DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
11th CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE MEETING

Summary of Meeting
September 21, 2010

Bethesda Marriott Hotel
Grand Ballroom Salon Rooms C, D, E
5151 Pooks Hill Road
Bethesda, Maryland

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
BETHESDA, MARYLAND
Summary of Meeting
September 21, 2010

The Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) convened for its 11th meeting at 8:00 a.m. on Tuesday, September 21, 2010, in Grand Ballroom Salon Rooms C, D, E, Bethesda Marriott Hotel, Bethesda, MD. Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis, NCI, presided during the meeting. The meeting was adjourned at 4:45 p.m.

Chair
Harold E. Varmus

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

Ad Hoc Members
Susan G. Arbuck
Lisa A. Newman
Peter G. Shields

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

Executive Secretary
Sheila A. Prindiville, NCI

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

Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis, National Cancer Institute (NCI), called to order the 11th Clinical Trials and Translational Research Advisory Committee (CTAC) meeting. He welcomed the Committee and *ex officio* members and introduced three new ad hoc CTAC members: Drs. Lisa Newman, Susan Arbuck, and Peter Shields. 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/. He also noted that the next CTAC meeting date was rescheduled to December 15, 2010.

Motion. A motion was made to approve the minutes of the March 10, 2010 CTAC meeting. The motion was seconded, and the minutes were approved unanimously.

II. DIRECTOR'S UPDATE—DR. HAROLD E. VARMUS

Dr. Varmus, Director, NCI, welcomed the members and thanked them for their efforts on behalf of NCI and clinical and translational research. He began by explaining that the CTAC will be led in the future by an external Chairperson and that Dr. Doroshow has been asked to serve in that capacity for the present meeting.

Noting that he had been on the job as NCI Director for two months, Dr. Varmus said that he is excited about leading the National Cancer Program at a time when remarkable scientific advances are being applied to the mission of preventing and treating cancer. He added that as an Institute Director, he now enjoys more direct involvement in research programs than he had as Director of the National Institutes of Health.

Dr. Varmus reported on changes in NCI personnel and organization. Dr. Douglas R. Lowy is a newly appointed Deputy Director and also serves as Acting Director of the Center for Strategic Scientific Initiatives. Dr. Al Rabson remains an NCI Deputy Director. A third Deputy Director, with major responsibilities over clinical and translational research, is being sought. Recruitment is under way for leadership of two new NCI Centers—the Center for Cancer Genomics and the Center for Global Cancer Research—as well as for a Director for the Center for Strategic Scientific Initiatives and an executive officer to serve as the Deputy Director for Management. The Executive Committee (EC) has been separated into two groups: the Scientific Program Leaders (SPL) and an Office of the Director (OD) staff group.

The recent Institute of Medicine (IOM) report, *A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program*, which was requested by NCI, is leading to a number of changes in NCI programs and activities designed to improve the clinical trials enterprise. The report and efforts to implement its recommendations would be discussed later in the meeting by Dr. Doroshow and Dr. Sharyl Nass, Director, National Cancer Policy Forum, Institute of Medicine, National Academies.

One of the aspects identified in the IOM report—something that many have been calling attention to in recent years—is the inordinate amount of time required to launch, conduct, and conclude clinical trials. Other issues highlighted in the report focus on the need to redesign cancer clinical research networks and infrastructure in response to new advances in oncology, particularly in genomics and molecular medicine. As Dr. Doroshow would explain later in the meeting, NCI's efforts to address these issues were already under way when the report was released in April. Ideas for reorganizing the Cooperative Groups to create a more hospitable environment for conducting large-scale, multidisease trials are being discussed with Cooperative Group leadership, and useful ideas are being generated. Another area being explored is improving biological sample collection and expanding the capacity for following up on molecular properties of tumors after the trials for which they are collected have ended.

Dr. Varmus has also focused much of his time since joining NCI on the status of clinical research within the intramural program. He expressed concern that the Mark O. Hatfield Clinical Research Center is being underutilized. The NIH Scientific Management Review Board (SMRB) has developed a number of recommendations for improving Clinical Center operations. One focuses on greater integration of extramural clinical research into the Clinical Center. Also, intramural investigators may be motivated to work with the Clinical Center by proposed changes in the way Clinical Center expenses are reimbursed. The SMRB has recommended making part of the Clinical Center budget a line item in the budget of the Office of the Director. This could overcome fears of some intramural investigators and program leaders that participation in the Clinical Center would be detrimental to their overall scientific support.

NCI is also expanding its interactions with clinical research and training programs at The Johns Hopkins University. Hopkins has satellite locations throughout the Washington area, including Suburban Hospital. Similar interactions are being instituted with the Department of Defense. Talks are also under way to extend NCI's relationship with the Walter Reed Army Medical Center when its move to Bethesda is completed.

Much of the current meeting agenda is concerned with efforts to realize the potential of clinically important discoveries by better coordinating the research continuum from basic laboratory research through clinical studies and implementation in clinical practice. This effort reaches into many areas of concern, including regulatory issues, integration with industry, comparative effectiveness, and health information technology (IT). There is increasing interest within the scientific community to use cancer as a domain in which to illustrate the potential benefits of advances in health IT. NCI staff are discussing these ideas with staff of the White House Office of Science and Technology Policy.

A new funding mechanism that promises to accelerate the movement of discoveries into clinical practice is the Special Translational Research Acceleration Project (STRAP). This mechanism grew from recommendations of NCI's Translational Research Working Group (TRWG). A funding announcement focusing on immune modulators as a first topic for this program has produced a number of good applications, and at least one project will be funded.

Another new NCI funding program provides leadership awards to young investigators working at clinical centers. The program aims to help young investigators deal with the conflicting demands of clinical work and research activities.

A recent judicial ruling has at least temporarily halted intramural research using embryonic stem cells. The injunction does not apply to extramural scientists making use of grant funds to conduct such research. NIH efforts to establish a stem cell research facility and recruit strong international leadership are on hold until the legal issues are clarified. Legal appeals and legislative action are being considered in order to remove this barrier to biomedical research.

Questions and Discussion

Dr. Stephen Grubbs of the Helen F. Graham Cancer Center asked whether the Community Clinical Oncology Programs (CCOPs) and the NCI Community Cancer Centers Program (NCCCP) will continue as separate entities. Dr. Varmus observed that each program has unique virtues. It is unclear how NCI's efforts to support clinical research in community settings will be organized in the future. However, these activities in some form are essential considering the fact that many health care organizations have been slow to adopt what are considered to be essential features of modern oncology. This slowness has been caused in part by inadequately involving community organizations and health management organizations (HMOs) in the research process, which retards dissemination of research findings.

III. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations, NCI, reported on the status of appropriations and highlighted recent congressional activities.

Fiscal Year (FY) 2011 Appropriations Activities. The President's Budget was announced on February 1, 2010. The budget has allocated $32 billion to NIH and $5 billion of that amount to NCI. In May, the Senate held their NIH Budget hearing and the Subcommittee passed the appropriations bill; it was then reported out to and passed by the full Committee at the end of July. The House held their NIH budget hearing the end of April and the Subcommittee passed their appropriations bill on July 15. The bill has not moved forward since Subcommittee approval.

In order for the appropriations bill to become law, both the Senate and the House need to pass the bill. Presumably, these bills would not be identical and, thus, would require a Conference Committee. The Conference Committee would reconcile the differences and draft a bill that would then need to be passed by the House and Senate and signed by the President. Given that there are only two weeks remaining in FY 2010, it is unlikely this process will be completed. Many people believe a Continuing Resolution will be issued, but it is unknown when it will be passed or how long it will last.

Health Care Reform Follow-up. The Cures Acceleration Network (CAN) is a particularly relevant provision of the Healthcare Reform Bill. The purpose of CAN is to provide funding via grants and other partnerships that bridge the translational gap between laboratory discoveries and lifesaving therapies. CAN will fund grants as well as partnerships for this purpose. The Network will be established within NIH's Office of the Director. The law requires a 24-member advisory board to be appointed, and establishment of this board is currently under way.

The Healthcare Reform Bill authorized $500 million per year for CAN. However, the Senate Subcommittee chose to allocate $50 million for this year to get the Network organized and initiated. Subcommittee Chairman Senator Tom Harkin, Iowa, explained the reason for the lower appropriation by saying that because appropriations will not be finalized until several months into the fiscal year, NIH will only have time to establish the network and will not have time to complete funding actions. He recommended that CAN approach Congress again next year when it has a grant-making strategy and the appropriators are better able to decide how much to allocate.

The Patient-Centered Outcomes Research Institute (PCORI) is a patient-centered comparative research model that was included in the Healthcare Reform Bill. The PCORI is an independent institute

that will fund research and evaluate and compare health outcomes and the clinical risks and benefits of medical treatments or services. It is ruled by a Board of Governors, including the directors of NIH and the Agency for Healthcare Research and Quality (AHRQ). Nineteen other governors have been nominated and must be vetted and appointed by September 23.

Congressional Outreach. On July 30, the NIH, in collaboration with the Association of American Cancer Institutes (AACI), held a special event, Project Cancer Education: An Introduction to Translational Research at NCI. This pilot program invited Congressional staff and members of advocacy organizations to learn about translational research. Based on the success of this event, NIH has planned additional events of the same kind with the hope of inviting members of Congress to attend.

Outlook – 111th Congress. Congress' target adjournment date is October 8, 2010. Congressional leadership is currently developing a strategy for the Continuing Resolution. It is expected that the Continuing Resolution will last until December, when Congress will either issue an additional Continuing Resolution or pass the FY 2011 appropriations bill before the end of the year.

Congressional elections will occur on November 2, and a new Congress will convene in January 2011. The majority status could change in the new Congress; should that occur, each Congressional Committee would have a new chair. In addition, many members of Congress have announced retirement, several of whom are on the Appropriations Committee; thus, it is likely that Appropriations Committees in both the House and Senate will comprise new members.

Questions and Discussion

Ms. Nancy Roach, Consumer Advocate, C3: Colorectal Cancer Coalition, expressed her satisfaction with Project Cancer Education: An Introduction to Translational Research at NCI, stating that it is a great tool to help people understand what is needed to move research forward. She suggested a possible partnership with advocacy organizations, and recommended inviting them to NIH during Lobby Day to learn more about translational research.

IV. PROCESS TO ACCELERATE TRANSLATIONAL SCIENCE (PATS) WORKING GROUP UPDATE—DRS. LYNN MATRISIAN AND KENNETH COWAN

Dr. Lynn Matrisian of Vanderbilt University Medical Center reported on the PATS Working Group. PATS is charged with advising CTAC on the implementation of the Translational Research Acceleration Initiative proposed by the Translational Research Working Group. In 2007, the TRWG generated a report detailing NCI's investment in translational research, ways to improve translational research, and six pathways to be used as a framework for identifying translational research. The six pathways include biospecimens, imaging, agents, immune response modifiers, devices, and lifestyle alterations. The TRWG made 15 recommendations, many of which were to enhance existing NCI functions recognized as critical for translational research. Three initiatives, which together make up the Translational Research Acceleration Initiative, focused on setting up a system that could be overlaid on top of the existing NCI structure. The Initiative ensures that progress through the translational pathway is as rapid, efficient, and effective as possible.

There are many NCI programs that facilitate translation—Specialized Programs of Research Excellence (SPOREs), Rapid Access to Intervention Development (RAID), P01, the Early Detection

Research Network—but there is not enough money to allow all potential translational research to progress to clinical trials. At any particular time, only certain projects are ready to be translated. The TRWG recommended using the pathways as part of a prioritization process to ensure that those projects that are ready are translated promptly and effectively. Both funding and project management are critical to achieve this goal. The TRWG conceived the Special Translational Research Acceleration Projects (STRAPs) to fund and manage projects that are prioritized for translation in any given year. The STRAPs was designed to leverage existing translational programs and not impact current discovery research programs.

The PATS Working Group started with a pilot project to prioritize projects in the immune response modifier (IRM) pathway. Through extramural competition, the Immune Response Modifier Prioritization Working Group drafted a short list of high-priority targets. The TRWG's recommendation was that the STRAPs fund only projects that would not be funded by other mechanisms and that have a high probability of significantly advancing the field. Projects funded by the STRAPs should include an assessment component, be fast and flexible, and be driven by timelines and milestones. The first call for applications for administrative supplements was released in May and offered up to $2 million for one project. NCI conducted the review of applications in August, and the grantees will be announced by the end of this month.

The PATS Working Group met in May and concluded that the assumptions on which the TRWG was based were still valid—current approaches are still insufficient and translational research needs to move forward faster. Improvements to the process require funding and project coordination. It is reasonable to start with two to three awards per year, and the pathways will compete for those awards. The Working Group also evaluated the adequacy of the selection process for STRAP awards and decided that the Request for Information approach in the pilot prioritization effort was not optimal. NCI's Experimental Therapeutics Program (NExT), which was not available when TRWG started, will be extremely valuable for future prioritization processes of projects within the agents pathway that have therapeutic intent. The prioritization process used in the pilot may be applicable to all other pathways, with incorporation of flexibility. The Working Group recommended going forward with an umbrella STRAP for all pathways; proposals must use the TRWG pathways as a guideline to reach human testing and should take advantage of existing work ongoing at NCI. Conglomerations of pathways will be allowed if justified. It is likely that multiple institutions and multiple programs will be involved in accomplishing a project. It was also recommended that, in place of a Request for Information, applicants should submit short concepts; more information would be requested for those concepts ranked high in the prioritization. NCI could also recommend modifications to the concept or use community expertise to advance a project. An NCI-based project coordinator should coordinate the activities of different groups. It was also decided that applications received for the agents pathway should be forwarded to NExT for the first few cycles.

The PATS Working Group also recommended looking at the prioritization of the other four pathways. Any subgroups created within a pathway should have clearly defined goals, such as prioritizing opportunities within a pathway, informing NCI of opportunities, or advising on infrastructure needed in a particular pathway. The program would start with two to three STRAP awards per year, with milestones driven up to a five-year period.

Dr. Kenneth Cowan, Director, Eppley Institute for Cancer Research, University of Nebraska Medical Center, commended Dr. Matrisian for spearheading the Working Group effort and added that while there are numerous funding mechanisms available to support basic and translational research, there are difficulties in extending the research to clinical trial testing. The major goal of the STRAP mechanism is accelerating the progress of basic science ideas to clinical trials. The Immune Response Modifier

Pathway Prioritization Working Group has been successful in prioritizing opportunities in that pathway, but support is needed for prioritization of devices, biomarkers, and imaging.

Questions and Discussion

Ms. Roach commented that it is difficult to make rational choices about projects, as all reviewers have biases. The IRM Prioritization Working Group used a specific technique to eliminate personal biases and make rational strategic choices. That process was not accepted by all Working Group members as the best way to prioritize, and it will be necessary to carefully consider how to make the most rational choices in the future.

Dr. Joel Tepper, Professor and Chair, Department of Radiation Oncology, University of North Carolina School of Medicine, asked about the practical application of the project management goal, whether funding would be cut off for projects that do not meet their milestones, and, if so, how this would be implemented. Dr. Matrisian stated that every project would have a steering committee and different sites would have input. The committee would have members—perhaps from NCI—with industry project management experience, but there would be flexibility, with project managers on site. The TRWG recognized that productive failure is a possibility. At the time that a project seems to fail, it can be decided whether to attempt to fix the problem or to abandon it and invest the funds elsewhere.

Dr. David Parkinson, President and CEO, Nodality, Inc., asked whether the solicitations would ask for a service function to be available for a particular technology, many clinical trials, or a specific project around a specific clinical trial. Dr. Matrisian responded that the solicitation is for specific projects, which could take many forms—biomarkers, imaging, etc.

Dr. James Abbruzzese, Chairman, Department of Gastrointestinal Medical Oncology, University of Texas, asked how prioritization across different areas (e.g., different pathways, different points in the pipeline) would occur. Dr. Matrisian responded that the criteria for prioritization include scientific validity, feasibility, clinical need, and appropriateness of NCI investment. The PATS Working Group did not have enough time to delve deeper into the details of prioritization. Dr. Abbruzzese then asked whether the STRAP committee would be expanded to include expertise that is currently not represented. Dr. Matrisian responded that NCI will likely set up a committee in response to the solicitation.

Dr. Susan Arbuck, a research and development consultant with Cancer Drug Development, asked if there are funding mechanisms that address the variable duration of projects. Dr. Matrisian clarified that the TRWG envisioned selecting projects that are relatively ripe and will not take more than five years to complete. For the IRM STRAP, NCI awarded supplements to existing grants, though the mechanism might be different in the future.

Dr. Parkinson suggested that each of the pathways be prioritized such that projects that are generalizable to entire fields or classes of therapeutics, for instance, are not overlooked due to opportunism. Dr. Cowan stated that it is up to NCI to decide how to set up review committees and review criteria as the proposals come through. It would be easier if there were separate STRAPs for different pathways, instead of an umbrella STRAP, but an umbrella STRAP allows for submission of projects in multiple areas.

Dr. Paulette Gray, Division of Extramural Activities, NCI, stated that this must eventually become an NCI activity; NCI will have to develop a concept or funnel criteria that will go into an announcement. Once a concept is developed, it must be submitted to NCI's Board of Scientific Advisors,

which will give its opinion on how the activity will evolve and advance. After that, NCI will examine the budget. The PATS Working Group will not develop the overall requirements for this activity.

Dr. Deborah Bruner, Professor of Nursing and Director, Clinical Trials Recruitment, Retention, and Outreach Core Facility, Abramson Cancer Center, The University of Pennsylvania, expressed deep concern that using an umbrella STRAP would drown the best ideas in favor of the best grant writers. Dr. Matrisian added that the IRM Prioritization Working Group showed the value in prioritization.

Dr. Mitchell Schnall, Matthew J. Wilson Professor of Radiology, Magnetic Resonance Imaging Section, Department of Radiology, The University of Pennsylvania School of Medicine, noted that the goal is to create a fundamentally different kind of mechanism to advance research across the pathways. The success or failure of the group's attempt will not be known until the initial projects are under way or have been completed.

Dr. Arbuck asked about aspects that will fall to NCI. Dr. Doroshow indicated that NCI is capable of conducting active project management. Moving a prepared project into the clinic is doable but takes a lot of effort. Dr. Varmus added that researchers do not do experiments if they know the answer; the assumption is that the outcome is unknown. NCI has seen a lot of successes. Industry fails as often as NCI, and this is the reason new devices in therapeutics are so expensive. One has to accept that most investments are not going to be successful, yet trying something new is a good thing. NCI has to carry the burden and responsibility of making decisions, providing oversight, and developing metrics for review and monitoring of proposals. It is not yet clear whether NCI has set up the right review process, prioritization process, funding levels, or oversight, but failing to move forward would be a mistake.

Dr. Abbruzzese expressed concern regarding the umbrella STRAP. The IRM prioritization process was cumbersome, but instead of streamlining that process and processes for the other pathways, the umbrella system will dump all of the processes together in the hope that the issues will be worked out later. Dr. Matrisian stated that some members of the PATS Working Group felt that it is important to move projects forward so that they can inform the process in the future; other members felt that the pathways should be prioritized before more projects are funded. The end product is a compromise of the two ideas. Also, some members felt that the community should be given the opportunity to put together good STRAP proposals on its own. Dr. Varmus added that the umbrella STRAP will likely yield a large number of applications, and there will be a very low success rate. Deciding where to focus would save time and make the prioritization easier.

Dr. Bruner stated that lifestyle science is a tremendous opportunity, but it is the least understood. The community of lifestyle researchers is still learning about the STRAP opportunity. Dr. Bruner expressed concern that an umbrella STRAP would not allow a fair chance for lifestyle science proposals because they would be competing against proposals in more familiar fields, such as imaging and chemotherapy. Dr. Bruner suggested a motion to accept the STRAP proposal if it includes intra-pathway prioritization, rather than umbrella prioritization.

Motion. A motion to accept the Process to Accelerate Translational Science Working Group report and recommendations with the modification that there will be pathway-specific prioritization for all of the TRWG developmental pathways, was approved with 13 yeas, 1 nay, and 0 abstentions.

V. THE CLINICAL ASSAY DEVELOPMENT PROGRAM (CADP): AVAILABLE SERVICES AND HOW TO ACCESS THEM—DR. BARBARA CONLEY

Dr. Barbara Conley, Associate Director, Cancer Diagnosis Program, Division of Cancer Treatment and Diagnosis, NCI, presented the organization and goals of the new Clinical Assay Development Program (CADP). The Program has a budget of approximately $9.5 million and is primarily supported with ARRA *(*American Recovery and Reinvestment Act of 2009) funds. Clinical trial protocols often involve assessment of molecular markers in order to determine eligibility, stratify participants, and inform treatment assignments. However, the assays used to measure these markers often do not meet the standards for clinical decision making set forth by the U.S. Food and Drug Administration (FDA). NCI has been using grant mechanisms to support efforts to identify biomarkers and develop clinical assays, but the translation of those assays into the clinic has been very inefficient. The mission of the CADP is to efficiently develop and validate diagnostic, predictive, and prognostic tests that address clinical needs, including tests that measure pharmacokinetic, pharmacodynamic, and pharmacogenomic markers. To do this, it will identify promising tests, assess the need for further development, and provide services to facilitate optimization of analytical performance and establish clinical validity.

Clinical assay development proceeds through two phases—discovery and feasibility. The activities in the feasibility testing phase include assessing whether a marker can be detected in context; evaluating the reproducibility, sensitivity, and specificity of an assay; and establishing/testing cut points. The assay development process is often iterative, with the results of feasibility tests leading to refinement of the assay.

The CADP comprises four components: the Patient Characterization Center (NCI/Science Applications International Corporation [SAIC]), the Clinical Assay Development Center (CADC; NCI/SAIC), the Clinical Assay Development Network (Clinical Laboratory Improvement Amendments [CLIA]-certified laboratories), and the Specimen Retrieval System (contract). The Program will also collaborate with caHUB. The Patient Characterization Center verifies biomarker discoveries emanating from the Cancer Genome Anatomy Project, academic investigators, and the literature. Some of the samples used by the Patient Characterization Center will come from the community and will be collected through HMO contracts (Specimen Retrieval System). Samples will also be provided by caHUB. The Patient Characterization Center will develop standard operating procedures, assay controls, and calibrators, and establish a public database of raw data. The CADC will develop optimized, robust, validated novel genomic assays and platforms that will support clinical studies; train external sites in assay performance; and assist and participate in network activities. The Clinical Assay Development Network is a network of CLIA-certified laboratories that have expertise in one or more traditional assay platforms and will participate in the Program on a contract basis. The Specimen Retrieval System is also contract based and includes HMOs from the Cancer Research Network that will provide specimens annotated with clinical and outcome data. The Specimen Retrieval System is a resource for the other components of the Program.

The Program's resources will be offered to the community through an application process, similar to that of the NExT program. Proposals will be reviewed and ranked by several committees, including a special evaluation panel of external experts, an internal steering committee, and a senior advisory group. Applications will be evaluated on scientific merit, feasibility, clinical need, and plans for commercialization. At the time of application, applicants will need to have discovery work and initial assay development completed and present a clear clinical purpose of the assay. The Program will transfer the assay to a CLIA-certified laboratory, assess its analytic performance in the intended use context, set preliminary cut points, and check clinical validity in a retrospective data set. The Program will also provide successful applicants with assistance in the following areas: consultation, project management,

contacting of commercial entities, assay optimization, platform migration, development of standard operating procedures, location of specimens, identification of reference sets and calibrators, reagent preparation, and statistical design.

All four components of the Program are expected to be operational in the first quarter of 2011.

Questions and Discussion

A participant asked if samples would be collected from patients on clinical trials as well as from patients who are off-study (from the community). There is more variability in treatments received outside of clinical trials and some outcomes (e.g., neuropathy, fatigue) are not always reliably documented, so it may be difficult to interpret the data. Dr. Sheila Taube, contractor and former head of NCI's Program for the Assessment of Clinical Cancer Tests (PACCT) initiative added that the Program is working with HMOs largely because they have inpatient and outpatient information together in an electronic record, making it easier to select specimens that meet specific assay criteria. Clinical trial samples are more suitable, however, for testing of predictive value and clinical utility. The Program has a plan for accessing the full spectrum of specimens that would be needed, including specimens from Cooperative Groups, depending on the applications received.

Dr. Parkinson asked if the purpose of the Program is development of new (currently unavailable) clinical assays to support clinical research. Dr. Conley stated that the Program is focused on bringing new assays developed in a laboratory to the patient; however, it is possible that some applicants will request assistance with optimization of an assay that is currently available or development of a different platform or feature. Dr. Parkinson added that all Class III laboratory tests are subject to FDA regulation and encouraged the Program to consider how it could facilitate the process of moving some of these assays into the commercial sector, which would be associated with numerous technical and regulatory issues. Dr. Conley clarified that once an assay is proven to be reliable and accurate, the Program will help find partners that will take the assay into further clinical development. Dr. Parkinson suggested that the Program work with representatives from the FDA to ensure that the evidence necessary for assay approval is prospectively collected during clinical trials.

Dr. Lee Helman, Chief of the Pediatric Oncology Branch and Deputy Director, Center for Cancer Research, NCI, stated that the Program's goal is to conduct preliminary work and then partner with or hand off to a commercial sponsor who would gather the necessary level of evidence needed for commercialization. Dr. Conley added that the Program's primary focus is on ensuring that high-quality assays that yield reproducible results in different laboratories are developed; however, it will also help to facilitate interactions with regulatory agencies, as well as with commercial organizations if an assay has strong commercial potential. Dr. Daniel Sargent, Professor of Oncology, Division of Biomedical Statistics and Informatics, Mayo Clinic College of Medicine, asked how commercial partners would be involved in the Program. Dr. Conley stated that a commercial partner or an academic commercial conglomerate could apply to the Program. Additional intellectual property issues may arise when commercial partners are involved, but the Program is working with the appropriate parties within NCI to ensure that these issues are addressed.

A participant asked whether efforts are being made to ensure that the tissues collected from HMOs include adequate numbers of tissues from minority populations. Dr. Conley stated that, at present, the samples have already been collected and there has not been oversampling from any group. She also noted that the specimens used in the development of any particular assay will be selected based on characteristics relevant to that assay. It would be reasonable to do oversampling if a diagnostic test were

relevant to a particular group. It will be possible to gain knowledge about the expected population distribution of the HMO samples based on the racial/ethnic makeup of the area served by the HMO.

Dr. Carolyn Compton, Director of the Office of Biorepositories and Biospecimen Research, NCI, stated that the Request for Proposals for the tissue collection sites for caHUB is still open. Sites will be selected based on the various applicants' expected ability to collect certain types of tissues. Efforts will be made to prospectively match the collections to the requirements and needs of the community and the Patient Characterization Center. The role of caHUB in the CADP is to provide tissues that have been collected according to a standard protocol, which is not necessarily the case for tissues collected in the community. Use of these standardized samples will facilitate troubleshooting during the assay development process. For example, if an assay does not work on existing samples, it will be possible to determine whether the problem lies in the assay or in the processing of the biospecimens. If specific tissue-processing procedures are needed for a particular assay, these will need to be integrated into the clinical trial protocol. caHUB will be a source of standard benchmark samples for all assay development initiatives at NCI.

It was noted that many assays have different reference ranges for different racial and ethnic groups, so it is important to ensure there is representation from different groups in the sample pool. Dr. Conley stated that all NCI programs need to have at least representative samples of the U.S. population and that the Program is continuing to look for sample sources that will lead to the collection of a representative set of samples.

VI. COST-EFFECTIVENESS ANALYSIS WORKING GROUP REPORT—DR. SCOTT RAMSEY

Dr. Scott Ramsey, Member, Fred Hutchinson Cancer Research Center, noted that the Cost-Effectiveness Analysis Working Group (CEA WG) was formed following the July 2009 CTAC meeting in response to his presentation on the question of requiring economic evaluations of NCI-funded clinical trials. The CEA WG's mission is to advise CTAC on the development of a trial prioritization process and identification of funding mechanisms for adding cost-effectiveness analysis to the most important trials in a timely manner. An implicit goal for the CEA WG is to implement CEA in clinical research without placing undue burden on the clinical trials program. The rationale for developing prioritization criteria included the understanding that explicit criteria must exist to guide allocation of funds to prevention and treatment trials where CEA could have an important impact on science and policy; also noted is the fact that economics is an ancillary part of a clinical trial and is not intended to supersede other factors.

The CEA WG recommends that high priority be given to randomized Phase III prevention and treatment trials. Eligibility should be limited to trials with potential to substantially influence patient care and accompanying CEA studies that are feasible and expected to have significant impact. A Cooperative Group or Community Clinical Oncology Program research base should submit the parent treatment trial and proposed CEA study. The control arm should be relevant to current clinical care. Trial length should be adequate to allow for patient follow-up, and trials should provide enough statistical power for key cost-effectiveness outcomes. There must be some uncertainty about the outcome of the CEA study; otherwise, there is no point in conducting the study.

CEA studies should be optional for prevention and treatment trials due to constraints on the availability of expertise and financial resources. Proposals to conduct these studies should be evaluated through a competitive process. Both the parent studies and accompanying CEA studies will be evaluated

on their scientific merit. If a CEA proposal is deemed to be scientifically unacceptable, it probably should be dropped to avoid slowing approval of the parent study.

After discussion of appropriate funding mechanisms for CEA studies, the CEA WG decided to recommend that the current Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP) mechanism and prioritization process be considered for the evaluation and prioritization of CEA proposals paired with treatment trials.

Task forces, where available, within each Scientific Steering Committee should recommend whether CEA studies should be included during the development of clinical trial concepts. A brief statement should be added to the Cancer Therapy Evaluation Program (CTEP) concept template to address the rationale for conducting cost-effectiveness studies in conjunction with trials. If Cooperative Groups and CCOPs do not already have internal procedures for supporting development of CEA proposals, they can convene external CEA committees. NCI should use a combination of internal resources and outside expertise to evaluate concepts submitted for approval.

CEA proposals will be submitted to CTEP or the Division of Cancer Prevention (DCP) and then evaluated by the appropriate Scientific Steering Committee, which should include a CEA expert (either as an NCI member or an ad hoc external expert). If approved at that level, they will be forwarded to the Clinical and Translational Research Operations Committee (CTROC) for final review and funding approval. CEA proposals and trial concepts should move in parallel. To facilitate this tandem review process, the CEA WG recommends adoption of its proposed CEA Proposal Evaluation and Prioritization Criteria for CEA plans as well as for the associated parent trial proposals. CEA studies should be funded through the existing Biomarker, Imaging and Quality of Life Studies Program. CEA concepts will be reviewed by CTAC on an annual basis. Prioritization and eligibility criteria have been drafted to guide CCCT in managing this process.

Questions and Discussion

Ms. Roach suggested that rigorous reviews be conducted at the task force level; Dr. Ramsey agreed.

Dr. Grubbs asked about the additional data collection burden that would be placed on clinical research associates and nurses. Dr. Ramsey replied that some economic information could be collected from Medicare data. It may also be possible to obtain data from other insurers. Trial consent forms will have to be modified to allow for this use of personal data. Short forms will be needed to collect quality-of-life data.

Dr. Bruner observed that institutional review boards (IRBs) are reluctant to allow use of Social Security data to match with Medicare data for these types of purposes. Unlike the Southwest Oncology Group (SWOG), most Cooperative Groups have not had much success in this arena and lack the necessary infrastructure to design and launch CEA studies. Dr. Ramsey said that obtaining data from Medicare is becoming easier as IRBs become better informed about the need for CEA studies. In terms of infrastructure, he acknowledged that few CEA studies will be accomplished in the short run. If additional support becomes available, more experts are likely to move into this field.

Dr. Parkinson noted that those responsible for application of new discoveries are becoming more interested in cost-effectiveness. The Medicare provider in California will not consider a laboratory-developed test unless the developer has demonstrated not only clinical validity but also clinical utility.

Dr. Ramsey agreed that the demand for economic evaluation is increasing. If the clinical trials program does not meet the needs of health plans for cost-effectiveness information, they will have to rely on studies conducted by drug developers, which may be less objective than NCI-funded studies.

Dr. Tepper expressed support for the concept presented by Dr. Ramsey but also concern that a substantial amount of overhead will be associated with creating new task forces and committees to guide and review proposals that may not be funded. He suggested an alternative approach in which protocols are moved through enough of the approval process to reasonably predict success before the CEA study review begins. Dr. Ramsey replied that the CEA WG was concerned that initiating the CEA review process after review of the parent concept would slow initiation of the clinical trial itself.

Dr. Schnall asked why the CEA WG limited its recommendations to prevention and treatment trials. Dr. Ramsey replied that diagnostic trials already have mechanisms to address cost-effectiveness issues.

Dr. Edith Perez, Deputy Director, Mayo Comprehensive Cancer Care Center, expressed concern about asking each Cooperative Group to develop proposals for CEA studies rather than creating a system that could be consistently applied to important trials. This would avoid the kind of proliferation of methods that exists in quality-of-life studies. Dr. Ramsey acknowledged this concern but stated that there is already more consistency in the field of CEA than in quality-of-life science. The U.S. Preventive Services Task Force has developed explicit guidelines on CEA in medicine. He suggested development of guidelines specific to oncology trials for publication in a major journal or as a white paper.

Motion. A motion was made to accept the CEA WG report and move forward with its recommendations on a one-year pilot basis. The motion was seconded and passed unanimously.

VII. A NATIONAL CANCER CLINICAL TRIALS SYSTEM FOR THE 21ST CENTURY: REINVIGORATING THE NCI COOPERATIVE GROUP PROGRAM (INSTITUTE OF MEDICINE REPORT)—DR. SHARYL NASS

Dr. Nass discussed the recent IOM report entitled *A National Cancer and Clinical Trials System for the 21st Century*. The committee that generated the report was chaired by John Mendelsohn of M.D. Anderson Cancer Center and the vice chair was Harold Moses of Vanderbilt. The membership represented a broad range of experts and experience. The bulk of the funding came from NCI, which requested the study; support was also provided by the Centers for Disease Control and Prevention (CDC), the American Cancer Society (ACS), the American Society for Clinical Oncology (ASCO), C-Change, and the Association of American Cancer Institutes.

Cooperative Group trials complement industry trials, which play a key role in drug development, by conducting research important to the well-being of patients, such as trials comparing the effectiveness of approved therapies, trials assessing therapies for rare diseases and multimodality therapies, and screening and prevention trials, etc. The committee was impressed with the track record of the achievements of the Cooperative Groups. Besides treatment, Cooperative Groups have made advances in cancer prevention, detection, and treatment risks. Major challenges of the Cooperative Group program include an infrastructure that has not evolved sufficiently with technological advances, extensive government oversight, and stagnant funding.

The committee concluded that an ideal cancer clinical trials system would efficiently respond to emerging scientific knowledge, involve broad cooperation of stakeholders, and leverage evolving

technologies to provide high-quality practice so that trial participation is the preferred option for patients and physicians. Academic, governmental, and commercial sectors must join with the public to develop a 21st century cancer clinical trials system to more effectively leverage scientific advancements and translate them into public health benefits by improving the science/technology, efficiency, and timely completion of the very best clinical trials.

The committee put forth 12 recommendations, falling under 4 goals: (1) improve the speed and efficiency of design, launch, and conduct of clinical trials; (2) incorporate innovative science and trial design into cancer clinical trials; (3) improve prioritization, selection, support, and completion of clinical trials; and (4) incentivize the participation of patients and physicians in clinical trials. Recommendations falling under goal one are: reduce the number of disease site committees through consolidation; consolidate back-office functions such as patient registration and storage of data and images, and credential sites and streamline the protocol development process; undertake trans-agency efforts to streamline and harmonize government oversight and regulation; and facilitate more public-private collaborations to leverage available resources. Goal number two recommendations are: maintain accessible central biorepositories of tumor specimens collected in the course of trials; develop and access innovative designs for clinical trials for evaluating cancer therapeutics, biomarkers, and combinations for therapies; and develop national unified standards for imaging procedures and biomarker tests to ensure quality and comparability. Recommendations for goal number three are: change the focus of NCI's role from oversight to facilitation of trials; strengthen prioritization via peer review; increase the speed, volume, and diversity of patient accrual in higher-priority trials; and allocate a larger portion of the NCI research portfolio to Cooperative Group trials, including an increase in the case reimbursement rate. Lastly, recommendations falling under goal four are: ensure that the clinical investigators have adequate training, mentoring, paid protective time, and necessary resources and academic recognition to participate; and develop health care payment policies that value the care provided to patients in clinical trials and that cover nonexperimental costs.

Each Cooperative Group has its own data collection, management, and analysis infrastructures and capability. Many of the reviews that take place before a trial is launched are redundant and repetitive. The IOM committee proposed consolidating data management functions of Cooperative Groups. The Cooperative Groups would still be responsible for data analysis and publication, and most local IRBs would defer to decisions of the NCI Central IRB (CIRB).

The committee concluded that the process for designing, opening, and completing clinical trials should be more efficient and streamlined with more rigorous prioritization. All stakeholders (investigators, industry, government funding entities, regulatory agencies) share the goal of improving patient care. Increasing emphasis should be placed on the use of biomarkers. Designing and carrying out clinical trials must be reimbursed and nonexperimental costs should be covered by insurance.

Questions and Discussion

Ms. Roach inquired about setting benchmarks to justify requests for increased funding. Dr. Nass said that the report did call for new standards or benchmarks to assess performance. She acknowledged that some might find it difficult to justify investing money in a system that is not functioning as well as it could be. However, it is also hard to see how one would make improvements without money. It is important that investigators have their costs covered so that they have an incentive to participate in the clinical research program. Dr. Perez added that the committee placed a higher priority on funding for infrastructure than on reimbursement.

Dr. Helman inquired about the option of Cooperative Groups collaborating with industry to participate in international trials so that industry partners might accrue patients outside of the United States. Dr. Nass stated that this matter is discussed in Chapter 3 of the report.

A participant noted that an increasing number of patients will have better access to health care with the passage of the Patient Affordable Care Act, and inquired if the committee discussed ways to make clinical trials more broadly available. Dr. Nass replied that the matter had not been discussed in depth because the legislation was passed after the committee had completed its draft report. But she added that having health care coverage does not guarantee having coverage for clinical trials.

Dr. Grubbs remarked that, in the wake of health care reform, it is important to secure funding for clinical trials to make sure they can continue.

Dr. James Wade, III, Director of Medical Oncology, Department of Clinical Research, Decatur Memorial Hospital Cancer Care Institute, asked whether the committee addressed the necessary trade-off between data quality and efficiency that could result from creating an open system that introduces more open-ended accrual across sites. Dr. Nass acknowledged this concern but suggested that if the transition is handled well, investigators will build a strong allegiance to the national network and quality will not suffer. Dr. Perez agreed that credentialing and quality control are major issues. There should be a centralized way of credentialing individuals who want to participate in the consolidation process.

Dr. Schnall noted that many of the interactions between quality assurance, data management, and the trial team are unique to trials and context, so it is difficult to imagine how a central data management warehouse would work efficiently. Dr. Nass clarified that the committee did not specifically call for having only one data management center. There might be two, or four, but it is not necessary to have ten.

Dr. Sargent indicated that it is critical that the data management staff and the IT staff remain responsive to Cooperative Group leadership, as those functions are directly linked to the science of the Groups. Dr. Nass noted that the IOM report calls for standards and peer review of data management and IT operations to ensure high quality and responsiveness to the Group leadership. Dr. Arbuck said that the committee did not intend to isolate data management and IT from other components of Cooperative Groups.

Dr. Bruner stressed the need for polarity and balance and that combining too much can result in losing a lot, such as the amount of volunteerism found in the Cooperative Groups, along with the gain from increased efficiency.

VIII. FINANCIAL, ORGANIZATIONAL, AND MANAGEMENT ANALYSIS OF THE COOPERATIVE GROUPS—DR. JUDITH HAUTALA

As outlined by Dr. Judith Hautala, Science and Technology Policy Institute, the goals of this Cooperative Group analysis were to: (1) gain a comprehensive, functional understanding of the individual and collective financial, organizational, and management structure of the Groups; (2) develop organizational and funding strategies to improve operational efficiency and cost-effectiveness; and (3) identify improved practices for shared strategic management of this complex, goal-oriented research enterprise.

NCI's nationwide network of ten Cooperative Groups is funded through a family of clinical trial infrastructure awards. Four are adult multidisease, multimodality Groups, and six focus more narrowly on specific diseases, modalities, or populations. Nine are funded by the Cancer Therapy Evaluation Program and one, by the Cancer Imaging Program. Awardees range from major universities to not-for-profit organizations.

The primary mission of the Cooperative Groups is to conduct late-phase efficacy trials, but they are also involved in the conduct of some early-stage exploratory trials. Patients are enrolled in Cooperative Group trials by Cancer Centers, major academic medical centers, and community practices.

The Cooperative Group financial structure has two components. The first is infrastructure funding for the development and management of clinical trials. Infrastructure support also includes scientific services, such as biospecimen banks, reference laboratories, and clinical reviews. The second is reimbursement to sites for enrolling and managing patients. Most of this support takes the form of per-patient reimbursement; in some cases accrual is supported through institutional U10 awards and member site infrastructure subcontracts. About 20 percent of accrual in Cooperative Group treatment trials is supported by the Division of Cancer Prevention through the Community Clinical Oncology Program.

The analysis was organized into seven topic areas. The first was to examine the various organizational models adopted by Cooperative Groups. The second component involved a comprehensive cross-Group financial and organizational comparison. Detailed analysis of financial structure focused on unit costs, institutional cost sharing/pro bono time, non-NCI funding, and variations in application of indirect cost rates. Additional analyses addressed accrual patterns and funding models, common services and tools, application and review processes, and system governance.

The analysis began with mapping of requested direct cost budgets to a functionally based Common Budget Outline framework. This was followed by site visits with individual Groups, interviews with NCI staff (e.g., CTEP, Cancer Trials Support Unit [CTSU]), and examination of NCI trial, accrual, membership, and award data.

Due to time limitations, in this first presentation of analysis results to CTAC, the emphasis was placed on findings in five key areas: high-level cross-Group budget allocation, unit costs, institutional cost sharing/pro bono time, non-NCI funding, and accrual patterns.

For the high level cross-Group comparison, direct costs requested in grant applications were mapped to 11 functional cost categories, 8 infrastructure categories, and 3 accrual categories. This process was complicated by the fact that most Cooperative Group budgets are organized by institution rather than by function. For each Group, a competitive year budget and a noncompetitive year budget were mapped to functional cost categories. The cross-Group analysis was performed based on the percent allocation to various budget categories in the noncompetitive year, because this budget reflected what Groups spent, whereas the competitive budgets reflected what they hoped to be awarded.

Eight of the Cooperative Groups allocated between 50 and 60 percent of their budgets to infrastructure cost categories, with the remainder allocated to accrual cost categories. The other two allocated 75 percent to infrastructure, due in part to lower accrual volume. Allocations to infrastructure cost categories were remarkably consistent among the Groups despite varying institutional settings and types of trials. Statistics and data management was the cost category with the highest allocations, averaging 37 percent. Core services received an average of 21 percent (ranging from 14 to 30 percent). Scientific leadership accounted for 5 to 10 percent (with outliers at 1 percent and 16 percent). Other categories included administrative functions, trial operations, and travel, each at 8 to 10 percent; Group leadership accounted for 3.5 percent. Some Groups requested special funds, which accounted for

allocations of 2 to 7 percent. Based on this analysis of percent budget allocation to various cost categories, there was no evidence for major differential cost efficiency or inefficiency among the Groups in allocations as percentages of their budgets. Rather, observed variations resulted from Group-specific differences in trial volume or character, institutional setting, organizational structure, etc. It was not apparent that any Groups had discovered a substantially better way to carry out any area of functional activity and thus reduce the required budget allocation.

Unit cost analysis was performed using a statistical regression model that analyzed infrastructure costs as a function of various parameters of trial activity for the nine CTEP Groups. There was a very strong correlation of total infrastructure costs with the number of active Phase III trials. There was a much weaker correlation with total trials led by the Groups (Phase II and Phase III). This means that Phase II trial activity does not substantially impact overall infrastructure costs. Site visit findings suggest that this lack of impact arises from the fact that most Cooperative Group staff schedule Phase II work in the gaps between Phase III activities. Applying the regression model to infrastructure costs as a function of total Phase III trials plus one-tenth of the Phase II trials for each Group gave an equally strong correlation. This indicates that, across the system, a Phase III trial consumes approximately 10 times the infrastructure costs of a Phase II trial.

The regression model was used to calculate predicted annual infrastructure costs per Phase III trial for each Cooperative Group. Most predicted costs were between $500,000 and $600,000. Two outliers with higher predicted costs were the two Groups with the lowest numbers of Phase III trials. Actual annual costs per trial were computed by dividing actual infrastructure costs by the number of trials (counting ten Phase II trials as one Phase III trial). For six Cooperative Groups, actual costs were within 10 percent of predicted costs. One outlier with higher costs had a small number of large Phase III trials. For the two low outliers, no single functional cost category seemed to explain the variance. These two Cooperative Groups appear to be more cost-effective across all areas of infrastructure.

A similar analysis examined actual infrastructure costs per accrual. Costs per accrual varied widely among Groups and appear to be driven by the specific character and volume of a Group's trials. The average infrastructure cost per accrual across Groups was $3,000 over and above the $2,000 reimbursement.

Analysis of institutional cost sharing and pro bono time began with an examination of scientific leadership. A consensus estimate among Groups was that the average time commitment for scientific committee chairs was 20 percent; scientific committee vice chairs, 5 to 10 percent; clinical research associate (CRA) and nursing committee chairs, 5 to 10 percent; committee members, 1 percent; and protocol chairs, 10 percent for Phase III trials and 5 percent for Phase II trials. Dollar values were calculated for these time commitments. Using a comparison of these commitments with funds budgeted for personnel, it was determined that 77 percent of the time required for scientific and administrative committees and protocol chairs was provided pro bono by investigators or covered by their home institutions. Individual Groups ranged from 50 to 98 percent cost shared/pro bono time, which translates into $27.7 million of "donated" funds, including fringe benefits and indirect costs. This represents 17 percent of the annual total NCI Cooperative Group budget. The most significant component of cost sharing and pro bono time is support for accrual. Approximately $90 million, or 60 percent of total accrual costs, are supported through cost sharing and pro bono time. Overall, institutional cost sharing and pro bono investigator time account for approximately $120 million per year. This means that institutions and investigators are donating about 50 cents for each dollar provided by NCI.

Non-NCI funding obtained by the Groups totals about $56 million annually (industry, $41 million; philanthropy, $6 million; parent institutions, $9 million) or about 25 percent of the annual

Cooperative Group cash expenditure. The Groups themselves are highly variable, generating from zero to 50 percent of their funding from non-NCI sources.

In summary, approximately 53 percent of the cost of running Cooperative Groups comes from NCI through Cooperative Group awards, CCOP accrual, and the CTSU contract. A little over 30 percent comes from pro bono time and cost sharing, and 15 percent comes from funds raised by the Groups. Thus, the Cooperative Groups program is a $360 million effort for which NCI pays about half the cost.

Dr. Hautala stated that findings of an analysis of accrual patterns found that Cooperative Group main members and their affiliates provide 75 percent of the accrual across the system; cancer centers and their affiliates provide over half of that accrual. Cooperative Group main members that have infrastructure funding contribute three to four times more accrual than those without infrastructure funding; thus, paying for infrastructure does have an effect on accrual within Groups. Also, 90 percent of accrual across the system is contributed by 60 percent of the main member/affiliate and CCOP/CCOP component networks; if the lowest-contributing 40 percent were eliminated, only 10 percent of accrual would be affected. Interestingly, there is no evidence of a significant financial or operational burden associated with maintaining low-accruing sites, particularly because most of them are affiliates or CCOP components.

Most sites are members of more than one Group, resulting in a high level of cross-Group accrual from the sites' perspective. Among the three large adult medical oncology Groups, the level of true cross-Group accrual (members accruing to a trial led by a Group of which they are not a member) is approximately 50 percent.

Dr. Hautala noted that the analysis resulted in several major recommendations focused on improving and standardizing internal Group organization, developing a new accrual funding model, revising subcommittee H review criteria, and addressing system governance issues. The recommendations are currently being reviewed by NCI leadership. A CTAC working group or subcommittee may be formed to address them.

Questions and Discussion

Dr. Parkinson noted that in industry the organizational structure of early-stage trials is very different from that of late-stage trials. The Cooperative Group program may need to give some thought to emulating this approach as a means of improving cost-efficiency.

Dr. Grubbs observed that the cited estimate of $6,000 as the average total cost per accrual is probably too low.

Ms. Roach asked why data were anonymized at the Group level. Dr. Doroshow replied that Groups shared data on the condition that specific numbers for each Group would remain confidential. He suggested that this had not been a barrier to developing the findings that NCI wanted from the analysis.

Dr. Parkinson suggested that individual trials with significant amounts of non-NCI funding be studied to determine the effect of that support on timeliness and productivity.

Dr. Abbruzzese asked how infrastructure costs in the Cooperative Group program compare with those in industry. He noted that many people who donate money to a philanthropic organization would be concerned if half their contributions were spent on infrastructure. Dr. Doroshow stated that those costs are

much higher in industry compared with the Cooperative Group program. Dr. Hautala added that among the functional areas gathered under the umbrella of infrastructure costs in this analysis, only Group administration can be described as overhead. Activities such as protocol development and scientific leadership directly contribute to the studies being conducted by Cooperative Groups. Data from this analysis, she stated, show that significant reductions in infrastructure costs are probably not feasible.

Dr. Abbruzzese asked whether improved prioritization of studies could reduce the number of Phase III trials and thus improve efficiency. Dr. Hautala replied that fewer trials would mean reductions in data management activities, protocol development, and scientific services, thus reducing overall costs.

Dr. Perez argued that cutting the number of trials would hinder progress in improving outcomes for patients. Improvements in efficiency would be a better way to reduce costs than reducing the number of trials conducted. Dr. Abbruzzese noted that all trials do not have the same scientific merit. Prioritizing trials can improve outcomes while reducing costs. Dr. Perez agreed that only the most promising Phase III trials should be supported.

Dr. Parkinson asked whether the analysis looked at the quality of data collected by low-accruing sites. Dr. Hautala replied that evidence from site visits and interviews did not reveal concerns about the quality of those data. In fact, she added, most data quality issues are associated with high-accruing sites, at which accrual volume makes it more difficult to keep track of data.

Dr. Sargent noted that industry support is usually passed on to accruing institutions. This should be taken into consideration in calculating non-NCI costs. Dr. Hautala replied that industry funds were not subtracted from the accrual cost sharing in the analysis.

Ms. Roach commented that the estimate of $6,000 per-accrual costs should be reexamined, at least in terms of the effects of inflation. She also stated that the transparency of this analysis should increase public trust in the clinical research program. Dr. Doroshow agreed that this analysis has demonstrated that there are few opportunities to reduce costs in the Cooperative Group program.

IX. COORDINATION OF DATA MANAGEMENT AND BIOSTATISTICS OF NCCTG, ACOSOG, AND CALGB—DRS. MONICA BERTAGNOLLI AND DANIEL J. SARGENT

Dr. Monica Bertagnolli, Chief, Division of Surgical Oncology, Brigham and Women's Hospital, began the presentation by reviewing the mission of the NCI Cooperative Groups. The Groups are designed to provide a scientific and operational infrastructure for innovative clinical research. The program was launched in 1955 to create a publicly funded research program that engages the widest possible network of clinical investigators so that the Groups' results are applicable to the broadest range of U.S. health care settings. The Groups also provide a mechanism for translational research across the spectrum from discovery to validation.

Trials are designed by disease-centered committees within Groups and undergo scientific review in the NCI-sponsored disease-specific steering committees. These trials are designed to produce not only practice-changing conclusions, but also hypothesis-generating data that can be fed back into the process of developing new research projects. There is an increasing emphasis within the Cooperative Groups to develop biomarker-driven trials, adaptive trial designs, and public-private partnerships in order to address cutting-edge research questions.

Cooperative Group scientific teams are led by a Group Chair, assisted by a Group Statistician, with support from modality committees, disease-oriented scientific committees, and outside scientific advisors. Cooperative Group operational teams comprise administrative support, statistical teams, scientific committees, modality committees, and core infrastructure (e.g., statistical and data management centers, biospecimen repositories). Cooperative Groups also receive support from the institutions that provide homes for them, as well as from not-for-profit foundations.

The purpose of the new integrated Cancer and Leukemia Group B (CALGB)-North Central Cancer Treatment Group (NCCTG)-American College of Surgeons Oncology Group (ACOSOG) Statistical and Data Center is to improve the Groups' ability to direct resources toward science by reducing each Group's infrastructure costs; enhance capability to conduct challenging, labor-intensive collaborative research; and increase the depth and breadth of available statistical talent. These three Cooperative Groups account for almost one-quarter of all Cooperative Group accrual; thus, the merger of statistical and data management functions of these Groups is a major undertaking. A large U01 statistical center grant had to be transferred from Duke University to the Mayo Clinic. Dr. Daniel Sargent, formerly Group Statistician for NCCTG, was selected to lead the new, integrated Center.

In June 2010, the CALGB Board of Directors approved both Dr. Sargent's appointment and the plan to integrate the Group's center with those of NCCTG and ACOSOG, which were already in the process of merging. Plans for governance and management of the Center are being developed. The two primary goals of Center design are to produce better science faster while preserving existing strengths and Group loyalty at each institution.

Dr. Sargent outlined the mission and goals of the CALGB-NCCTG-ACOSOG Statistical and Data Center. In the operational realm, the Center will be responsible for managing millions of data points. In addition to its operational support, the Center will support Group protocol design, lead selected clinical trials, and conduct methods research to improve clinical trial statistical operations.

The model for the new CALGB-NCCTG-ACOSOG Statistical and Data Center is the existing joint center operated by NCCTG and ACOSOG. Progress has already been made in developing common systems, initiating remote data capture, synchronizing systems for registration and randomization, harmonizing committee structures, developing joint standard operating procedures for quality control, and sharing supervisory structure.

A key priority for the new Center is to hire, train, and retain dedicated faculty with the requisite passion and skill for innovation in statistical, translational, and clinical research. It will be important to deeply integrate Center staff into ongoing research activities at all levels, as the Center will continually develop and improve IT and human resource systems as well as processes to maximize efficiency and timeliness.

Operational benefits of sharing a data center among three Cooperative Groups will include sharing best practices, leveraging Group resources (e.g., IT, administrative support), creating a single process for adapting to changing standards, eliminating redundant systems, and sharing staff as needs fluctuate.

Each Cooperative Group will maintain its own Statistical Unit due to differences between the scientific missions of the groups; however, they will use the same data systems and procedures. The Programming Unit will be fully integrated to build a unified IT infrastructure to support all three Groups. The Data Management and Quality Control Unit will use integrated standard operating procedures (although staff will be allocated to individual trials). The Center will also house an integrated Clinical

Trials Coordination Unit. The result of this integration and coordination will be expanded expertise with greater efficiency and an example of a way in which the Cooperative Groups can truly cooperate.

Questions and Discussion

Dr. Schnall noted that the American College of Radiology Imaging Network has a similar structure to the integrated systems and resources described by Dr. Sargent. It is critical when creating integrated infrastructure, he emphasized, to ensure that the member Cooperative Groups continue to be presented to the scientific world as distinct scientific organizations with separate missions.

X. CHANGING NCI'S CLINICAL TRIALS SYSTEM TO MEET THE NEEDS OF THE 21ST CENTURY: IMPLEMENTATION OF THE CLINICAL TRIALS WORKING GROUP (CTWG) AND INSTITUTE OF MEDICINE RECOMMENDATIONS—DR. JAMES DOROSHOW

Dr. Doroshow provided an update on operational changes that are being put in place to improve the efficiency of clinical trials. He stated that NCI has invested a great deal of effort into developing standard terms and research agreements for academic centers working with industry. The Operational Efficiency Working Group (OEWG) set 300 days as the target timeframe for activation of Phase III clinical trials and 210 days for activation of Phase II trials. Of 18 Phase III concepts submitted between 4/1/2010 and 8/20/2010, 3 have been approved. The Phase III trial concepts and Phase II trial letters of intent were reviewed within the 90-day and 60-day target timelines, respectively. These guidelines apply to the intramural program as well.

NCI provided ARRA funding to help Cancer Centers and Cooperative Groups hire project managers and other employees to facilitate these activities. CTEP has made many process changes and improved communication. For example, contract services are used to provide investigators with "track changes" documents so they can make changes with one push of a button.

As of January 1, 2011, all Phase III trials that have been in process for two years and are still not opened will be terminated. The same rule applies to Phase I and II trials that have not received IRB approval within 18 months. CTEP has also initiated teleconferences conducted within five days of review by the steering committee or review of letters of intent. The focus of the calls is major scientific issues, not formatting. CTEP has also put together a portal that allows principal investigators and disease chairs to see where protocols are in the review process, in real-time.

Many of the proposed process changes do not cost money (e.g., teleconferences). The improvements in the timeline could not have been achieved either by the Groups alone or by CTEP alone; it has been a joint effort.

The Biomarker, Imaging, and Quality of Life Studies Program supports trials that would never have been funded through the grant mechanism. Thanks to Dr. Barbara Conley and the subgroups from CTAC who developed standards for biomarker assays, a clinical assay development program will be started in January. NCI is trying to think through how a biospecimen banking program can be integrated with caHUB and utilized as a national system with uniform IT. The Investigational Drug Steering Committee has moved very aggressively to develop and publish novel designs for Phase I and II activities related to incorporation of biomarkers into trials.

NCI is developing the first comprehensive database of NCI-supported clinical trials. Input from extramural stakeholders, including the Association of American Cancer Institutes, has been helpful in the implementation of this initiative. Development of a complete set of standardized case reports is under way. NCI is also developing a repository of investigator credentials, which will likely facilitate audits. It is important to note that NCI is not a credentialing body in this activity, but rather is facilitating retrieval of investigators' credentials. NCI is working to provide software that will potentially revolutionize the way clinical trials are conducted. It is hoped that the software will be made available to all 2,000 sites nationwide. The Clinical and Translational Science Awards (CTSA) program has expressed interest in having NIH adopt the software for use in clinical trials for all diseases, and the National Center for Research Resources (NCRR) is taking this proposition very seriously.

The per-patient reimbursement rate for large Phase II trials has been increased. Almost all disease-specific steering committees are operational; the pediatrics committee will be added in January. The CTWG has established the Cancer Clinical Investigator Team Leadership Award for investigators at Cancer Centers who do not have their own grants. The candidates are nominated by Cancer Center directors, and the first 11 awardees were funded last year. The funding is for two years and covers about one day a week to do institutional clinical trials research. Resources are available to fund up to 20 investigators per year. Each Cancer Center can have only one of these awards per two-year period. The first reports on the success of the awards program will be available within the next year.

Over the past five years, NCI has increased the level of review and prioritization across all diseases in the Cooperative Group system, which has helped to increase the focus on the best trials to move forward. Improvements in the function of the CIRB should help decrease the regulatory burden of clinical research.

XI. DISCUSSION OF THE APPROACH TO IMPLEMENTATION OF THE IOM REPORT—DR. JAMES DOROSHOW

Dr. Lisa Newman, Professor of Surgery, University of Michigan Comprehensive Cancer Center, remarked that career development of clinical investigators is vital to maintaining the individual identities of Cooperative Groups. There are very exciting career opportunities within each Group. It is important to ensure that the thought leaders of tomorrow assume greater visibility. She added that in terms of pooling services, it is important to allow some of the lower-visibility committees, such as education, patient advocate, special populations, and outreach, to interact with one another.

Dr. Abbruzzese remarked that many Cancer Centers participate in more than one Cooperative Group, at least in more than one subspecialty group. There are overlaps between various medical oncology groups, especially where there is common scientific interest. Dr. Abbruzzese suggested integrating the scientific components of the Groups along with the integration of data management and statistics. This would result in tremendous synergy, but also in competition of ideas.

Dr. Monica Bertagnolli noted that it is important to know what other Cooperative Groups do and understand where synergistic activities may exist.

A participant commented that when merging functions of Cooperative Groups, there is a danger of losing interest of volunteers involved in the Groups.

Another participant remarked that scientific strengths of one Group could be made stronger through a collaborative agreement with another Group. Some degree of collaboration is already in place; very few large Phase III trials are conducted by a single Cooperative Group. Patient populations need the combined resources across the country and around the world, and international collaboration is on the rise.

Ms. Roach noted that it is easier to volunteer for a small organization than for a large one. An important challenge is prioritizing trials, as proposals come in serially.

Dr. Schnall noted that some Groups use their connections with the community to raise funds from philanthropic organizations and foundations. These resources might be lost if the individual Groups disappear. Strategies need to be developed to make the entire ensemble of sites that can accrue to trials available to all Groups, as appropriate, and to prioritize the best trials.

Dr. Tepper stated that some of the task forces of the Gastrointestinal Steering Committee are virtually consolidated and functioning as a cooperative group on trial concept development. Prioritization and introduction of new ideas occur mainly at the task force level, rather than at the steering committee level.

A participant remarked that it is important to have a steady stream of hypothesis-generating Phase II protocols available for investigators to maintain enthusiasm and offer the feasibility and promise for the next Phase III trial.

Dr. Tepper noted that while it is difficult to find protocols that would be suitable for all sites across the United States, it is helpful to keep all the trials open to all the sites.

A participant indicated that molecular tools to answer critical scientific questions are generally available. However, the ability to sample tumors is a challenge. Even in cases where there is a clear target in the patient's tumor, biopsy is a voluntary rather than mandatory part of the protocol. Dealing with IRBs is a big impediment.

Dr. Tepper added that imaging is also often voluntary, resulting in low data acquisition. The problem usually rests with the individual sites, because research associates find it difficult to coordinate any additional activity. If it is voluntary, the sites will not do the imaging, as they do not have resources to coordinate the activity.

Dr. Bruner noted that the same problem occurs when trying to obtain quality-of-life data. It appears that there is insufficient infrastructure support for obtaining correlative endpoints, which are integral to the trials.

A participant argued that it is better to do two studies and get all data than to do ten studies and get incomplete data.

Dr. Wade noted that it would be an interesting experiment to allow trials to be designed internationally as a voluntary effort, such as the way Wikipedia is built.

Dr. Abbruzzese commented that it remains to be seen if the innate nature to work in smaller groups will override the potential benefits of consolidation.

A participant suggested that the next IOM report address the scientific alignments and missions of the Cooperative Groups.

Dr. Sandra Horning, Senior VP, Genentech, Inc., remarked that people usually gravitate to the disease with which they most closely identify. The European colleagues are organized around diseases and doing definitive trials that are changing the practice in oncology. This is a model that is functioning very well internationally and is the way industry-sponsored trials are functioning.

Dr. Cowan proposed consolidating Cooperative Groups in such a way that the individual identities of Groups are preserved. Statistical and data management functions could be merged into a centralized facility to enhance efficiency. Or, one Group could be in charge of conducting statistical reviews for other Groups. Another option is to look at it in a disease-oriented way and have disease groups from different Cooperative Groups participate in some sort of model system. It may be helpful to consider other models instead of trying to modify the existing model. Individual constituencies of the Groups should be preserved, as well as pro bono work. The experts in different diseases and international groups should be working together on different ideas.

Dr. Tepper remarked that the Cooperative Groups were originally disease oriented, and that much is lost when one group is doing everything. It is important to have enough groups to create tension and competition of ideas. Having too many groups carries the danger of groups doing redundant work. In Dr. Tepper's opinion, the main problem is the optimal number of groups, not how they are organized.

A participant remarked that according to the financial analysis, merging the Cooperative Groups will not save money. Dr. Doroshow added that, according to Dr. Hautala's analysis, merging the Groups will cost money in the short term; however, there might be efficiencies in the long term.

Dr. Schnall proposed having Groups offer potential answers to important questions to be considered by CTAC and NCI as a whole.

Ms. Roach remarked that it would be helpful to talk to industry about their ways of dealing with the FDA and the Centers for Medicare and Medicaid Services (CMS) as they bring a drug through the pipeline. She added that it is important to hear the opinions of experts other than medical oncologists, such as translational scientists, device experts, and community oncologists.

A participant asked Dr. Sargent about the potential size of the merged groups. Dr. Sargent indicated that it would be unreasonable to have only one statistical group for the whole country. The tripartite agreement is scalable but it would not be a good idea to scale it to all ten Groups. It is good to have some redundancy and protection in case something goes wrong in one instance.

Dr. Arbuck asked if the plan is to do more consolidation for IT and less consolidation for data management and statistics. Dr. Sargent responded that each of the three functions probably has a different benefit structure of consolidation versus maintaining individuality. Even at the level of IT, the Groups develop innovative IT solutions to different problems, partly because there is competition between Groups. In the past, Groups have shared ideas.

Dr. Horning asked Dr. Doroshow to clarify the issue of facilitating interactions with FDA and CMS. Dr. Doroshow stated that some important issues raised by the IOM report are not simply under the purview of NCI. NCI has a strong interaction with FDA; on the other hand, there has been a waxing and waning of interactions between NCI and CMS. Past interactions with CMS have facilitated research. There are many new aspects related to management of the new health care legislation.

Dr. Horning remarked that it would be helpful to synchronize the endpoints of clinical trials with endpoints that are acceptable to FDA and CMS.

Dr. Parkinson stated that to be valuable to the community, clinical trials should be adequate to change either indications on the regulatory side or reimbursement levels of evidence on the reimbursement side. Unless clinical trials can change daily practice, they are not accomplishing what they are supposed to do. Dr. Doroshow indicated that, through conferences with the Brookings Institute and FDA, NCI has had an impact on the formulation of those endpoints and the kinds of data needed to meet them.

XII. CENTRAL INSTITUTIONAL REVIEW BOARD UPDATE—MS. JACQUELYN GOLDBERG

Ms. Jacquelyn Goldberg, Head, Central Institutional Review Board, NCI, stated that the goal of the CIRB is to reduce the duplication of efforts involved in IRB review for multisite trials. There are two functioning central IRBs. The adult central IRB, which was initiated in 2001, reviews adult Phase III Cooperative Group trials, and the pediatric central IRB, which was started in 2004, reviews Children's Oncology Group (COG) Phase II-III and pilot studies. NCI developed a facilitated review model in which central IRBs work in partnership with local IRBs. If a local investigator wants to open a trial, he or she downloads the consent document and already completed application from the CIRB Web site and submits it to the local IRB. The investigator does not have to complete the application.

The local IRB then downloads the CIRB review documents, which pertain to CIRB's initial full Board review. Therefore, the local IRB has access to primary reviews, correspondence, and meeting minutes, so they can understand how the CIRB came to its decision. The local IRB chair or subcommittee reviews those documents for local (regulatory) context concerns. The full local Board does not need to meet. If the local IRB (or chair or subcommittee) has no concerns, the central IRB becomes a reviewing IRB for that protocol at their institution, reviewing all subsequent documents, annual continuing reviews, and unanticipated problems distributed by the Cooperative Group. If the local IRB has concerns, they do not have to participate in the CIRB process for that protocol. Thus, the use of the CIRB system is determined on a protocol-by-protocol basis.

At present, 295 institutions have enrolled in the CIRB initiative (165 using the adult CIRB, 44 using the pediatric CIRB, and 86 using both.) The 295 institutions enrolled bring with them outside institutions and affiliates, bringing the total number of institutions to 880. Forty-one of 59 eligible Cancer Centers are enrolled. Since the beginning of the initiative, over 11,000 facilitated reviews have occurred (roughly 6,700 adult and 4,600 pediatric). There are currently 159 adult and 89 pediatric studies available for facilitator review.

In the past year, a great deal of effort has been dedicated to process improvement. A parallel review process was established in which the Cooperative Groups and the CIRB receive CTEP-approved protocols at the same time. This allows sites not using the CIRB to begin their own local review parallel to that of CIRB. The Groups and the CIRB have agreed upon timelines for responses to CIRB stipulations and eliminated the requirement for the Groups to amend their informed consent documents per CIRB stipulations. Communication has been improved as well. Principal investigators attend CIRB meetings when their protocols are being reviewed so that the Board's questions are answered during the meeting, reducing the need for correspondence after the meeting. More teleconferences are being scheduled to address problems in advance. With the implementation of these changes, the median numbers of stipulations requiring a Group to respond have been substantially reduced, and the timelines for CIRB review have been shortened.

The senior staff of the Association for the Accreditation of Human Research Protection Programs (AAHRPP) have suggested a redesign of the current facilitated review model into an independent commercial model in which the CIRB alone would be the IRB of record and there would be no need to partner with the local IRB. They are encouraging adoption of this model because CTEP has a comprehensive human subjects protection program in place, and the Clinical Trials Monitoring Branch (CTMB) conducts audits and credentials investigators. The problem with this model is that the CIRB would have to take over the function of local context review, an added burden and expense.

On the other hand, switching to the independent model would likely help in recruitment of sites that have been previously reluctant to join due to concerns over accountability and regulatory reliability. In the independent model, all of the responsibility would lie in the hands of the CIRB. ASCO conducted a survey of IRBs and research staff of institutions participating in the CIRB to determine their feelings about the new model. Seventy-five percent of the IRB staff and 95 percent of research staff favored the model. Only 35 percent thought there might be an increase in workload for IRB staff, and 40 percent thought there would be an increase in workload for research staff. Eighty-five percent of survey respondents indicated they would be willing to open studies in the new system, even though 65 percent stated that they prefer the current model. There appears to be an attachment to the current model, as some institutions invested a substantial amount of money in IT to have an interface with the CIRB.

It was decided that the redesign will be piloted in 2011. Plans for the pilot will be developed during the first half of 2011, after which a pilot will be started with 20 institutions. Institutions' satisfaction, operational efficiency, and feasibility will be assessed after a year. By late 2012, the CIRB will decide whether to switch to the new model.

Questions and Discussion

A participant asked whether the CIRB will use supporting documents similar to those used by the Western IRB. Ms. Goldberg replied that the CIRB will have to adapt those documents to the specific situation and needs. Development of the new forms and new operating procedures will be a substantial undertaking.

Dr. Perez asked whether the 800 institutions currently enrolled would join under the new model. Ms. Goldberg indicated that the shift to the new model would be a big aid in recruitment. ASCO is considering conducting a second survey of institutions not included in the first survey. The percentage of institutions willing to accept the shift should become known within the next several months.

Dr. Wade complimented Ms. Goldberg and her team on reducing the protocol approval time.

Dr. Perez inquired about the process the CIRB will use in dealing with international trials. Ms. Goldberg indicated that the CIRB has not yet addressed this matter.

Dr. Sargent asked whether the process might become so efficient that it could be used for Phase II trials. Ms. Goldberg stated that the CIRB has considered doing that.

XIII. ADJOURNMENT—DR. JAMES DOROSHOW

Dr. Doroshow asked CTAC members to email himself or Sheila Prindiville with any concerns or possible agenda items for the next meeting in December.

There being no further business, the 11th meeting of the CTAC was adjourned at 4:45 p.m. on Tuesday, September 21, 2010.

12/15/10
Date

James Doroshow, M.D., Chair

12/15/10
Date

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