needed as opposed to further x-ray evaluations, as well as complication rates associated with those individuals who had biopsies, will be made available. Dr. Schnall noted that only a very small fraction of the false-positive screens were biopsied. Guidelines were distributed, but there were no protocol-specific events mandated by a positive screen. Dr. Berg added that they will be able to examine rates of complications, yield rates, reader variability, etc., by site.

Dr. Stephen Grubbs, Chief of Oncology at Medical Oncology Hematology Consultants, wondered whether the mortality rates would have been even lower with a longer period of serial CT, since screening is often most effective in mortality outcome when it is able to detect slow-growing cancers. Dr. Berg stated that it is possible that there might have been some increase in benefit if the CT screens had been conducted for a longer period, but modeling would likely show only a 30 to 35 percent increase.

Dr. Peter Shields, Deputy Director of the Lombardi Comprehensive Cancer Center, expressed great relief that an actual research base has developed for something that private practitioners are already doing. The emphasis on former smokers is critical; however, it is important to continue helping smokers to quit. Many begin smoking as adolescents and cannot quit easily; the best methods for quitting have only 10 to 15 percent success rates. Dr. Shields wondered whether the results are potentially biased via difference in quit rates between the two study arms. Dr. Berg responded that those differences would not have an impact on lung cancer mortality rates. The former and current smokers were randomized and evenly distributed; quit times were evenly distributed across arms. Smoking cessation follow-up studies will be examining questions of persistence related to smoking, quit rates, and lung cancer mortality. It was noted that quitting does result in a sharp reduction in all-cause mortality.

Dr. Lee Helman, Deputy Director of the Center for Cancer Research, NCI, noted that the technology for optimizing diagnostic algorithms will only grow. It will be important to look for cost-effective ways to develop that technology. Dr. Berg added that the biospecimen resource (data, images, and specimens) coming out of NLST will be available to the research community through a peer-reviewed process.

IV. CLINICAL TRIALS ACTIVATION TIMELINE: OPERATIONAL EFFICIENCY WORKING GROUP (OEWG) IMPLEMENTATION UPDATE—DR. JAMES DOROSHOW

Dr. Doroshow provided an update on the implementation of the Operational Efficiency Working Group recommendations.

Recommendations of the OEWG, which were implemented on April 1, 2010, address activation timelines for Cooperative Group Phase III trials, Cancer Center investigator-initiated trials, Cancer Center activation of Cooperative Group trials, and Phase II trials involving drugs for which the NCI Investigational Drug Branch (IDB) holds the Investigational New Drug (IND). Through frequent deliberations, OEWG members developed these recommendations and implementation plans to achieve target timelines and established firm dates by which all protocol issues must be resolved. The target timelines are aggressive, but necessary.

Cooperative Group Phase III Trials. The OEWG target timeline for Phase III trials is 300 days, beginning with concept submission and ending with trial activation. The 300-day timeline excludes issues related to Institutional Review Board (IRB) review, contracting, and drug supply, which are out of the control of the Cooperative Group; however, protocols will be terminated if they are not activated within 2 years of concept submission, regardless of the reason for the delay. Since April 1, 13 proposed Phase III concepts have been received. Four of these concepts were approved; four concepts were disapproved or withdrawn; three concepts are in review or timeout (company and/or drug commitment); and two concepts have been submitted to the Cancer Therapy Evaluation Program (CTEP) and are awaiting Steering Committee approval. The target timeline for concept approval is 90 days. This timeline was met for all four approved concepts, which are now in the 90-day process of protocol submission.

Cooperative Group Phase I and Phase II Letters of Intent (LOIs). The target timeline for Phase I and II LOIs is 210 days, which is meant to be consistent with industry and international standards. Protocols will be terminated if they are not activated within 18 months. Since April 1, 45 unsolicited

Cooperative Group LOIs have been received. Ten of these LOIs were approved; 11 are in review or timeout; and 24 were disapproved, withdrawn, or declined by the pharmaceutical industry. All 10 of the approved LOIs met the 60-day timeline for approval. Six protocols have been submitted, all within the 60-day timeline for LOI approval to protocol submission. These six protocols are in the final activation stage and must be activated within 90 days of protocol submission.

U01/N01 and Intramural LOIs. The target timelines for U01/N01 (Phase I grantees and Phase II contractors) are the same as the Cooperative Group LOI timelines. Fifty U01/N01 LOIs have been received since April 1. Sixteen of these were approved and fell within the targeted 60-day timeline. Ten protocols have been submitted and were received within the 60-day timeframe. These 10 protocols are now in the activation stage and have 90 days from protocol submission to activate. All approved intramural LOIs were approved within the 60-day timeline. All submitted protocols also met the targeted timeline.

NCI Initiatives to Achieve OEWG Goals. Multiple NCI initiatives have been established to implement the recommendations of the OEWG. Internal standard operating procedures (SOPs) have been developed or modified to streamline processes and improve communication. Many at-risk protocols have been identified; there are ongoing interactions between the Cooperative Groups, IDB, and CTEP to identify other protocols that are at risk for termination. Conference calls to discuss and resolve outstanding issues have also been established. Conference calls between the study team and NCI are held to clarify and discuss comments in the consensus review in order to prevent review iterations that may otherwise slow the approval process. Two OEWG working groups meet via monthly or quarterly conference calls to discuss the OEWG Cooperative Groups Working Group and the OEWG Early-Phase Clinical Trials Working Group. There are also weekly OEWG coordination committee meetings. Additionally, a secure, role-based Web portal has been developed to share tracking reports with intramural and extramural investigators and to support staff. All of these initiatives will facilitate commitment to OEWG's target timelines; however, success will not be fully achieved without incremental funding.

Steve Friedman, Branch Chief, CTEP Operations and Informatics Branch (OIB), along with his colleague, Shanda Finnigan, demonstrated the OEWG secure Web site for timeline reports. The Timeline Reports module was launched the end of July and is an application primarily for CTEP internal and external collaborators to access data reports generated from the CTEP Enterprise System. The first version of the application will allow users to generate Protocol Development Timeline (PDT) reports to track the amount of time it takes to develop a protocol from concept or LOI receipt to protocol activation. The PDT reports will be available in four different formats for comparison and analysis.

There are two levels of access to the timeline reports site. The first level is NCI internal access, which permits NCI staff to see the entire clinical trials portfolio. There is also an external access level. Principal investigators or grant holders involved with any NCI trial are granted access as soon as the Protocol Information Office saves the study in the database. When logging in with external access, the list of available studies is filtered to include only those associated with the investigator's institution. Institutional access privileges can also be set up for Cooperative Group or Cancer Center operations offices.

The search page on the timeline reports site has the capability to search under the following categories: lead organization, document number, phase, type of document, agents, and diseases. The search page features an auto-complete function when typing in search terms. The only data currently

searchable on the timeline reports site are the LOIs, concepts, and resulting protocols that CTEP received after January 1, 2010. Eventually, the entire CTEP portfolio will be available and searchable on the site.

The timeline reports' Web site features four separate reports to track OEWG timelines. The Tracker Report contains administrative details, such as the principal investigator, target dates and deadlines, study milestones (e.g., LOI or concept approval), agents and diseases, specific pathway the protocol is on, and recent protocol activity (e.g., conference call dates). The second type of report, the Gantt Chart, is a graphic representation of all information included in the Tracker Report. The Sequential Chart is a snapshot of current study status; this Chart is still undergoing revisions on the site. The last report is the Compare Protocols Report, which can be used to compare any of the studies within a site user's portfolio. All four of the reports available on the timeline reports Web site can be exported as PDF or PowerPoint files.

Questions and Discussion

Dr. Abbruzzese asked whether NCI has considered how to influence Cancer Centers in terms of protocol/study timeouts for contracting. These timeouts are a huge issue and will become the rate-limiting step in trial development. Dr. Doroshow commented that the START (Standard Terms of Agreement for Research Trial) clauses presentation, scheduled for later in the afternoon, would address this issue and provide results of a follow-up evaluation on the START clauses and the impact the clauses have had on the overall effort to develop contracts with companies.

Dr. Adamson questioned whether or not one could view a snapshot of a Cooperative Group's or Cancer Center's entire portfolio on the timeline reports Web site. This would be beneficial in terms of identifying systems issues (i.e., if many studies get delayed at the protocol review phase). Mr. Friedman responded that OIB is trying to provide this function by expanding the Compare Protocols Reports. Currently, Compare Protocols Reports are limited to only five protocols. Dr. Adamson also asked whether back-end data from the site could be made available in read-only format so that Cooperative Groups or Cancer Centers could develop their own reports. Mr. Friedman commented that the back-end data include an immense amount of information that would be extraneous to the sites and would likely make it difficult to generate meaningful reports; thus, he does not believe it would be helpful to provide this function at this time, although it is an option that could be considered for the future.

Dr. Schilsky suggested a few short- and long-term outcomes to consider when evaluating the impact of the OEWG timelines. A major long-term impact that should be assessed is whether the completion rate of studies improves with a more rapid study activation rate. An intermediate endpoint to consider is whether there is any increase in pharmaceutical industry interest in NCI studies; they may be more willing to access the NCI clinical trials system if it is more efficient. A short-term issue that needs to be looked at is the impact of timeline implementation on staff resources: Are other protocols being pushed back even further in their development because all resources are being applied toward meeting OEWG timelines? Dr. Doroshow commented that the timeline implementation process needs to be given at least 1-2 years before the impact of the timelines on protocol activation can truly be assessed.

Dr. Curt Civin, Associate Dean of Research and Director of the Center for Stem Cell Biology and Regenerative Medicine, University of Maryland School of Medicine, asked whether if one phase of the protocol activation process exceeded the target timeline, the subsequent phases would be penalized. Dr.

Doroshow responded that all protocols must meet the target endpoint, so if one phase of the process exceeds a deadline, the other phases will have less time for completion.

Ms. Roach commented that the standardized toxicity language used in informed consent documents is not patient friendly and lengthens the informed consent process and that she would like to directly address this issue at a future CTAC meeting. Dr. Doroshow agreed that this issue needs to be addressed at a future meeting.

V. TRANSFORMING NCI'S CLINICAL TRIALS SYSTEM—DR. JAMES DOROSHOW

Dr. Doroshow updated the Committee on the effort to transform NCI's clinical trials system. Several members of CTAC were part of the Institute of Medicine (IOM) committee that called for a restructuring of the clinical trials system, providing CTAC a unique perspective of the recommendations and NCI's response. The goal of the restructuring process is to create a national clinical trials network—as opposed to a series of individual clinical trials operations—comprising Cooperative Groups that interact with one another to co-develop, co-implement, and co-conduct innovative and practice-changing trials in order to improve the nation's cancer care. The approach and plans for a new funding opportunity will be presented to the Board of Scientific Advisors.

Several assumptions underlie the proposed change. NCI is interested in supporting a national clinical trials system to design, conduct, and rapidly complete large, randomized, multisite Phase II and III clinical trials of the highest scientific priority for treatment, control, screening, diagnosis, and prevention. NCI should 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. NCI should also develop a more precisely focused NCI peer-review system to stimulate and maintain transformative change. Substantial operational, management, and cultural change by the Cooperative Groups, NCI, and the clinical trials community will justify the additional investment in the system.

There is also scientific rationale for transforming the current system. The ability to prioritize molecular characterization resources and develop molecularly driven trial designs is critical to the future success of multisite clinical trials, and this can be achieved more easily with fewer competing research organizations. Extramural scientific prioritization of the Phase III portfolio across all disease entities is essential to efficiently develop and complete multicenter trials. A smaller number of competitive Cooperative Group disease committees is better suited to building consensus.

Currently configured Cooperative Groups have disincentives to study less-common diseases due to potential failure of disease-specific committees in review for taking any risk in accrual. This problem might be alleviated through a national network with dramatically altered review criteria. In addition, a shared information technology infrastructure with a common "front end" for clinical data and tissue resource management will constantly require modification, which is more manageable with fewer independent entities.

In order to screen enough patients to define molecular subgroups appropriate for study, NCI-supported clinical research groups must function as a coordinated network. Scientific interactions around imaging would be facilitated by integrating ACRIN into a setting with more access to patient resources

for investigational studies. There must be significant effort to harmonize procedures for scientific/administrative oversight for quality-of-life, cancer control, and therapeutic trials between the Divisions of Cancer Prevention and Cancer Treatment and Diagnosis. There is also critical need to better operationalize the collection of crucial tissue specimens from NCI-supported prospective trials, which is currently difficult due to lack of a national information technology tissue locator resource, standard operating procedures, and a transparent process to prioritize the distribution of specimens on a national scale. Finally, open access to a national clinical trials network for clinical/translational investigators not currently involved in the Cooperative Group platform will ensure the best competition of ideas and the movement of high-priority science into the clinical trials arena. It is imperative to think about how to reposition this important clinical trials infrastructure so that it is central to the clinical and translational research enterprise.

Dr. Doroshow outlined several endpoints for success of the new clinical trials network. The successful system will not only provide the essential infrastructure for the majority of Cooperative Group trials in treatment, control, screening, diagnosis, and prevention, but will be a major enabler of cutting-edge translational investigation across all of NCI's clinical research programs. The system will rapidly open trials that are approved by the Scientific Steering Committees (SSCs) and complete accrual according to defined guidelines by leveraging an integrated national network of performance sites. It will also provide a unified clinical and translational infrastructure for the extramural cancer community, including investigators, patients, advocates, and industry, that will be at the forefront of translational oncologic discovery, efficiently answering critical questions not well supported in a commercial environment.

There are currently 10 Cooperative Groups and many disease committees, operations, statistical operations, and tumor banks. Dr. Doroshow questioned whether 10 independent entities are necessary. If not, how many groups should there be? If the groups are to molecularly characterize patient populations, they must be large enough, with a substantial number of sites, to allow access to the necessary numbers of patients. A few large groups would meet the needs of investigators for training, education, and adoption of new discoveries. Three or four multidisease Adult Groups should provide ample creative outlets for disease leaders across the nation and promote competition for the best trial ideas. While these groups can focus their research on different cancers, they should all be capable of performing multidisciplinary trials across the spectrum of cancer treatment, control, diagnosis, screening, and prevention. The four pediatric clinical trials groups were merged previously into one entity, the Children's Oncology Group (COG), which should remain intact.

The broad recommendations to CTAC are to integrate the current adult-focused Cooperative Groups into no more than four Adult Groups with multimodality capacity in a broad range of diseases, all fully committed to a national clinical trials system. Potential strategies to assist integration include utilizing existing NIH grants that permit multiple principal investigators, which may help with the leadership transition; incentivizing the transition with provision of additional resources; allowing a distributed data management and operations system to avoid disruption of ongoing trials; and combining, rather than disbanding, overlapping disease committees to include all current participants. NCI's clinical trials review system should also be reconfigured with emphasis on incentives for a national system. The emphasis of the four Adult Groups will be left to the investigators; it is hoped that the revised peer-review process will provide infrastructure that is able to take advantage of scientific opportunities not only in pediatric malignancies but in adult malignancies as well.

The expected outcome of the clinical trials program redesign is four harmonized operations centers, four harmonized data management centers, a maximum of four disease-specific committees per cancer type, four Cooperative Group cancer control/prevention research bases, and three tumor banks. This networked system will be better able to perform studies that focus on less-common malignancies; require sophisticated imaging modalities; necessitate rapid molecular characterization of tumors; involve access to nationally integrated tissue resources; and/or are initiated by investigators not currently involved in Group activities. The new system must have a way to prioritize these resources across all diseases and modalities of care.

Specifically, the new Groups will be fully integrated infrastructures that can move from idea generation and trial implementation to accrual and analysis, with scientific committees, operations offices, membership, data management, statistics, and tumor bank resources. However, the current structure will be transformed to support a system that functions as a network of groups with harmonized infrastructures and shared responsibilities, including support for all concepts approved by the SSCs, regardless of their source. Study chairs will be assigned to every SSC-approved study; sharing of expertise and technology will be rewarded. There will be common practices for partnering with industry and philanthropic organizations, an equitable and transparent accrual reimbursement system, and promotion of public access across the system (tissue, clinical raw data, etc.). Study ideas can be generated from any Group as well as investigators not affiliated with a Group. Any Group will be able to manage a trial whether or not it has a disease committee. All Group Phase III and certain Phase II trials (as approved by the SSCs) will be on the Cancer Trials Support Unit (CTSU) docket, and a co-chair will be named by each Group with a relevant disease committee. Investigators will obtain credit from any Group to which they belong, and that Group will reimburse for that trial. Group operations will be required to support and manage studies originated by investigators or investigator networks outside of the Group, provided that the study is approved by Steering Committee review. Funds for this activity must be budgeted in new awards.

Maintenance of four Adult Groups with appropriately resourced infrastructures will allow preservation of NCI's long-term investment in the positive attributes of the current system. The new system will maintain investigator volunteerism and participation in patient accrual through scientific engagement and commitment to a shared mission. This model of integrated, not-for-profit entities with distinctive histories and identities also facilitates leveraging of non-NCI resources; external funding, institutional cost-sharing, and pro bono time will enable a Phase II–III clinical trial program at relatively low cost to NCI. The new structure will also improve trial operations by facilitating close interaction among scientific and operational elements of protocol teams.

Of course, there are risks in consolidating the adult Cooperative Groups. The system currently depends on investigator volunteerism; hence, infrastructure change involves risk. Costs will increase due to short-term transition costs to harmonize operations (software, hardware, etc.) and committee structures. There will be leadership issues among multiple Group principal investigators and committee co-chairs; change will require the buy-in of Group board members, Group members, the broader scientific community, scientific societies, industry, patients, and patient advocates.

In order to produce the desired change in the clinical trials program structure, several components of the review process must exist. The scientific review system must be able to evaluate how well new clinical trials are developed and completed, with scientific review of each network component. The review process must also ensure that the components of the clinical research infrastructure are efficient,

cooperative, well coordinated, and integrated, as well as that each funded component plays into the effectiveness of the national system as a whole.

The challenge in reconfiguring the system is that fundamental transformation of a complex, goal-oriented clinical research enterprise requires new, shared strategic management. NCI and the Group leadership must manage the program as a collaborative national program in order to reach shared goals; each Group must be managed and reviewed not as separate "grants" but as components of an integrated system. Likewise, the "Cooperative Agreement" should be viewed by all as a way of doing business, not as a funding mechanism. Recognition and support for the public/private nature of the funding structure requires shared NCI and Group decision-making in Cooperative Group awards, Group-generated industry and philanthropic support, as well as investigator volunteerism and institutional cost sharing. The system must be managed and reviewed as both a scientific and an operational enterprise; this will require major change in the peer-review process to incentivize performance of every component of the new system.

Trials from disease committees are currently prioritized by an open process of scientific/clinical peer review by a broad spectrum of experts (i.e., SSCs); NCI has a voice within these committees, but its primary role is to be facilitative. Current incentives must be refocused away from "credit" to the Group for leading a trial; SSCs must focus exclusively on developing trials that will address the most important scientific questions in a timely way. Also, SSCs need feedback and assistance in developing national clinical trial priorities, which will be provided by a cross-disease panel comprising leadership from extramural scientists, Group scientific and statistical co-principal investigators, SSC chairs, advocates, and NCI staff.

The four newly configured Adult Groups and COG will undergo competitive review every 5 years, coordinated by the NCI's Division of Extramural Activities. The Group reviews will occur in the same year so that they can be directly compared and resources can be allocated appropriately. Reviews will be shorter and limited to Group leadership only; Group scientific, statistical, and operational leadership can defend the Group without participation by disease committee chairs. Because review will no longer focus on trials put forward by disease-specific committees, emphasis will shift to assessing the role of the Group as part of an integrated clinical trials system.

Groups will be evaluated on scientific, operational, and collaborative criteria. Scientific criteria will include: accrual to trials of any Group in the relevant disease areas across the system; collaboration with other Groups and other NCI-funded investigators, including combining trial concepts to design the most effective trials; leadership and participation in Steering Committees and Task Forces; number and quality of trial concepts proposed and trials approved over the full award cycle; design and leadership of Clinical Trials Planning Meetings; timely implementation and completion of trials, as well as analysis and dissemination of trial results; and mentoring of young investigators to provide opportunities for them to develop concepts and lead trials. If the Group receives a passing score on these criteria, the review committee will evaluate new treatment strategies for selected diseases.

The revised review will also have an operational efficiency component. The Groups will be evaluated on implementation and maintenance of an integrated operational framework for the operations office and data management functions; coordination and streamlining of operational processes; development and implementation of system-wide and Group-specific information technology infrastructure and tools to enhance coordination and productivity; achievement of agreed-upon timeline goals for each step in trial activation; achievement of target accrual goals for trials led by the Group as well as other system-wide trials led by other Groups or components of the network; implementation of

processes for effective trial oversight and response to safety issues; and data quality as evidenced by audit results. The goal is to create the most in-demand clinical trials infrastructure, which, in order to be achieved, must be coordinated and streamlined and must produce high-quality data. The scientific criteria must have priority, but operational efficiency is an important part of evaluating the way resources are spent.

The third group of criteria for review will cover collaborative management of the system as a whole. Groups will be reviewed on their contribution to the development and maintenance of a national, highly integrated clinical trials system. Criteria will include: active participation with NCI in collaborative management of the overall Group program; identification of system-wide issues; identification of management and operational best practices applicable across the system; development of new cross-Group initiatives and/or policy/procedural changes; demonstration of NCI-Group liaison activities to solve problems and promote dialogue; implementation of agreed-upon improvements in operational and management policies and procedures; provision of clinical trials infrastructure resources for prioritized multicenter Phase III and II trials originating outside the Group; and effective management of assigned cross-Group committees for rare diseases and implementation of prioritized trials in rare diseases.

Community Clinical Oncology Program (CCOP) research bases will also be recompeted every 5 years at the same time but on a different cycle from the treatment RFA. CCOP RFAs will be released annually, with the opportunity for new and recompeting CCOPs to submit. The tumor bank U24 RFA will be recompeted on a different cycle from the treatment U10 RFA.

The new system will go from 10 independent groups to 5 connected groups, including COG, which has done an impressive job of melding science and protocols and should be integrated closely with the Adult Groups. For this network to be healthy, it must be viewed as a central part of Cancer Center interaction; Cancer Center researchers who are not part of the Cooperative Groups should be brought into the fold.

NCI began implementing this system change in September 2010, when the program announcement that had previously been used to allow competitive renewals for currently funded grants ran out; henceforth, NCI will not accept renewal applications and will pay only at current levels via supplements until a new Funding Opportunity Announcement (FOA) is released. The new FOA will call for a National Clinical Trials Network that envisions all of the changes outlined and will welcome proposals from current grantees and Cancer Centers, among others.

The proposed timeline for the development of the new FOA and Guidelines for the system and submission, review, and support of new awards is complicated. NCI will gather information and input from stakeholders and the community for the new FOA and Guidelines from December 2010 to July 2011. The concept will be developed and reviewed by NCI Divisions and the Clinical and Translational Research Operations Committee (CTROC) in August 2011. In September, the NCI scientific program leadership will review the Concept, and the Board of Scientific Advisors will conduct their review in November. DEA will review the FOA and Guidelines from November 2011 to March 2012; NIH will continue the review from March to July 2012. The new FOA will be released in July 2012, with receipt of competing applications expected in November 2012. DEA will then review the competing applications in February 2013, and the National Cancer Advisory Board will continue the review in May 2013. Awards will be distributed after October 2013.

Dr. Doroshow stated that an extensive timeline is necessary to provide the time needed for extramural input and to develop the RFA. The leadership of both NCI and NIH must approve the Concept, FOA, and Guidelines. This timeline, however, also provides ample opportunity for input from many stakeholders, including the current Cooperative Group principal investigators, CCOP principal investigators, professional associations, advocates, and the public; it is important to gather as much input as possible *before* the RFA is written, as many stakeholders will be applying for the program.

Dr. Doroshow posed several questions for discussion to the Committee: How many Cooperative Groups should there be and how should they function? How will NCI maintain engagement of core investigators who contribute to the system on a pro bono basis? What is the scientific infrastructure necessary for modernizing translational research? In constrained economic times, how can NCI maximize scientific progress while prioritizing investment in clinical trials? What should a National Clinical Trials Network look like when change occurs?

Questions and Discussion

Dr. Olivera Finn, Professor and Chair of the Department of Immunology at the University of Pittsburgh School of Medicine, noted that this is an excellent opportunity to change the mindset of the system, as well. Some groups interested in different types of trials have not traditionally found homes in the current structure. Those who have been outside of the system may become insiders in the new system.

Dr. Edith A. Perez, Deputy Director of the Mayo Comprehensive Cancer Center, requested definition of the sorts of trials to be conducted by the Groups versus the Cancer Centers, SPOREs, etc. Currently, trials through the Cooperative Groups are considered less "scientifically valid" than trials conducted by those other groups. Dr. James Wade, Director of Medical Oncology at Decatur Memorial Hospital Cancer Care Institute, added that it is difficult to comment on the success of studies at Cooperative Groups versus Cancer Centers, etc., without data on the entire enterprise. He wondered whether there is reason to believe that these studies will flow easily into the new system. Dr. Doroshow responded that data could be obtained through a portfolio analysis using the methodology developed by the Science Technology Policy Institute (STPI) for NCI. These data will allow evaluation of Phase I and II grants and contracts and Cooperative Group studies. NCI does not have data on early-phase trials. Dr. Doroshow and his colleagues are working to finalize a plan for collecting, in a searchable database, all of the accrued data for all NCI-supported studies in and outside of Cancer Centers. One of the latest papers published by Dr. David Dilts included data from Vanderbilt-Ingram Cancer Center, University of North Carolina Lineberger Comprehensive Cancer Center, Ohio State University Comprehensive Cancer Center, and Fox Chase Cancer Center; Dr. Dilts outlined accrual issues at these institutions.

Dr. Deborah Bruner, Director of the Clinical Trials Recruitment, Retention, and Outreach Core Facility at the Abramson Cancer Center, wondered how the decision on the number of groups was reached. At the last meeting, Dr. Doroshow had noted that he did not see the savings in consolidation given all of the volunteer work inherent in the Cooperative Groups. Dr. Doroshow responded that the core issue is how many patients will accrue; if X number of patients are accrued, then Y number of statisticians and Z number of data managers are needed. One group is likely inefficient, as are nine groups. Integration will cost money rather than save it. Ultimately, advice is needed from the extramural community.

Dr. Schilsky noted that aligning the review cycle for all of the groups provides an opportunity to examine the potential relationship between success, peer review, and budget by comparing one group's success against another's in the same cycle, with the same review criteria, etc. If funds are allocated based upon success and review, there could be a substantial shift in funds across groups. This could present problems if all four groups are to be essential to the maintenance of the system. Dr. Doroshow responded that if certain groups do better than others, accrue better than others, and help the entire system conduct studies faster, they should be rewarded for it. Having all reviews coincide will allow the peer reviewers to evaluate contributions and adjust budgets in a new way. Other advisory boards have suggested to DCTD that they may put additional funding to the network if it is proven that changes can be made to increase efficiency.

Dr. Susan Arbuck, an R&D consultant in cancer drug development, suggested that a more straightforward review process—with very directed objectives and criteria—could possibly be held more often than every 5 years; this would allow the network more flexibility to respond to changes in the field. Dr. Schilsky agreed and added several suggestions, including one that submitted applications should be well written and focus on major accomplishments. Presentations should be streamlined, with only group leadership present in person and scientific leadership available by telephone.

Dr. Joel Tepper, Professor and Chair of the Department of Radiation Oncology at the University of North Carolina School of Medicine, stated that four is a reasonable number of groups. A number of factors should be considered, including how many groups are needed to allow different ideas to be explored and what number are necessary to ensure appropriate support for mentorship.

Dr. Tepper also expressed concern that some groups will represent certain disease sites. If such a group does badly in the review and loses funding, what will happen to that disease site? It will be important to ensure that appropriate research can still move forward without loss of expertise.

Dr. Adamson stated that the more structure imposed, the less innovation will result. He also noted that the overarching rationale for the creation of Steering Committees was twofold: to bring peer review into the process and to provide a workaround for dysfunctional networks of adult Cooperative Groups. Now that the issue of groups not completing studies is being addressed, Dr. Adamson wondered whether the Steering Committees would remain intact and continue to set priorities. Dr. Doroshow responded that peer review is still necessary, as is having a way for groups to work together to develop ideas. Likewise, NCI hopes that the new structure will allow for *prior* collaboration in competitive idea development, with buy-in once a study has been selected. The structure that is needed is whatever structure best encourages collaboration and buy-in. NCI should not be making decisions about which science is the best science; NCI should facilitate decision making, but the best science should be decided by the experts.

Dr. Grubbs asked what the relationship will be between the Cooperative Groups, the SSCs, and the Cancer Therapy Evaluation Program with regard to improving study design. Dr. Doroshow responded that CTEP will not conduct full reviews of the protocols separate from those of the SSCs.

Dr. Schnall expressed concern that unless they are given appropriate priority and credit in review, non-therapeutics trials will be excluded from the system as Cooperative Groups propose therapeutics trials that may be more likely to achieve high scores.

Ms. Roach expressed her hope that NCI is working with change management experts as they embark on the development of this new system. She also suggested that the proposed oversight panel

comprise experts from a wide range of fields that reflect the breadth of research being conducted across the extramural community.

Dr. David Parkinson, President and Chief Executive Officer of Nodality, Inc., noted that there is value to having standing Cooperative Groups, in that they bring with them existing relationships. However, because it is difficult to predict what technological, biological, and therapeutics development changes will occur, variability and flexibility will also be important. The machinery of infrastructure will be central, but it should not be so fixed that the system exists only to justify the machinery. NCI may want to consider fixed infrastructure costs with variability in the competition among the groups.

Dr. Helman echoed earlier concerns about the new system's flexibility. There is no more innovative time in oncology research than now; no one has any idea what a study should look like in 5 years.

Dr. Bruner asked how NCI would ensure that a broad range of disease sites is studied; RFAs generally do not specify scientific priorities, and all four groups could propose to study the same popular disease site. Dr. Doroshow agreed, adding that there have been emerging scientific opportunities that have been deemphasized because the system was inflexible or the disease site was at a disadvantage in the review process. The proposed system must keep in mind what the pharmaceutical industry can do—that the system must be able to address areas that are not very commercial. At the same time, NCI must be as non-directive as possible. Dr. Bruner added that orphan disease sites are not the only areas that are lacking in attention; it would be wonderful to address accrual of patients over age 75, for instance.

Dr. Parkinson stated that while Cancer Centers have always been involved in some way in the Cooperative Groups, SPOREs, consortiums, etc., this involvement has not played a primary role in the Cancer Center review process. The idea of engaging more investigators and researchers from the SPOREs and consortiums is great, though it may be more difficult for them to take leadership roles if there are fewer groups than there are currently. Many of the Cancer Centers have started thinking about how to be more involved in the national system; the California groups have already initiated some active cases and the Midwest Centers have begun preliminary discussions about how to work together. A Cancer Center review process that encourages participation in the new system would be beneficial. Currently, the Centers receive some support, though not much money is used for clinical trials. One idea is to have the Centers compete for a pool of funds within the national network that would provide additional supplemental support, perhaps on a per-patient basis, to launch new trials.

Dr. Abbruzzese suggested that there might be some advantage to setting out basic scientific and financial accrual goals and allowing the existing groups to decide whether to compete or consolidate, without setting a target number of groups.

Dr. Schnall noted that the Cooperative Groups actively engage and compete with each other for outside research funding in order to supplement the relatively small amount of infrastructure funding they receive. ACRIN is not a membership group; if a consortium of investigators approached ACRIN to use its infrastructure, he would find creative ways to work with them and compete for funding with them.

Dr. Grubbs stated that there are some common operational issues among the Cooperative Groups that might be alleviated via a common audit system, with common formats for rating protocols, etc. Dr. Jeffrey Abrams, Associate Director for CTEP, responded that he expects the new structure will allow NCI to develop more common approaches. NCI is already working on a common data management system

across all groups that will hopefully enable groups to produce common case report forms and common protocol implementation. Dr. Grubbs noted that the group chairs should still have access to operational systems that respond to their needs.

Dr. Grubbs also brought up the issue of a Central IRB and suggested that the use of the Central IRB should be mandatory for every site that participates in the new system. Dr. Abrams noted that a recent editorial from the head of the HHS Office for Human Research Protections (OHRP) suggested the same thing. However, there are difficulties in mandating use, in that IRBs are used for more than cancer research in many institutions and organizations and, thus, have rules that go beyond cancer research. Another Committee member noted that in order to meet the timeline for protocols set out by the Operational Efficiency Working Group, the protocol must have been approved by an IRB and CTEP and then opened. There are only a few IRBs around the country that can approve a protocol as quickly as the Central IRB. It was mentioned that use of the Central IRB may give a group a competitive advantage.

Dr. Schilsky stated that the new system will have a finite capacity, as the current system does. Some of the investigators the new system sets out to attract will be turned away; if people do not have an opportunity to move studies through the system, they may walk away entirely. On the other hand, a system that works well could be attractive as a means of getting studies done. Dr. Schilsky wondered how the system could be used to leverage other sources of support—public, private, commercial, and otherwise—to enhance the system's capabilities. Dr. Doroshow would like to organize the network in such a way that it attracts public-private support for the infrastructure. The goal is to have such competitive timelines and a unified information technology structure that it will look extraordinarily attractive from the outside. Dr. Parkinson suggested that once the infrastructure is in place and standardized, NCI could charge to use the system for capacity; this would be very attractive to small companies who are not capable of creating their own networks. Dr. Finn noted that the new Immune Tolerance Network, sponsored by the National Institute of Allergy and Infectious Diseases, is a good example of this. Companies are very interested in the Network's centralized system.

Mr. Leung responded that the small company is one important aspect of leveraging funding, but even the largest company cannot muster the resources to conduct a major study of a rare cancer. NCI is in a unique position to facilitate an infrastructure that will enable genetic studies of rare diseases.

Dr. Arbuck noted that most companies are interested in working with NCI on compounds, as long as they receive speedy access to quality data at the appropriate time, and value for the money. They are willing to collaborate as long as they cannot do the study better and cheaper themselves.

Ms. Roach added that the new system will make it easier to highlight clinical work and advances when presenting to Congress.

Dr. Civin noted that the U.S. Food and Drug Administration (FDA), the Clinical and Translational Science Awards networks, and the new addiction institute—which may or may not include tobacco and cancer studies—have not been a part of the discussion. He also wondered whether there is a fair way for NCI intramural researchers to participate substantively in either the new infrastructure and/or in one of the groups. Dr. Helman responded that there are many examples where various components of the intramural community have participated in Cooperative Groups. Also, the Scientific Management and Review Board has recommended that the NIH Clinical Center be open to extramural researchers; CTEP should be creative about using facilities that will move a particular question forward quickly, regardless of which group posed the question.

The Committee agreed to have another discussion of changes of the clinical trials system at the next CTAC meeting.

VI. CLINICAL TRIALS.GOV: BASIC RESULTS AND OUTCOME REPORTING—DR. DEBORAH ZARIN

Dr. Deborah Zarin, Director, ClinicalTrials.gov, National Library of Medicine (NLM), indicated that a substantial amount of information on clinical trials is now available. Data exist on more than 100,000 clinical trials from nearly 10,000 sponsoring organizations; less than half of these trials are being conducted only in the United States. There are about 2,600 entries in the results database.

The content of a ClinicalTrials.gov registry record, which is generally submitted at trial initiation, comprises several parts: summary of the protocol, recruitment information, and an administrative section. The results record, which summarizes trial results, is completed at the end of the trial. The clinicaltrials.gov record is linked to PubMed and to a number of journals via the use of the NCT number, the unique identifier assigned by ClinicalTrials.gov.

The FDA is starting to use the NCT number in its regulatory process. In the future, this number will also be listed on product labels. Section 8 of the FDA Amendments Act requires trial registration for non-Phase I trials that involve a drug or device and mandates a broader set of data elements than previously required. In the past, only a very small subset of trials was legally required to be registered. In addition, this ruling requires results reporting. The enforcement provisions range from notices of noncompliance to civil monetary penalties up to $10,000 a day and withholding of NIH grant funds.

The FDA, which is the agency in charge of enforcing the Act, uses the term "responsible party" to describe the subject of an enforcement action, typically the study sponsor. If a study involves an IND and/or Investigational Device Exemption (IDE), the sponsor is usually the IND or IDE holder. If there is no IND or IDE and the study is funded by NIH, the responsible party is the grantee, which is usually an organization. If neither of those situations applies, the responsible party is the study initiator.

When planning future trials, investigators should determine who the legal sponsor will be. The sponsor can designate the principal investigator to be the responsible party under certain conditions, such as when there are no restrictions on the ability to report results, access all data, etc. If the principal investigator is unable or unwilling to perform that function, the responsibility falls back on the sponsor. This law pertains to applicable clinical trials: non-Phase I interventional studies that involve a drug or device and that either have at least one site in the United States or are being conducted under an IND or IDE. In addition, applicable clinical trials must meet the date requirements. Trials that were completed before the law was passed are not held within the scope of these restrictions.

Dr. Zarin noted that it is sometimes difficult to distinguish between interventional and observational studies. FDA's definition of devices includes diagnostic devices such as PET and imaging studies, but also *in vitro* diagnostics. The law further states that investigators must report on the results of these trials once the FDA-regulated products are approved. Results must be submitted within 1 year of the completion date of the trial. The results page includes the participant flow, baseline measures (e.g., age, gender, Karnofsky performance status, hormonal receptor status, etc.), primary and secondary outcome

measures, and a table of all serious adverse events. Records at clinicaltrials.gov should be kept up to date, and all changes made to the records are publicly tracked.

It is estimated that about 32 percent of industry-sponsored trials and only 4 percent of NIH trials (none from NCI) that should have reported results have actually reported them on clinicaltrials.gov. In order to fully report a study, it is beneficial to have familiarity with the system and requirements, general clinical trial expertise, and relevant data from the trial review. This process is similar to a cognitive task such as writing a manuscript, rather than being purely administrative. The International Committee of Medical Journal Editors has also declared that tabular reporting of results does not interfere with journal publication.

Dr. Zarin gave several examples of inaccurate, inconsistent, and erroneous reporting. There have been numerous problems with illogical or inaccurate entries ("time to survival") into the record, as well as inconsistencies (e.g., enrollment does not match participant flow).

Although reporting on the use of a data monitoring committee is optional, among those individuals who have chosen to report on this process, the rates of committee usage are low: 17 percent among industry-sponsored trials and 48 percent for non-industry-sponsored trials. Efforts are being made to improve compliance.

Dr. Zarin commented that the European Medicines Agency has a similar law requiring reporting of clinical trial results. The European results database will be made fully compatible with its U.S. counterpart. Any investigator conducting a study with a site in the European Union (E.U.) must report the results in the European database, even before the drug is approved. U.S. investigators with at least one site in the E.U. must report to both databases; thus, there is substantial interest in compatibility.

Principal investigators who assume the role of responsible parties need some central support to help them understand the system and the requirements. The individuals responsible for entering data have tended to lack understanding of clinical epidemiology principles, such as units of measure and confidence intervals.

Questions and Discussion

Dr. Parkinson asked if the Data Monitoring Committee (DMC) percentages include some of the laboratory-developed *in vitro* tests and whether DMC would apply to a retrospective analysis of prospectively collected samples. Dr. Zarin clarified that the DMC analysis is conducted only on interventional studies, not observational or retrospective studies. If the FDA considers a particular genetic test a "regulated device," then that would be an applicable device study. Dr. Parkinson indicated that a lot of *in vitro* diagnostics studies are conducted on samples that have been collected on previously completed trials. Dr. Zarin clarified that in FDA's device terminology, "human subject" includes tissue samples. She advised Dr. Parkinson that a study should be registered when there is any doubt.

Dr. Helman asked how frequently the data are accessed by the public. Dr. Zarin responded that it is not known how many people are accessing the results database per se, but there are about 900,000 unique visitors per month.

Dr. Adamson stated that the timeline for reporting results on clinicaltrials.gov does not coincide with the timeline in which the results would normally be analyzed. In pediatric oncology studies, 1 year after the last patient finishes treatment is too short a timeframe to have meaningful analysis of outcomes. Dr. Zarin noted that results are not due until 1 year after the "primary completion date." This date is when the final data collection for the primary outcome measure occurs. It is not determined by the timing of the intervention. In other words, the intervention could cease long before the primary completion date occurs.

Dr. Arbuck discussed her experience with the system while she was working at a large pharmaceutical company. The company took reporting to clinicaltrials.gov very seriously but had difficulties understanding the system at first. Dr. Zarin remarked that at least 10 companies have invested substantial resources and set up a central team specifically for this effort.

VII. NCI'S CLINICAL TRIALS REPORTING PROGRAM (CTRP) IMPLEMENTATION UPDATE—MR. JOHN SPEAKMAN

Mr. John Speakman, Associate Director, Clinical Trials Products and Programs, Center for Bioinformatics and Information Technology (CBIIT), NCI, presented an update on the implementation of the Clinical Trials Reporting Program. The CTRP was established to provide a comprehensive database containing regularly updated information on all NCI-funded clinical trials. The recent IOM report on NCI's clinical trials system also reiterates the need for a comprehensive database of planned and active trials. In accordance with NIH policy enacted since the FDA Amendment Act of 2007, NIH Institutes are no longer allowed to register trials on behalf of responsible parties (e.g., via any NCI system). The Act also requires registration of all applicable trials (Phase II/III) with ClinicalTrials.gov. NCI is not in control of these requirements.

Registration of interventional trials in CTRP is already open to all NCI grantees. As of December 2010, over 3,000 trials from 36 NCI-designated Cancer Centers and 14 other organizations have already been submitted to CTRP. Registration can be completed manually or via the Internet. Only 10-15 data elements are required for registration, including principal investigator, lead organization, trial title, phase, purpose, and status of the trial. The Clinical Trials Reporting Office (CTRO), an NCI resource, abstracts information from the protocol into CTRP, including brief and detailed descriptions, trial design, outcome measures, disease/conditions, and interventions. A Trial Summary Report is then sent from CTRP to the submitter for verification. An electronic file (XML format) can also be sent to the submitter that can be uploaded to ClinicalTrials.gov in response to the registration requirement. Entry of accrual data has been piloted via a Web interface.

NCI is working with the CTRP Strategic Subcommittee to review data elements for registration and accrual, discuss issues regarding collection of outcome data, and define a feasible timeline for implementation. NCI currently only receives outcome data in the form of "CDUS Complete" on Phase I and II DCTD treatment trials involving NCI agents. NCI is assessing the feasibility and added value of outcome data reporting for other NCI-supported trials. "CDUS Complete" and NLM Basic Results Reporting do not contain the same data set. Extramural input will be needed to determine outcome data-reporting requirements. NCI will continue to work with NLM to avoid duplication of data-reporting requirements.

NCI-designated Cancer Centers were provided with administrative supplements to enable successful registration of interventional clinical trials in CTRP. The supplements also support implementation of electronic reporting into CTRP to submit patient accrual on registered trials. NCI will continue to work with the CTRP Strategic Subcommittee to establish implementation timelines for complete registration and accrual reporting, as well as continue the discussion of outcome reporting with extramural stakeholders. Mr. Speakman presented tentative implementation timelines that need to be discussed with the Strategic Subcommittee and CTAC members. Registration of new Cancer Center interventional trials should be complete by the end of 2011, with ongoing new trial registrations continuing after this point.

Questions and Discussion

Ms. Roach asked whether accrual reporting is intended to be real-time. Mr. Speakman responded that it had been discussed that accrual should be reported quarterly. Ms. Roach also inquired whether NCI could support reporting of results the way it facilitates registration reporting. Mr. Speakman confirmed that NCI intends to do so; however, results reporting will be difficult to automate.

Dr. Abbruzzese asked if institutions are successfully using ClinicalTrials.gov for reporting purposes. Mr. Speakman stated that institutions are successfully using NCI-prepared electronic files to upload to ClinicalTrials.gov. No statistics on the quality of system usage are available; however, Dr. Prindiville commented that some institutions, such as M.D. Anderson Cancer Center, have chosen to report trials to ClinicalTrials.gov themselves rather than use the NCI-prepared file.

VIII. IMPLEMENTATION OF THE RECOMMENDATIONS OF THE CTAC GUIDELINES HARMONIZATION WORKING GROUP REPORT—DRS. JAMES ABBRUZZESE, SHEILA PRINDIVILLE, TOBY HECHT, LINDA WEISS, AND MARGARET MOONEY

Dr. Abbruzzese indicated that the overarching goals of the Guidelines Harmonization Working Group were to: (1) integrate the NCI clinical trials program by harmonizing the guidelines of the major clinical trials programs and (2) develop incentives to foster collaboration among all components of the clinical trials infrastructure. Attempts have been made to eliminate redundancy and duplication while proactively encouraging collaboration. The Working Group tried to identify examples of successful collaboration, such as the I-SPY trial. NCI looked at current guidelines for clinical and translational research and identified disincentives for collaboration. A vision document with recommendations was developed and approved by CTAC in July 2009. Dr. Abbruzzese summarized the recommendations from that document.

The Working Group recommended revising the guidelines to describe in greater detail the collaborative efforts that are anticipated or expected across mechanisms and include a specific section of the application that credits collaboration separately from the overall score. Transmechanism collaborations would potentially bring more novel interventions into early Phase II and Phase III trials to be conducted by Cooperative Groups. Different types of incentives were discussed: salary support, expanded institutional U10 awards, career development awards, and per-patient reimbursement, as well as the augmentation of the CTSU capacity to accommodate Cancer Center and SPORE trials. Formalizing

and streamlining the process may be a way to increase collaboration between Cooperative Group and non-Cooperative Group study teams.

The Working Group also recommends evaluating the effectiveness of the Grand Opportunity grants and, perhaps, the creation of a new way to support long-term science that moves ideas, concepts, and interventions from early preclinical research to Phase I, II, and III trials; this goal might also be reached via combination with STRAP awards.

The recommendations also contain some specific outcome measures: consistency of guidelines across the mechanisms, priority score credit for collaborations, and increased contributions of SPORE leaders, Cancer Center directors, and Cancer Center investigators to the NCI clinical trials program.

Dr. Prindiville discussed NCI's implementation of the recommendations. She noted that implementation has been a group effort, and particularly thanked Dr. Doroshow and Ms. Anna Levy (CCCT). First, all of the recommendations from the Guidelines Harmonization and Operational Efficiency Working Groups were mapped to the current SPORE, Cancer Center, and Cooperative Group guidelines. Harmonized guideline revisions were subsequently drafted. New sections on collaboration have been added to the SPORE and Cooperative Group guidelines and integrated into multiple sections of the Cancer Center guidelines. Several incentives for collaboration have been implemented, including career development awards, cancer clinical team leadership awards (ongoing), and Grand Opportunity grants (funded by the American Recovery and Reinvestment Act program in 2009). A decision on continuing the Grand Opportunity mechanism will be made at a later time.

NCI has instituted the ability and funding to have organ-site-specific meetings to foster collaboration between SPOREs and groups that are conducting organ-based translational research with the clinical groups through the SSCs. The first meeting was held in November 2010.

Dr. Steven Krosnick from Dr. Prindiville's office (CCCT), in collaboration with DCP and CTEP in DCTD, set up a pilot process to support collaborative multicenter Phase II trials that are led by an NCI Cancer Center and/or SPORE. Through this process, Cancer Center or SPORE investigators can bring ideas to the Steering Committee for input and collaboration. If the idea is approved (by the Steering Committee, NCI, and the Clinical Trials Operations Committee), there is opportunity for support of that trial. Due to funding restrictions, the process is currently limited to Phase II treatment trials. It is estimated that up to two treatment trials will be supported through this mechanism in 2011. There must be at least four sites participating to qualify for the support, and there must be collaboration between a SPORE (with another SPORE), a Cancer Center, or a Cooperative Group. The award is meant for trials that cannot be led by Cooperative Groups at this time. Dr. Prindiville described the services that the CTSU offers and advised the audience to contact Dr. Krosnick or the medical officers in CTAC if interested in applying for those funds.

The implementation process has focused on incentives that could make an impact in the near term, but other incentives—such as tailoring K awards to senior investigators for salary support for facilitation and collaboration—will likely be implemented in the future.

Dr. Toby Hecht, Acting Associate Director of the Translational Research Program in the Division of Cancer Treatment and Diagnosis, NCI, presented the proposed changes to the SPORE guidelines. She stated that collaborative research has always been a key feature of the SPOREs, and is currently addressed in the Program Organization Capabilities (POC) section of the SPORE Guidelines. Until early this year,

that was just a reviewed section, whereas it is now a written and reviewed section. Given that the POC had seven review elements, NCI decided to remove the collaboration element and place it in a new independent section termed "Scientific Collaboration." That section will receive a separate score. The 70/30 overall impact/priority score has been eliminated; the reviewers are now asked to focus on the translational impact of the proposed research as supported by the Shared Resource Cores, POC, scientific collaboration, and developmental programs of the SPORE. The Scientific Collaboration section will include a description of collaborative efforts that have as their goal moving cancer therapeutic, biomarker, prevention, and epidemiological studies from the early discovery laboratory phases to early clinical trials and studies to later-phase studies and beyond, taking place within the SPORE community as well as across NCI-supported clinical trial and translational science mechanisms, and with other government and nongovernment programs. The section will also include a description of the leadership related to collaboration and a description of collaborative arrangements, where appropriate, such as separate grants, contracts, or Cooperative Research and Development Agreements (CRADAs) with industry for the continued development of SPORE concepts.

Collaborations are defined in two ways. A *horizontal collaboration* is one in which groups coordinate to accomplish a set of research aims on a single level (in the laboratory, a clinical trial, or a population study). This is the traditional way SPOREs have been collaborating. A *vertical collaboration* is one in which groups work together sequentially or with some overlap to move up the translational research pathway. Each SPORE will be asked to demonstrate a commitment to both vertical and horizontal collaboration in completing preclinical projects and moving promising results up the translational research pathway. New SPORE applications will be expected to describe plans for future horizontal and/or vertical collaborations for what NCI calls "direct translational projects"—projects that will eventually reach a clinical trial within the 5 years of the funding period or, in translational projects that move in the reverse direction, by using human biospecimens to discover and develop biomarkers, including analytical and clinical validation. Applicants for renewal will be asked to describe any prior, current, or proposed project, where appropriate; planned ongoing and/or completed horizontal collaborative projects; and milestones. They must also explain how these joint efforts will further translational goals of the SPORE and outline the accomplishments of any vertical collaborations.

Only Phase I and early Phase II clinical trials enrolling fewer than 100 patients may be supported by the SPORE without collaboration. However, for collaborations with other SPOREs, Cancer Centers, and other NCI-supported mechanisms on randomized Phase II therapeutic trials with 100 to 200 patients, SPOREs should use the appropriate SSCs and their task forces to work together to develop clinical concepts for early SPORE trials that could move forward to the Cooperative Groups. Correlative studies can also be included in this opportunity. A third option is a limited collaborative opportunity for large Phase II trials to access CTSU resources upon recommendation by the Steering Committees. Applicants are advised to obtain additional information from the staff at CCCT.

Rather than conducting clinical trials, many SPORE projects study human specimens to expand upon observations or outcomes in the clinic, a process called "reverse translation." When biomarker studies are ready for clinical trials, SPOREs are encouraged to collaborate with trans-NCI clinical trial mechanisms to validate the biomarkers.

It is hoped that the new guidelines can be approved by August 2011 with an amended program announcement the following month and application receipt by January 2012 for funding in fiscal year 2013.

Dr. Linda Weiss, Chief, Cancer Centers Program, NCI, clarified that the P30 Cancer Center Support Grant is not focused solely on supporting clinical trials. Rather, it encompasses the entire spectrum of cancer research from basic to population science. The grant does not manage specific research projects. Dr. Weiss indicated that because there are more than 40 elements in the Cancer Center support grant review, NCI decided to incorporate changes into 6 existing elements that have a high impact on the priority score rather than adding a new collaboration element. A new emphasis on how the Center facilitates movement of findings through the translational research pipeline has been incorporated, along with a new focus on how Center leadership develops and implements collaborative strategies that will advance scientific findings. The recognition of clinical staff who are making major contributions to the Center has been strengthened. A component related to support of clinical staff investigators was added in 2004 and will remain. A new emphasis on accruing to a diverse (supported by different mechanisms) portfolio of clinical trials has been added, as well as text on leadership of and accrual to Cooperative Group clinical trials. In the second-stage comprehensiveness review, greater emphasis has been placed on clinical training programs and dissemination of clinical findings.

Approval of the new guidelines is anticipated for midsummer, with an application receipt date in January 2012 and funding in 2013. Dr. Weiss is planning to present the guideline revisions to Cancer Center directors at the retreat in February.

Dr. Margaret Mooney, Clinical Investigations Branch, CTAC, stated that the Cooperative Group program will undergo major transformations, including revision of guidelines. The guidelines have been updated with the latest review criteria in an effort to retain elements that were previously agreed upon.

There should be a high value in review on meaningful participation across the Cooperative Group system. The Cooperative Groups program would like to coordinate with SPOREs, Cancer Centers, and DCP to put a high value into review for innovative collaborations with NCI-funded early clinical trials mechanisms. The new review criteria include evidence of accrual to trials led by other groups as well as those supported by other NCI mechanisms. The Funding Opportunity Announcement will probably be issued soon after those of the SPORE and Cancer Center programs.

Dr. Abbruzzese commented that the next steps include assessment of impacts and outcomes of guideline revisions.

Questions and Discussion

Dr. Schilsky noted that there is usually a lag between guideline revisions and change of attitudes in the study section review process. Dr. Paulette Gray, Director, DEA, NCI, added that for the peer-review process, the important criteria will be the criteria that the program staff develop, not the revised guidelines.

Dr. Schilsky commented that implementation of the revised guidelines by the peer reviewers will require a fair amount of discussion, reeducation, and rethinking so that the reviewers come to value the new elements. He suggested including a new element of support that would be a financial incentive for collaboration.

Dr. Gray remarked that peer review does not make funding decisions. Dr. Helman added that applicants are requested to estimate how much money they will need for a project and are seldom offered more than they requested. Dr. Schilsky added that the only difference between big infrastructure grants and the R01 grants is that applicants can request as much funding as they think they will need to do the work under the R01 mechanism. He noted that support is not permitted in some budget categories for many grants; this is one aspect of the current system that could be revised.

Dr. Kenneth Cowan, Director, Eppley Cancer Center, University of Nebraska Medical Center, commented that in the case of Cancer Centers, it is difficult to find resources to support new ways of doing things without some flexibility and supplements providing funding for translational components of research. The topic will be reviewed at the Cancer Center Directors Retreat. Dr. Cowan said that in his opinion, all Cancer Centers want to be more involved in the National Clinical Trials Network. There needs to be flexibility in the way Cancer Centers support the national clinical trials mission within the context of Cancer Center Support Grant (CCSG) guidelines. Cancer Centers can contribute if they see this effort as important to the National Clinical Trials Network.

IX. ANALYSIS OF THE UTILIZATION OF THE STANDARD TERMS OF AGREEMENT FOR RESEARCH TRIAL CLAUSES—DR. BRENT MILLER

Dr. Brent Miller, Research Staff Member, Science and Technology Policy Institute, gave an update on the utilization and impact of the Standard Terms of Agreement for Research Trials, also known as "START clauses." As background to the assessment, Dr. Miller described the genesis of the project and the clauses. During its deliberations, the Clinical Trials Working Group identified negotiation of clinical trial agreements as a key barrier to timely initiation of cancer clinical trials. At about the same time, the CEO Roundtable on Cancer Life Sciences Consortium (LSC) made standardization of clinical trial agreement clauses a top priority. The shared perception of the LSC and NCI was that the final negotiated agreements contained clauses reflecting a relatively consistent set of agreement concepts. Therefore, a partnership was formed between LSC and NCI to develop a commonly accepted set of clauses for clinical trial agreements between industry and academic medical centers. In addition to the 11 LSC member companies, 14 NCI-designated Cancer Centers were asked to become participants in the project.

Legal and business representatives from project participants provided input on the particular clauses that present the greatest problems in negotiation. Forty-eight final negotiated clinical trial agreements were provided and analyzed for convergence on common contractual concepts. With the help of legal counsel, the START clauses were drafted based on the identified common concepts and reviewed by the same legal and business representatives. The START clauses address both company-sponsored agreements (i.e., trials in which the company provides the protocol, the drug, and the funds) and investigator-initiated agreements (i.e., trials in which the investigator provides the protocol and the company provides drugs and/or funds).

The clauses were publicly released by NCI and LSC in the fall of 2008. At the time of their release, it was stipulated that the START clauses were intended only as a starting point for individual negotiations, that there was no agreement or understanding among any of the project participants to use the START clauses in their agreements, and that there would be no recommendation or promotion of START clause usage.

In 2010, NCI requested that STPI conduct an evaluation to study the impact of the START clauses on clinical trial agreement negotiations. For this evaluation, STPI held discussions with the 14 Cancer Centers and 9 LSC member companies that participated in the creation of the clauses (two of the 11 original LSC companies merged since 2008), as well as 31 nonparticipant Cancer Centers. The discussions were conducted individually with legal and business representatives from each organization. Information obtained from the discussions was organized into specific themes, allowing the identification of common ideas and unique variations at the level of individual clauses.

Overwhelmingly, the START clauses are perceived as an acceptable middle ground in negotiations. When asked if their organizations had implemented the START clauses, both companies and Cancer Centers typically explained that they had not implemented the clauses, *per se,* because the clauses were already close to concepts in their current practice or in their guidance documents. The discussions revealed that companies nearly always provide the template for starting negotiations with Cancer Centers. The exception was negotiations with small companies, in which case, Cancer Centers sometimes provide the template. Cancer Centers nearly always view the negotiation process as countering or responding to a company template. Half of the Cancer Centers reported perceiving the company templates as distant from the START clauses, and most Cancer Centers believe that using START clauses as a starting point would speed negotiations. Half of the Cancer Centers still perceive negotiations as a barrier to getting clinical trials quickly under way.

Companies reported perceiving that Cancer Centers' initial positions are closer to those of the START clauses than they were in 2008. Negotiations are perceived as less confrontational and rarely lengthy. However, the negotiations are also perceived as being more complex than before; companies reported that Cancer Centers have become more sophisticated in their negotiation tactics and in the requests they make. Companies indicated that they typically arrive at the START clause positions but, in general, only after one or more rounds of negotiation.

The evaluation also showed that nearly every organization uses master agreements. For the most part, particularly in the case of Cancer Centers, there is a push towards greater usage of master agreements.

Dr. Miller proceeded to provide highlights from the START clause evaluation, covering three clause areas: intellectual property in investigator-initiated agreements, subject injury in company-sponsored agreements, and indemnification in investigator-initiated agreements. With respect to intellectual property in investigator-initiated agreements, the START clauses stipulate that inventions can be conceived or reduced to practice in performance of a study and offer the company a paid-up, nonexclusive license for all purposes and an option to negotiate an exclusive royalty-bearing license for all purposes. The majority of companies believe that their stance is similar to that of the START clauses. They ask for a nonexclusive royalty-free license to commercially exploit the invention. However, companies indicated that there is significant pushback on that request from Cancer Centers. Just over half of the Cancer Centers' initial or fallback positions are similar to those of the START clauses. A minority of Cancer Centers attempt to narrow the definition of START clauses in a number of ways, such as "conceived and reduced to practice" instead of "conceived or reduced to practice." With respect to the license offered to the company, the majority of Cancer Centers reported taking a stance that is dissimilar to that of the START clauses. Twenty-three out of 39 Cancer Centers reported offering a nonexclusive, royalty-free license for research purposes only; 7 out of 39 Centers offer no license and move directly to an option to negotiate an exclusive, royalty-bearing license for all purposes.

With respect to subject injury in company-sponsored agreements, Dr. Miller noted that the START clauses stipulate that companies reimburse institutions for the treatment of study subjects for adverse events and bodily injury caused by the treatment in accordance with the protocol. There are two exemptions to this practice: if the research institution fails to comply with the agreement, protocol, or instructions or if negligence or willful misconduct is found to occur on the institution's behalf. Half of the companies stated that they arrive at the START clauses in the first round of negotiation. The other half reported they start with less-favorable rights but arrive at the START clauses after subsequent rounds of negotiation. All Cancer Centers stated that they reach concepts similar to the START clauses in their final negotiated agreements. While ultimately arriving at rights similar to the START clauses, there are some additional noteworthy areas of negotiation. Companies reported excluding coverage if a patient fails to follow instructions or if injury is due to an underlying or pre-existing condition, and limiting coverage for immediate or necessary treatment. In order to be accredited by the Association for the Accreditation of Human Research Protection Programs, Cancer Centers stated that agreements must require sponsors (companies) to give notice of adverse events resulting from use of the study drug and that there is significant pushback on this requirement. Because Cancer Centers must be compliant with the Health Insurance Portability and Accountability Act protected health information, they strive to require sponsor compliance as well and, again, there is significant pushback from sponsors.

In the interest of time, Dr. Miller did not present the portion of the presentation on indemnification in investigator-initiated agreements.

Dr. Miller discussed the impact of the process to create the START clauses. A number of companies and Cancer Centers indicated that identifying negotiation time as an important issue focused their attention on other factors that delay negotiation. For example, some organizations have become more flexible in their requirements for negotiations. Both companies and Cancer Centers have improved negotiation timelines by implementing automated monitoring systems and parallel processing of different aspects in negotiation, increasing personnel to handle the workload, and actively monitoring negotiation timelines. For organizations that are more advanced in addressing negotiation issues, the START clauses are used to corroborate previously established guidelines. Organizations that are just beginning to address the issue use the START clauses to develop guidelines, templates, or initial negotiation stances. For those organizations that have guidelines or templates that reach beyond the START clauses, the START clauses offer a secure fallback position.

Nearly every organization reported monitoring their negotiation time for clinical trial agreements. Companies provided consistent estimates on execution times (i.e., the time from proposal submission to trial activation). Execution times were reported to range from 86 to 123 days. Cancer Centers gave the most consistent estimates on the duration of contract negotiation—between 30 and 60 days. In some instances, this time includes IRB approval and negotiation of the budget when the activities are conducted in parallel.

Several emerging issues were identified through the discussions. Participants commented that negotiations surrounding biological samples are becoming increasingly problematic, and model language would help ease this area of negotiation. Clinical Research Organizations (CROs) have also become an issue because CROs have no real authority to negotiate. CROs simply relay information between companies and Cancer Centers, and this can significantly prolong negotiation times. Seven out of eight companies reported using CROs for negotiating oncology clinical trial agreements.

The main conclusions drawn from evaluation of the impact of the START clause project are that: (1) both Cancer Centers and companies are focused on the issue of duration and management of the negotiation process; (2) START clauses are generally acceptable and perceived as representing a middle ground; (3) Cancer Centers perceive that company templates are more pro-company than START clauses; and (4) START clause implementation is successful, as can be reasonably expected since their "use" is limited by culture, policy, and a desire to "give and take" in negotiations.

Questions and Discussion

Dr. Civin asked how much a research institution gains from intellectual property generated from a clinical trial, given the legal expenses required. He proposed giving intellectual property away in exchange for a better indemnification. Dr. Miller stated that some institutions take Dr. Civin's position. Those institutions recognize the low probability of intellectual property from a clinical trial and, depending on the situation, balance that against other clauses. Dr. Civin asked if there is an impetus to revise the START clauses based on this experience or other thinking. Dr. Prindiville stated that people have been discussing the clauses, and NCI does not think it would be helpful to revise the clauses at this time because the companies merely use them as a tool for benchmarking.

Mr. Leung stated that emerging issues with diagnostics and biological samples warrant updating the clauses. Dr. Prindiville explained that NCI originally planned to include biologics in the START clauses.

Dr. Abbruzzese asked if budget negotiations are as much of a problem as contract negotiations. Dr. Miller said that most respondents now view contract negotiation as being easier than budget negotiation and that budget negotiations are taking an equivalent amount of time as contract negotiations.

Dr. Schilsky expressed disappointment that the START clauses have not been embraced by both parties. He indicated that it may not be worthwhile to revise the clauses unless there is commitment from both the companies and institutions to use the clauses as their starting position in negotiations.

Dr. Adamson disagreed with Dr. Miller's assessment of the implementation as "the best that we can expect." He asked if final agreements could be analyzed to see how they reflect the START clauses and proposed marketing the START clauses to increase their usage. Dr. Doroshow responded that Quintiles, a large organization, begins all their negotiations with START clauses and that Pfizer also routinely uses those positions. The big issue is budget negotiation, and progress has been made in that arena.

Dr. Arbuck asked if organizations are starting from different positions and arriving at START clauses a high percentage of the time. Dr. Miller confirmed that this is true. Dr. Arbuck commented that a large amount of resources could be saved if organizations began negotiations with the START clauses.

Mr. Leung added that it might be helpful to update the START clauses to make them more comprehensive. Companies will always get to the middle ground, and the focus should be on other issues that need to be negotiated and are not currently included in the clauses.

Dr. Finn inquired how often indemnity issues are deal-breakers. Dr. Miller responded that indemnity is nearly never a deal-breaker, although indemnification varies across companies. As an example, some companies will not give indemnification for investigator-initiated trials.

X. BIOMARKER, IMAGING, AND QUALITY OF LIFE STUDIES FUNDING PROGRAM (BIQSFP) ANNUAL UPDATE—DRS. RAYMOND PETRYSHYN AND MALCOLM SMITH

Dr. Raymond Petryshyn, Program Director, Coordinating Center for Clinical Trials, NCI, provided the annual update for the Biomarker, Imaging, and Quality of Life Studies Funding Program.

Background. BIQSFP is a unique and first-of-its-kind pilot project initiated in 2008 as the result of CTWG recommendations. The Program is unique in that it provides a funding mechanism and prioritization process to ensure that the most important biomarker, imaging, and quality-of-life (QOL) studies can be initiated in a timely manner in association with clinical trials. The primary purpose of the Program is to fund studies conducted in association with Phase III clinical trials when the cost of such studies is too large to be covered by the Cooperative Group/CCOP funding mechanisms in a timely manner. In response to the OEWG report, BIQSFP was expanded in 2010 to include large, Phase II clinical trials with integral assays or tests.

Two categories of studies are considered and prioritized in BIQSFP: integral studies and integrated studies. Integral studies are those tests or assessments that must be performed in order for the trial to proceed (e.g., to establish patient eligibility or assign patients to treatment arms). Integrated studies are tests or assessments that are intended to identify or validate assays, markers or imaging tests, or symptom management and QOL instruments that might be used in future trials. Exploratory and discovery studies are not eligible for BIQSFP. Since integral studies are required for the trial to advance, they receive the highest BIQSFP funding priority. It was noted that the review and funding process for BIQSFP is consistent with OEWG timelines.

Current Status. Since BIQSFP was initiated in 2008, 40 proposals have been received. Eleven of these proposals have been funded; four are currently in evaluation. Sixty percent of the received proposals are for biomarker studies; 32 percent are for QOL studies; and 9 percent are for imaging studies. Of the 10 Cooperative Groups eligible to submit a BIQSFP proposal, 9 have submitted a proposal and 7 have received funding.

The total cost of BIQSFP-funded proposals between 2008 and 2010 was about $18 million. Eighty-six percent of the funding went to biomarker studies, 10 percent went to QOL studies, and 4 percent went to imaging studies. A wide variety of biomarkers, assays, and tests have been incorporated into BIQSFP-funded studies. If all of the funded studies reach completion, about 14,000 patients will have the opportunity to have a biomarker or quality-of-life measurement completed. Currently, one study has completed accrual, five are open for accrual, and five are anticipated to open in 2011.

Proposed Changes and Future Considerations. In November 2010, CTAC recommended that the evaluation and prioritization of cost-effectiveness analyses (CEA) be paired with NCI-sponsored treatment trials and be funded through BIQSFP. CEA provides a scientific economic analysis of study endpoints, with a focus on collecting information that may have the greatest influence on both clinical

decision-making and health policy. BIQSFP is in the process of developing CEA evaluation guidelines and proposal review templates. The new BIQSFP funding announcement, including the CEA component, will be released in April 2011. An additional proposed change to BIQSFP is the limitation of BIQSFP funding to $5 million for any one clinical trial.

For future consideration, it will be important to develop a BIQSFP Program Evaluation Plan. Dr. Petryshyn proposed potential metrics for the added value of the program and the perception of stakeholders; however, he requested input from CTAC members on the ideal program evaluation.

AAML0531 and AAML1031 BIQSFP Projects. Dr. Malcolm Smith, Associate Branch Chief, Pediatric Oncology, CTEP, gave an overview of two approved BIQSFP study proposals that were submitted by the Children's Oncology Group (COG). The first proposal, AAML0531, was submitted in 2008. The parent trial, which recently closed, was a Phase III randomized trial of gemtuzumab ozogamicin (Mylotarg®) combined with conventional chemotherapy for *de novo* acute myeloid leukemia (AML) in children, adolescents, and young adults. The parent trial included one BIQSFP integral study, which was performed at Seattle Cancer Care Alliance's Molecular Diagnostics Laboratory. The integral study was needed to determine the mutation status of the *FLT3* gene, which is known to have prognostic significance for AML. In this case, the presence of *FLT3* internal tandem duplication (ITD) was assessed, as was the ratio of mutant to wild-type forms of *FLT3* (allelic ratio). Two BIQSFP integrated studies were also funded in concert with the parent trial. One of the studies was to validate the prognostic significance of *CEBPA* mutations; whereas the other study was to optimize the utility of multidimensional flow cytometry to identify patients in morphologic remission with minimal residual disease who are at high risk of relapse. The investigators observed from study results outside of AAML0531 that patients with *FLT3* ITD and a high allelic ratio had poorer outcomes with standard chemotherapy and that these patients appeared to have more favorable outcomes if they received a stem cell transplant; thus, halfway through the study, these patients began being assigned to the stem cell transplant arm of the study. The flow cytometry study found that patients with minimal residual disease following initial induction therapy were less likely to achieve complete remission following the second round of induction therapy.

AAML1031, a Phase III randomized trial for patients with *de novo* AML using bortezomib and sorafenib (the latter for patients with *FLT3* ITD), is the successor study to AAML0531 and will open in early 2011. The parent trial contains two BIQSFP integral studies. The first is to determine the mutation status of genes with known prognostic significance for AML (*CEPBA*, *NPM1*, and *FLT3*). The second integral study will determine minimal residual disease (MRD) level by flow cytometry, with patients positive for MRD being assigned to allogeneic stem cell transplantation. The goal of these studies is to be able to more accurately determine whether patients should undergo stem cell transplantation and/or treatment with certain therapeutic agents.

Questions and Discussion

Dr. Schilsky expressed concern over the proposed $5 million funding cap on BIQSFP studies. By implementing this cap, studies may be jeopardized before completion due to insufficient funds; for example, only giving $5 million to an integral biomarker study that is essential in order to proceed with the clinical trial when it is estimated that the study needs $7 million to be completed. It was agreed that there should not be an upper limit to the funds that an investigator can request.

Dr. Schilsky also commented that a portfolio of analytically validated biomarker assays is being developed from the funded BIQSFP studies. It was suggested that these assays should be continually updated in a registry so that other investigators have access to them.

XI. ADJOURNMENT—DR. JAMES DOROSHOW

There being no further business, the 12th meeting of the CTAC was adjourned at 4:00 p.m. on Wednesday, December 15, 2010.

3/3/11
Date

James Doroshow, M.D., Acting Chair

3/3/11
Date

Sheila A. Prindiville, M.D., M.P.H., Executive Secretary