DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
10th CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE MEETING

Summary of Meeting
March 10, 2010

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

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
BETHESDA, MARYLAND
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The Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) convened for its 10th meeting at 8:00 a.m. on Wednesday, March 10, 2010, in Conference Room 10, C-Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. Dr. John Niederhuber, Director, NCI, presided during the meeting. The meeting was adjourned at 3:32 p.m.

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

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

Executive Secretary
Sheila A. Prindiville, NCI

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WEDNESDAY, MARCH 10, 2010

I. CALL TO ORDER AND OPENING REMARKS—DR. JOHN NIEDERHUBER

Dr. John E. Niederhuber, Director, NCI, called to order the 10th Clinical Trials and Translational Research Advisory Committee meeting. He welcomed the Committee and *ex officio* members and introduced three new CTAC members: Drs. Olivera Finn, Scott Lippman, and Lisa Newman. Dr. Niederhuber also introduced Andrea Bernardo, a new NCI addition to the NIH Deputy Ethics Counselors. Dr. Niederhuber 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, Coordinating Center for Clinical Trials (CCCT), NCI, within 10 days of the meeting. Any written statements by members of the public will be given careful consideration and attention. Dr. Niederhuber also noted that this meeting was being videocast for the first time by the NIH VideoCasting and PodCasting Web site: http://videocast.nih.gov/PastEvents.asp?c=115.

Motion. A motion was made to approve the minutes of the November 4, 2009 CTAC meeting. The motion was seconded, and the minutes were approved unanimously.

II. DIRECTOR'S UPDATE—DR. JOHN NIEDERHUBER

NCI Fiscal Year (FY)2009 and FY2010 Operating Budgets and the President's Budget for FY2011. The FY2009 operating budget of $4.966 billion was supplemented with $1.26 billion through the American Recovery and Reinvestment Act (ARRA), for a total of $6.223 billion. The FY2010 allocation is $5.1 billion, an increase of approximately 2.7 percent. The President's proposed budget for FY2011 is $5.26 billion, which would entail an increase of 3.1 percent.

Approximately 80 percent of the FY2010 budget is being distributed throughout the research community in the form of research project grants, other research programs, research and development contracts, and training activities. The NCI intramural research program accounts for 16 percent of the budget; this includes NCI support to the NIH Clinical Center. Currently, the Institute has a "wish list" of potential programs and infrastructure building that would cost approximately $300 million.

The President's budget proposal for FY2011 contains the following statement: "To accelerate progress in biomedical research, NIH investments will focus on priority areas including genomics, translational research, science to support healthcare reform, global health, and reinvigorating the biomedical research community." These priorities reflect the research priorities emphasized by NIH Director Dr. Francis Collins. The President's budget also includes $6.036 billion to support a range of "bold and innovative" cancer research efforts. These include initiating new drug trials in 2011, doubling the number of new compounds in clinical trials by 2016, and completing a comprehensive catalog of cancer mutations within the next 10 years.

NCI recently released a new edition of *The Nation's Investment in Cancer Research*, also known as the Bypass Budget, which reports on progress to date and spells out the Institute's perception of the needs of the cancer research community. This edition takes into account the effect of the one-time infusion of ARRA funds on future fiscal years and suggests ways to maintain the momentum of programs launched with ARRA dollars.

Report on National Cancer Advisory Board (NCAB) Working Groups. The NCAB has formed a Working Group on The Cancer Genome Atlas (TCGA) to consider issues that must be

addressed as TCGA and similar initiatives continue to accelerate technology development and data collection. Part of the group's discussions will focus on NCI's participation in cancer-related genomic research and development activities supported by a broad range of organizations, including the National Human Genome Institute. Dr. Jennifer Pietenpol, NCAB member and Director of the Vanderbilt-Ingram Cancer Center, will chair this working group.

The NCAB has also formed an ad hoc working group to create a strategic scientific vision for the National Cancer Program and review the National Cancer Institute. This group will examine NCI's operating structure and strategic vision to assess the effectiveness of its scientific programs and business management structure in order to determine the gaps and opportunities for delivering scientific progress in understanding, diagnosing, treating, and preventing cancer. The group will consider whether NCI's special authorities mandated by the National Cancer Act of 1971 are being optimally utilized and discuss the types of authorities and resources that may be needed as NCI moves into a new scientific era.

Co-chairs of this group are Dr. Phillip Sharp, former NCAB chair, and NCAB members Mr. William Goodwin, Mr. Robert Ingram, and Dr. Bruce Chabner. Membership will include a broad representation from the academic, industry, and advocacy communities. The working group will hold several meetings, form subgroups to address specific issues, and deliver a report to the Secretary of Health and Human Services, the President, and the Congress in September.

Executive Committee (EC) Scientific Retreat. The goal of the February 16-17 NCI EC Scientific Retreat was to inform NCI's leadership about the directions that its cancer research efforts might take to maximize the impact of personalized medicine in clinical care and public health within the context of current cancer research opportunities, patient care priorities, and the healthcare environment. Presentations by invited speakers were followed by panel discussions. The retreat was videocast so that all NCI staff could benefit from the discussion.

Keynote speakers included Dr. Mark McLellan on *Current Realities and the Future of Personalized Cancer Medicine*; Dr. Ronald A. DePinho on *Informing the Cancer Biological Space—Genomics and Beyond*; Dr. Stephen Friend on *The Role of Computational Sciences, Systems Biology, and Modeling*; Dr. Keith Yamamoto on the Institute of Medicine (IOM) report *A New Biology for the 21st Century*; and Dr. Charles Sawyers on *How to Translate Genomics for Patient Benefit.*

Dr. Niederhuber identified several themes that arose during the retreat. Biospecimens are needed not only for tumor characterization and patient care but also for the use of the scientific community. Collection of specimens for these purposes is being piloted by the NCI Community Cancer Centers Program.

Another need is to develop systems for tracking patients starting with diagnosis and feeding their electronic health records and specimens into a national database through the course of their disease, creating a virtual cohort for numerous studies. As technology advances, patients can be further characterized, providing expanded data for scientific use. Developing models for managing, sorting, and analyzing electronic health records is an important challenge for the cancer community.

Another need is to discover ways to convert this valuable information into a better understanding of functional biology. The five ARRA-funded sites in NCI's Target Discovery and Development Network are already making significant progress in using genomic information to address basic research questions about molecular targets and networks of pathways. NCI has also launched multiple projects dedicated to making data more accessible and using data in a collaborative fashion, as well as infrastructure resources like caBIG and BigHEALTH to provide tools for those collaborations.

Needed growth in clinical trials research is restrained by the limited increases in NCI's budget. The Institute will need to make radical changes in the way trials are planned and conducted to move past the status quo. As the cancer research community endeavors to determine the directions cancer research should take, ideas for new investigations will need to come from scientists in the academic institutions and particularly in the Cancer Centers, where the interface of science and the generation of new ideas at the patient level is found.

Before closing, Dr. Niederhuber expressed his thanks to Dr. Lynn Matrisian for her selfless service in leading development of the Translational Research Working Group (TRWG). Now that implementation of the TRWG is up and running, she is returning to her departmental chair duties at Vanderbilt University.

Questions and Discussion

Ms. Nancy Roach, Consumer Advocate, C3: Colorectal Cancer Coalition, asked who would serve as the NCI champion for the TRWG in Dr. Matrisian's absence. Dr. Niederhuber replied that Dr. Prindiville will provide leadership in support of implementation of the TRWG recommendations by NCI. Dr. Matrisian will continue as Chair of the TRWG's Process to Accelerate Translational Science Working Group (PATS).

Dr. James Abbruzzese, Chairman, Department of Gastrointestinal Medical Oncology, M.D. Anderson Cancer Center, asked whether NCI is considering changes in the type of support provided to Cancer Centers to help them respond to the challenge of harnessing the power of new knowledge about proteomics and other scientific and technological advances. Dr. Niederhuber said that several options exist, including shifting some of the funds currently used to support Cooperative Groups. Careful deliberations between NCI and its advisory groups will be needed to ensure that 5 years from now the momentum of cancer research will have accelerated.

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.

Appropriations Activities. FY2010 appropriations were passed on December 16, 2009; NIH received $30.1 billion, with $5.1 billion going to NCI. The appropriations process for FY2011 began on February 1 when the President's Budget was announced. The President's Budget has allocated $32.09 billion to NIH and $5.26 billion of that amount to NCI. The FY2011 House NIH budget hearing will be held on March 24 and the Senate hearing, on April 21.

Congressional Hearing. On March 4, 2010, the House Committee on Oversight and Government Reform held a hearing titled: "Prostate Cancer: New Questions About Screening and Treatment." The hearing focused on prostate screening and treatment controversies, as well as current research efforts. The American Cancer Society's release of new screening guidelines for prostate cancer sparked debate about both screening and treatment for the disease. Representatives from NCI and the U.S. Army Medical Research and Materiel Command discussed their respective prostate cancer research programs. Health disparities, particularly the unequal burden of prostate cancer in African-American patients, were also

discussed. The NCI testimony from this hearing can be found on the Office of Government and Congressional Relations Web site (http://legislative.cancer.gov/hearings/research).

Legislation. The Small Business Innovation Research (SBIR) program expired about a year ago and needs to be extended and reauthorized. Congress is providing temporary extensions until terms of the reauthorization are agreed upon; the most recent extension funds the program through April 30, 2010. Issues delaying an agreement include an increase to the SBIR set-aside (i.e., percent of the NIH appropriation allocated to SBIR) and the allowed percentage of venture capital funds that can be used by a company receiving an SBIR grant. In addition, Senator Mary Landrieu introduced legislation that removes a provision from the American Recovery and Reinvestment Act exempting NIH from a set-aside for SBIR—this would require NIH to obligate $150 million of ARRA funds to the SBIR program. Currently, three different bills are in discussion for the long-term reauthorization of the SBIR program.

Each year since 2001, an Access to Cancer Clinical Trials bill has been introduced in Congress that would require health insurance companies to cover the routine costs associated with participation in clinical trials. This bill has never passed; however, its language has been incorporated into the Senate Healthcare Reform Bill this year. If enacted, Access to Cancer Clinical Trials will become law.

Questions and Discussion

Dr. David Parkinson, President and CEO, Nodality, Inc., expressed frustration over the failure of Congress to reconcile versions of the SBIR reauthorization bill. Venture capital majority-owned small businesses—which are probably the small businesses with the greatest technology in the United States—are ineligible to receive Federal funding until reauthorization occurs.

Dr. Niederhuber commented that a committee is being formed to assess the SBIR program across the Federal Government. He also noted that NCI's SBIR program serves as a model at NIH for its success in structuring competitive reviews and represents very high-quality investments.

IV. OPERATIONAL EFFICIENCY WORKING GROUP (OEWG) UPDATE—DR. JAMES DOROSHOW

Dr. James Doroshow, Director of the NCI Division of Cancer Treatment and Diagnosis (DCTD), provided an update on the final report of the OEWG.

Background. The OEWG was established approximately 1.5 years ago and charged with developing strategies to reduce the time to activation of Cooperative Group and Cancer Center clinical trials. The OEWG comprises 63 clinical trial stakeholders, including Cooperative Group chairs, Cancer Center directors, clinical investigators, statisticians, protocol/trial specialists, community oncologists, NCI clinical trials leadership and staff, and patient advocates, among others.

OEWG addressed Cooperative Group Phase III trials, Cancer Center investigator-initiated trials, Cancer Center activation of Cooperative Group trials, and Phase II trials involving drugs for which the NCI Investigational Drug Branch (IDB) holds the Investigational New Drug (IND). Other topics, such as industry-sponsored trials, human subjects protection, Center for Medicare and Medicaid Services (CMS) coverage determinations, state laws and requirements, as well as congressional funding mandates are outside of the purview of the OEWG and were not discussed by the group.

Through frequent deliberations, OEWG members came to agreement on key barriers to timely trial activation and developed a shared sense of commitment to achieve new target timelines for the activation of trials. The group then developed a series of new process maps for trial activation. Finally, recommendations and implementation plans were developed to achieve target timelines, and firm dates were established by which all protocol issues must be resolved. Most importantly, resources were developed to support the implementation of these activities.

Cooperative Group Phase III Trials. An analysis of Cooperative Group Phase III trials activated in 2006 to 2008 revealed that nearly 60 percent of the studies took more than 2 years to be activated. One element of particular concern is the time from protocol receipt to approval (348.5 days). One of the reasons for this protracted timeframe is that the vast majority of protocols require three or more revisions before they are approved.

The OEWG is proposing a 300-day timeline beginning with concept submission and ending with trial activation. The 300-day timeline excludes issues related to the Institutional Review Board (IRB), contracting, and drug supply, which are out of the control of the Cooperative Group; however, protocols will be terminated if they are not activated within 2 years of concept submission, regardless of the reason for the delay. This decision was based on data from Dr. David Dilts indicating that trials taking more than 2 years to activate are rarely completed. In order to achieve this 300-day goal, the OEWG target for time from protocol submission to approval is 120 days; this represents a significant reduction from the 348.5 days this process has taken over the past few years.

The OEWG developed a series of recommendations and implementation plans to drive Cooperative Group process improvement. The first recommendation calls for changes within the Cooperative Groups. These changes will likely involve additional staff tasked with keeping track of protocol development and making leadership aware of any issues that arise. Processes will need to be created to allow protocol development steps to be performed in parallel and issues to be resolved in a direct, coordinated fashion. Also, appropriate project management and tracking tools will need to be put into place so that leadership can determine the status of a protocol at any given time. The second recommendation relates to changes within the Cancer Therapy Evaluation Program (CTEP). CTEP should have project managers to oversee the protocol review, revision, and approval process and facilitate interactions with the Cooperative Groups. The third OEWG recommendation addresses the need for a collaborative Cooperative Group-CTEP process for the revision of concepts and protocols. The OEWG emphasized that there must be direct, coordinated interactions to resolve issues, and fundamental aspects of study design must be addressed at the concept stage. Discussions related to protocols should involve prompt resolution of major differences and minimal time spent on noncritical differences of opinion and routine revisions. The fourth recommendation calls for development of approaches to reward performance relative to the established timelines. To do this, a reliable system must be established for reporting timeline performance; this must be accompanied by clear definitions of what needs to be done at what point in time. After the first year, performance data should be assessed to determine the value and accuracy of the reports. Individual Cooperative Group performance as well as performance across the Groups should be analyzed and incentives linked to performance. CTEP should also include timeline performance in its annual staff performance evaluations.

IDB Early Drug Development Phase II Trials. Phase II trials of agents for which NCI holds the IND are conducted by Phase I/II grantees and contractors and Cooperative Groups. Nearly one-quarter of these trials take more than 2 years to activate. One of the primary reasons for this protracted time to activation is the number of protocol revisions; most protocols are revised two or more times, with some protocols being revised and resubmitted five or more times. Another time-consuming step is obtaining industry approval of letters of intent (LOIs). The OEWG has established a target timeline of 210 days for

activation of these trials. The 210-day goal excludes issues related to IRB, contracting, drug supply, and U.S. Food and Drug Administration (FDA) review; however, protocols will be terminated if they are not activated within 18 months of concept submission, regardless of the reason for the delay.

Cancer Center Investigator-Initiated Trials. Currently, it takes an average of 180 to 200 days to activate an investigator-initiated clinical trial at a Cancer Center. The OEWG determined that the target timeline for this process should be 90 days, excluding protocol writing, contracting, institutional finance review, and drug supply issues. To achieve this, the OEWG recommends Center-specific action plans be developed. Implementation will likely include specialized staff and direct, coordinated interactions to resolve differences, as well as project management and tracking tools. The OEWG recognizes that different timelines may be appropriate for different Cancer Centers, depending on the size of the Center and other factors; each Center should establish a reasonable target timeline for itself and measure performance against this benchmark. Guidelines should be modified as necessary to make it possible for Centers to utilize Cancer Center Support Grant (CCSG) funds for protocol development, and additional funds should also be made available if necessary.

Process Improvements Applicable Across Trial Categories. The OEWG also discussed several overarching issues that affect timelines to trial activation. One recommendation resulting from this discussion is that a working group involving NCI, Cooperative Group, and Cancer Center staff be formed to coordinate efforts to standardize tools and templates in order to facilitate rapid assembly of protocols. This would involve analysis of existing resources and ongoing standardization efforts, as well as development of a coordinated process for implementing standards. This would be a relatively low-cost way to improve the NCI-funded clinical trials system.

Additionally, OEWG recognizes that biomarkers are becoming an important part of cancer clinical trials and that securing funding for biomarker components of trials can be time consuming and result in significant delay. Thus, the Group recommends that funding and capabilities for use of biomarkers in NCI-funded trials be enhanced. With CTAC approval, the Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP) has been expanded to include randomized Phase II trials. There will be more Phase II trials in the future that need support in this area. Standards should also be developed to allow qualifying sites to conduct imaging studies associated with clinical trials.

Another OEWG recommendation that Cancer Centers perform rigorous review of clinical trial concepts in advance of protocol development would help optimize use of resources by reducing the number of protocols in development.

Process Improvements to Enhance the Overall Clinical Trials Program. The OEWG also discussed a number of issues not directly related to trial activation but relevant to improvement of the overall NCI-funded clinical trials enterprise. Efforts should be made to enhance Cancer Center participation in Cooperative Group trials. Strategies to accomplish this include integrating accrual to Cooperative Group trials into CCSG review criteria, recognizing investigators for their role in the design and conduct of Cooperative Group trials, and enhancing the stability and amount of funding available to support accrual to these trials. OEWG also discussed requiring Cancer Centers to develop strategic plans to help determine the best ways to allocate clinical trial resources based on research strengths and available patient populations. Changes also need to be made to enhance clinical research mentorship and training.

Summary and Next Steps. Administrative supplements have been awarded to all 10 Cooperative Groups to help them develop action plans, hire additional staff, and acquire and deploy project management tools to implement OEWG recommendations. There are currently 48 applications for administrative supplement requests in review for NCI-designated Cancer Centers.

CTEP is holding a meeting on April 1, 2010 with Cooperative Groups and Phase I/II investigators to initiate action plans. CTEP is also working hard to develop a transparent software system for concept and protocol tracking. The next implementation step is to launch phase II of CTEP's efforts, which will address rate of accrual and time to trial completion. There will be firm termination deadlines (24 months for Phase III trials and 18 months for Phase II trials) beginning January 2011. It will be necessary to create long-term economic incentives for meeting target timelines.

Motion. A motion to accept the Operational Efficiency Working Group report and recommendations was voted on: 10 Committee members were in favor; 8 abstained (these Committee members were also members of the OEWG and were asked to abstain from voting).

Questions and Discussion

Dr. Sandra Horning, Senior Vice President and Global Head, Clinical Development Hematology/Oncology, Genentech, Inc., asked how leadership and participation in Cooperative Group trials has been incorporated into reviews of Cancer Centers. Dr. Linda Weiss of the NCI Cancer Centers Program responded that there are generic review criteria in the current CCSG Guidelines; however, in the next version criteria will be broken down more specifically with Cancer Centers receiving credit for accruing to Cooperative Group trials.

Dr. Richard Schilsky, Associate Dean for Clinical Research, Pritzker School of Medicine, University of Chicago, brought attention to an issue with the firm termination deadlines. The deadlines unintentionally provide a mechanism for any pharmaceutical company collaborator to veto a protocol by failing to meet the timeline. Working with the Cooperative Group is often not the highest priority for pharmaceutical collaborators; however, they will still be subject to the termination deadlines. The OEWG needs to convey the importance of their goals to the pharmaceutical industry.

Dr. Carolyn Runowicz, Director of the Carole and Ray Neag Comprehensive Cancer Center, mentioned that approval from NCAB is needed in order to move forward with implementation, although the recommendations were presented at the November 2009 meeting. Dr. Paulette Gray, Division of Extramural Activities, commented that the report will go to NCAB in June 2010 for their acceptance. Once NCAB accepts the report (not approves), NCI staff can move forward with finalizing the implementation plan.

Ms. Roach commented that, from the patient perspective, she is worried that the efforts of the OEWG are only tampering with a broken clinical trial system. One of the issues with clinical research is that investigator-initiated trials at Cancer Centers operate in a silo and do not contribute to the larger body of clinical trial evidence that will ultimately benefit patients. Dr. Doroshow interjected that incentives are needed for investigators to work across the entire clinical trial system and that this issue would be discussed in more detail later in the meeting.

V. NCI CANCER HUMAN BIOBANK (caHUB)—DR. CAROLYN COMPTON

Dr. Carolyn Compton, Director, Office of Biorepositories and Biospecimen Research (OBBR), discussed NCI's new biospecimen support service for translational research: the NCI Human Cancer Biobank.

Background. In 2006, OBBR initiated the Biospecimen Research Network (BRN) to: bridge the gap between existing clinical practice using biospecimens and emerging technologies for personalized diagnostics and therapies; define the most significant variables for prospective collection of tissues, blood, and bodily fluids; and develop evidence-based biospecimen quality indicators for specific analytical platforms. By communicating the results of this research to the scientific community, the BRN aimed to significantly improve the quality of NCI-funded biospecimen-based research.

The consensus of the broad scientific community is that the lack of high-quality, clinically annotated human specimens has become the limiting factor for translational cancer research. In a first step to address this issue and create guidelines for the biobanking community, *NCI Best Practices for Biospecimen Resources* was published in June 2007. These practices unify policies and procedures for NCI-supported biospecimen resources for cancer research; however, they lack regulatory authority. The practices were recently updated this year and will be released in electronic format in April (http://biospecimens.cancer.gov).

caHUB. NCI capitalized on the resources provided by BRN and its *Best Practices* when developing the caHUB initiative to address the critical and problematic shortage of high-quality, well-documented biospecimens for cancer research. caHUB is a national, standardized human biospecimen resource that will serve as a continuous and reliable source of human biospecimens and associated data for the broader cancer community, including basic and clinical researchers and the biotechnology and pharmaceutical industries that rely on biospecimens for cancer diagnostics and drug development.

caHUB will be a nonprofit public resource run in a centralized manner to ensure efficiency. Sixty million dollars in ARRA funds were awarded to NCI to initiate this project. Surveys, interviews, focus groups, and user workshops were conducted to confirm that caHUB is a resource that is truly needed by the cancer research community. Surveys of NCI investigators revealed that the overwhelming majority of investigators used specimens from their own institutions and patients—there was little sharing across Centers and Institutes. NCI-funded investigators were also unsatisfied with the quantity and quality of the specimens they used for research; in fact, 50 percent of investigators said that it was difficult to very difficult to acquire either the number of specimens they needed or the quality of specimens they could trust. Interviews with senior academic decision makers revealed that these individuals were also enthusiastic about the prospect of a national biobank; they felt such a resource would standardize studies between laboratories and accelerate progress. Overall, all potential stakeholders, including the pharmaceutical industry, showed enthusiasm for a standardized national biobank.

It is expected that caHUB will be fully functional and collecting biospecimens by the end of 2010. Plans are currently being developed for execution of a public-private partnership, which will serve as the business model for caHUB after its pilot phase when it is in full operation, with maturation of biospecimen sets and data designed by continual feedback from the cancer research community. An example of the research support services caHUB will provide is a collaboration with CTEP and the Investigational Drug Steering Committee. CTEP conducts its own Phase II clinical trials with industry and is interested in utilizing caHUB to collect biospecimens in a standardized manner for each of its trials. Biospecimen collection kits will be created that are linked to specific trials. When an appropriate patient for a CTEP-supported trial is identified, the kit will be deployed to the patient location and specimens will be collected and then sent to caHUB for centralized pathology verification and quality control analysis. This collaboration is planned to be put in place in September 2010.

Dr. Compton described the vision and expectations for the benefits that caHUB will bring to the community. It is expected that research will be made more efficient by increasing the quality of biospecimens and thus decreasing time delays due to repeating experiments, as well as by leveraging the

resources of the caHUB infrastructure. Standardized biobanking practices could lead to a general improvement in quality and more efficient product and regulatory approvals, as well as technology development and clinical implementation. The thought is that providing this type of infrastructure will be as, if not more, beneficial to the community than directly providing commodities such as specimens and data.

Questions and Discussion

Dr. Abbruzzese questioned how willing the average patient or surgeon will be to participate in the caHUB effort. Dr. Compton explained that the process will be incentivized—payment can be provided to institutions for participation—and the buy-in of the institutional leadership and staff will be essential. The process of collecting specimens and data will be contractual; there will be timelines, deliverables, and sets of standards that must be followed. She also commented that, so far, the pathology and surgical staff from institutions that will potentially be participating in the effort are enthusiastic about the process. Patient participation will be entirely voluntary. It will be an opportunity for patients to contribute in an important way to the research enterprise.

Dr Abbruzzese also asked if there is a requirement on the size of the provider contracting with caHUB. Dr. Compton said the only requirement is that participants be Commission on Cancer (COC) approved. COC is the accreditation body for cancer centers across the country that monitors centers according to standards of care delivery.

Dr. Abbruzzese commented that there might be difficulties in acquiring biospecimens of metastatic disease for caHUB in terms of cost, technique, and the actual acquisition of a large enough amount of specimen to process. Dr. Compton stated that it is written into the request for proposals (RFP) language that tissue providers must be committed to providing follow-up data on patients (e.g., if a patient returns to the institution with operable recurrent disease, specimens from those surgeries would also be banked). Rapid autopsy sites can provide metastatic tumor specimens, along with primary tumor specimens in some instances. In those cases in which the patient donor has been diagnosed in late stage and elected to forgo treatment before death, access to untreated primary and metastatic disease specimens is possible.

Dr. Joel Tepper, Hector MacLean Distinguished Professor of Cancer Research, Lineberger Comprehensive Cancer Center, University of North Carolina, asked about the criteria for access to banked biospecimens—there is a possibility that high-quality, in-demand sample sets could diminish quickly. Dr. Compton stated that an access policy is in development and a workshop may be required to address the caHUB access policy. Additional workshops on intellectual property policy and return of results policy are already planned.

Dr. Scott Lippman, Professor and Chair, The University of Texas M.D. Anderson Cancer Center, questioned how follow-up annotated clinical data would be collected for premalignant biospecimens. Dr. Compton responded that they are not sure how these data will be collected until responses to the RFP are received—potential tissue providers must address this issue in response to the RFP.

Dr. Kenneth Cowan, Director, Eppley Cancer Center, University of Nebraska Medical Center, asked how many biospecimens are expected to be collected after the 2-year pilot phase period. Dr. Compton said that with $60 million in ARRA funding, it is expected that about 3,000 cases will be collected. A case includes a full specimen set—tumor tissue, adjacent normal tissue, tissue from before and after surgery, blood specimens, urine specimens, and multiple aliquots from the same sample.

Dr. Mitchell Schnall, Matthew J. Wilson Professor, University of Pennsylvania Medical Center, asked whether correlative imaging study data will also be collected and made available through caHUB. Dr. Compton confirmed that other clinical data will also be collected, including data on how the biospecimen was collected, processed, and stored, and data on all quality control and imaging procedures for the specimen.

VI. COMPARATIVE EFFECTIVENESS RESEARCH (CER): AN UPDATE ON FUNDING AND A FUTURE VISION FOR CER AND CANCER—DR. ROBERT CROYLE

Dr. Robert Croyle, Director of the Division of Cancer Control and Population Sciences, NCI, discussed the NIH strategy for allocating ARRA funds to CER. Prior to ARRA, there was less interest in comparative effectiveness and that varied across the different Institutes and agencies. Dr. Croyle noted several individuals who have been working on liaison activities with the Agency for Healthcare Research and Quality (AHRQ) and the Centers for Disease Control and Prevention (CDC), including Dr. Bryce Reeve, NCI, the lead psychometrician and outcomes researcher; Dr. Andrew Freedman, NCI, the lead pharmacoepidemiologist; Dr. Martin Brown, NCI, the lead health economist; and Muin Khoury, Director of the Office of Public Health Genomics at CDC, who is collaborating with NCI. While NCI and the cancer community have a long history of activity in CER, other Institutes and disease domains have been less active in this area of research. It is not unusual in cancer trials to compare one treatment with another. However, other disease domains are largely limited to placebo-controlled trials, do not focus on patterns-of-care studies, and do not have surveillance systems or cancer-center-like programs to match those of the cancer research community. Consequently, a smaller Institute that is just developing clinical trial networks is in a very different place when approaching CER compared with an Institute like NCI or the National Heart, Lung and Blood Institute (NHLBI). This discrepancy is a major challenge in implementing an NIH-wide approach to CER. The goal for NCI is to work with other agencies and CER investigators to make sure that cancer research remains a focus. One concern raised by many professional organizations and advocacy groups is how NCI and NIH will engage with other agencies, especially AHRQ, which has significantly increased its CER activity as a result of ARRA funding.

There are many definitions of CER. The operating definition that NIH, AHRQ, CDC, and other agencies are required to use when making decisions about stimulus funds focuses on comparing benefits, harms, and patient-reported outcomes in a real-world setting. The emphasis is on measuring a comprehensive array of outcomes, including not only drug-based outcomes, but also prevention, diagnostic testing, and behavioral intervention outcomes. CER should include development, expansion, and use of a variety of data sources and methods. Dr. Croyle commented that data sources became an issue of contention among NIH Institutes because some started with very different, or in some cases nonexistent, CER infrastructures in place, and CER funding across Institutes varies depending on that infrastructure.

The terminology for CER has changed slightly in the modified Senate bill for healthcare reform, but the meaning remains the same—the terms CER and patient-centered outcomes research are being used interchangeably. The lead healthcare reform bill now requires the creation of a new, nongovernmental organizational entity called the Patient-Centered Outcomes Research Institute. Many organizations have been involved in making recommendations for CER strategies, including the American Society of Clinical Oncology (ASCO), the American Association for Cancer Research (AACR), the Personalized Medicine Coalition, and Friends of Cancer Research. The basic message is that the oncology domain, especially as it relates to molecular oncology, should take care not to engage a one-size-fits-all approach given the promise of targeted and personalized therapies. Several types of CER are

supported by NIH, including clinical trials, observational studies and modeling, and secondary data analysis using registries and linked databases.

Even though many of the healthcare reform bills have given a leadership role to the AHRQ, NIH has supported CER for years. NIH is the largest funder of CER, although support is not equal across all disease domains. In the case of NCI, much expertise comes from Cooperative Groups, Community Clinical Oncology Programs (CCOPs), and various research networks. One topic of much discussion is the degree to which evidence, generated through CER, becomes a barrier to implementation of new medicine and therapies. Congress has stated that evidence gained in research funded by stimulus dollars through this initiative should not guide payment decisions. The June 2009 Institute of Medicine CER report played an important role in setting priorities for ARRA funds. This report listed 100 national priorities for CER; provided testimonials from advocacy, industry, and other groups; and guided U.S. Department of Health and Human Services (HHS) CER funding decisions. It provided a guide for NIH to allocate ARRA funding to top research priorities and fund a number of topic areas and disease domains that were not previously funded. In subsequent funding rounds, more targeted efforts have been made to fund rarer disease domains that were not initially funded by CER money.

Examples of CER priorities in cancer care include: comparisons of management strategies for localized prostate cancer in terms of survival, recurrence, side effects, quality of life, and costs; comparisons of imaging technologies in diagnosing, staging, and monitoring patients with cancer, including PET, MRI, and CT; and comparisons of genetic and biomarker testing with usual care in preventing and treating breast, colorectal, prostate, lung, and ovarian cancers, and possibly other conditions.

The IOM provided other recommendations for long-term investment, which NIH used to guide funding. These included ensuring meaningful consumer, patient, and caregiver participation; building robust information systems and research methods; developing and supporting a highly skilled CER workforce; and supporting efforts to translate CER knowledge into everyday clinical practice.

The ARRA legislation split funds for CER across three key entities: NIH, AHRQ, and the HHS Office of the Secretary. Money allocated to the Office of the Secretary was allocated largely through AHRQ for healthcare information technology infrastructure and dissemination, translation, and implementation efforts. Of the funds NIH allocated in FY2009, (85 percent, or $341 million), NCI received approximately 20 percent, or $72 million. In the first round of funding, money was primarily allocated to grants that were already submitted and met the criteria for CER, but were outside the Institute paylines. Funding was distributed as Challenge grants, competitive revisions, administrative supplements and Grand Opportunity (GO) grants. There were specific GO grant announcements for generalized CER and CER focused on genomic and personalized medicine. These are 2-year ARRA-funded projects, which include development of the CER infrastructure, development of multidisciplinary teams, proof-of-principle studies, communication between health economists and clinical trial researchers and population scientists, and development of health services and outcomes research. Other GO grants funded by ARRA focus on prevention, screening, and treatment. Overall, NCI fared well in terms of receiving NIH funds to support larger supplements; this is because cancer research has a larger infrastructure and more support compared with other research. The smaller supplements went to fund proof-of-principle and pilot projects in other Institutes. There are also funding announcements to develop new mechanisms for scientific training. In order to increase CER, more people with this expertise will be needed. There is a targeted effort to develop methodologies such as modeling, statistical techniques, outcome measurement, and clinical trial design. There are also broader initiatives focused on behavioral economics.

AHRQ has spent most of its ARRA appropriation to fund expansion and enhancement of its existing research networks. AHRQ has not received any direct appropriation in the last several years; the

Agency's activities have been funded by the Office of the Secretary using evaluation set-aside dollars. This situation resulted from controversies associated with evidence review and guideline development. Currently, AHRQ's only guideline domain is the Preventive Services Task Force. The evolution of evidence review processes will depend on the outcomes of healthcare reform.

Additional efforts to conduct and support CER focus on surveillance and outcome data. The goal is to determine how to enhance or modify the Surveillance, Epidemiology and End Results (SEER) Medicare database to enable people to do more CER; because secondary analysis is a key tool in complementing randomized controlled trial (RCT) evidence. NCI has been working with other agencies to link the SEER registry data with Medicare claims and patient survey data as a proof-of-principle study to determine what future national databases might look like. The linked data can be used for a number of analyses that span the course of cancer control activities, such as diagnosis, treatment, survivorship, second recurrence, and terminal care. NCI also supports the Cancer Intervention and Surveillance Modeling Network (CISNET) modeling network. Studies conducted through this network offer a substantial benefit because they are inexpensive but can be incredibly valuable in terms of understanding cancer trends, incidence, and mortality. They also contribute to cancer knowledge on a national level in terms of cancer control planning and effective strategies for reducing mortality at the population level.

NCI also supports the HMO Cancer Research Network (HMORN), which consists of 14 healthcare systems such as Kaiser, Partners Healthcare, and Group Health Cooperative. Recently, other Institutes have become involved with HMORN; for example, NHLBI. As a result of NIH support, this network, which originally focused on health services research, has been refocusing on the CER agenda. Part of NCI's CER agenda with HMORN includes national physician surveys, asking clinicians, "What do you do?" and "Why are you doing it?" This is an effort to understand different medical practices, especially for physicians outside the research domain; it is a study of physicians' attitudes and approaches towards cancer care and a means to evaluate what kind of care is being delivered and why. These projects complement other NCI surveillance projects, such as electronic medical record systems and cancer registries.

NCI supports the Breast Cancer Surveillance Consortium, and has developed new plans for monitoring cancer screening at a national level. One example is using mammography data to understand what happens to patients after mammography; a national mammography database can be leveraged by many investigators for research purposes. NCI also supports the CanCORS project, a prospective, observational, outcomes research project on lung and colon cancer. The goal of this study is to better understand care delivery, variations in quality of care, and reasons for variations in care.

NIH has been engaged in the personalized medicine debate to determine how personalized medicine interfaces with CER. NIH is working with other agencies, such as FDA, AHRQ, and CDC, to implement this interface. Currently, there is only a small investment in this domain, so it is important to get the research community engaged in understanding what is working and what is not working in terms of dissemination and implementation of personalized medicine into healthcare. This includes workforce development, which is often overlooked.

Although support and reimbursements are needed for new efficacious interventions, there is also a need to determine a mechanism for reducing healthcare costs. One strategy is to work with the community in an evidence-based manner to eliminate practices that are driving up costs. Organizations, scientists, and policy makers are just beginning to understand how to interface CER with personalized medicine. CER will require working in a variety of settings and populations, with emphasis on underserved and minority populations, developing data networks via electronic medical records and creating data links between private and public entities. The challenge for NIH will be how its research agenda and priorities will reflect and inform implementation of healthcare reform.

Questions and Discussion

Dr. Lippman asked how to better communicate with and educate the public, Congress, and primary care physicians concerning the various levels of CER evidence so that when practice guidelines are published or suggestions are made based on evidence-based medicine, support for CER is not withdrawn. Dr. Croyle responded that one provision in the stimulus bill is to enhance the model for practitioner and public engagement. Both NCI and AHRQ are making efforts to increase this interface in terms of CER implementation. Dr. Lippman added that many of the guidelines are not based on evidence; they are implemented because they are considered the "right thing to do." The challenge will be to overcome these beliefs. Efforts put into these types of studies will not be meaningful if the evidence cannot be translated into evidence-based guidelines. Dr. Croyle commented that the cancer domain has some influential sources such as the National Cancer Coalition and ASCO, which support guideline development. Other Institutes employ different agencies or consensus groups. There are a number of upcoming workshops, both cancer specific and NIH-wide, that are devoted entirely to the process of evidence synthesis and review. It will be important for NCI to more strongly support systematic development of the evidence review processes in terms of both the sociological and quantitative empirical aspects.

Dr. Parkinson commented that the presentation posed largely international questions, as well as issues not just of comparative effectiveness but absolute effectiveness. He felt that in some of the attempts to address these issues, like AHRQ guidelines or workshops, inappropriate people have been contributing to the decision-making process. He asked whether NIH shares information on an international level since these technologies transcend national lines. Dr. Croyle responded that in the observational data domain, NCI supports international work and funds investigators in international consortia. However, one challenge has been integrating evidence across studies with different designs and criteria. NCI representatives have met with leadership from other countries to discuss barriers and policies that prevent NIH from taking a more proactive, systematic approach to integrating RCT and other types of evidence on an international level.

VII. SEER: ANNUAL REPORT TO THE NATION—DR. BRENDA K. EDWARDS

Dr. Brenda K. Edwards, Associate Director, Surveillance Research Program, NCI, presented data from the SEER Program's 2009 *Annual Report to the Nation*. It is important to track and measure the population impacts of cancers—to know who is affected, what happens when they are diagnosed, and the progress being made to reduce cancer incidence and mortality. The SEER Program has been an ongoing program in NCI for over 30 years. Its focus is on all cancers, rare and common, and all populations, with a special focus on capturing data on populations by race and ethnicity. These data are used in many epidemiologic studies to help look at unusual patterns and etiology. Recently, the data have been used for planning and evaluation of public health and medical care. SEER releases its data as a public research file, which is accessed by more than 2,000 users every year. More than 6,000 publications have been developed using these data.

Cancer monitoring programs are diverse, diffuse, and distributed. To address this issue, several partners, public and private, united in 1998 to create the *Annual Report to the Nation*. The key players include NCI, CDC, the American Cancer Society, and the North American Association of Central Cancer Registries (NAACCR). The latter organization has been in existence for over 20 years and has helped NCI and other agencies promote data standardization and quality, analyze pooled data, unify the population-based registries, and connect hospital-based facilities that are typically identified through the

American College of Surgeons Commission on Cancer. The *Report* contains the latest data on incidence (new cancer cases) and mortality. In addition to updating the usual statistics, the group also tries to focus every year on a particular topic of interest, such as tobacco control and lung cancer. The group also focuses on population groups such as the aging, as well as on general topics like cancer control and survival.

The 2009 *Report,* issued in December, showed a nearly 1 percent decline per year in cancer incidence over the period from 1999 to 2006. Death rates continued to decline at about 1.6 percent per year over the period from 2001 to 2006, with declines in 10 out of the top 15 cancer sites in both men and women. Although some have criticized the *Report* for using old data, this is the best information available for the United States. NCI statisticians work with the American Cancer Society to generate data and develop statistical models for projecting future total U.S. estimates for new cancer cases and deaths; the 2009 estimates are 1,479,350 cases and 562,340 deaths, respectively.

When considering new sources of population data, the SEER Program is used as a benchmark; any new cancer registry must be both complete and current enough to be included in pooled analyses. At the inception of SEER in the 1970s, there was no legislation making cancer a reportable disease in all 50 states and the District of Columbia that currently exists today, but there were a limited number of states with laws and several population-based systems with community and academic support. The SEER Program covers about 10 percent of the population, with over 30 years of data and 26 percent of the population covered since 2000; some population groups are oversampled. The coverage for population-based cancer incidence has improved vastly over the decades due to better legislation for cancer reporting and Federal legislation that enables CDC to fund state registries within departments of health. SEER incidence data plus data from high-quality CDC registries are pooled by the NAACCR and made available for the *Report.* There are data for approximately 85 percent of the population for the past 5 years, and 10-year data that cover about 70 percent of the population. There are differences, however, between the pooled data and SEER data in terms of estimates for incidence due to differential cancer rates within population groups and quality requirements for inclusion in the pooled data.

The *Report* focuses on new cases or incidence by gender, and mortality for the top 15 cancer sites. While there has been almost a 1 percent yearly decline, this has not occurred uniformly throughout the reporting period. Also, incidence has been increasing for some cancers, such as kidney cancer, although mortality is decreasing. Similarly, incidence rates for thyroid cancer are going up dramatically, especially in women, but death rates for women are not increasing. There are several cancers, such as pancreatic and liver cancers, where incidence and mortality have been increasing; pancreatic cancer is, in fact, the fourth most common cause of cancer death in the U.S. Dr. Edwards noted that when one looks at the cancer patterns by population groups, there is a wide range of incidence and death rates, with whites and blacks having higher overall rates than Hispanics, Asians, and Pacific Islanders or Native Americans.

Lung cancer is the leading cancer in men and women. Black men have a significantly higher incidence and mortality rate from lung cancer compared with all other groups, although these rates have been decreasing for all groups. For women, who took up smoking later than men, incidence continues to increase. There has begun to be a plateau in lung cancer death rates for most women. Some sectors of American Indian/Alaska Native populations have high smoking rates and their mortality continues to rise.

Breast cancer is the leading cancer diagnosed in women. Early on, death rates for breast cancer were relatively similar between black and white women; however, over time, as rates decrease, a disparity is developing, and black women now have a substantially higher mortality rate. Prostate cancer is the leading cancer in men. The pattern of incidence has been highly variable, with some rapid increases and some declines. This is likely due to the discovery of clinical identifiers used for diagnosis and screening, such as prostate-specific antigen (PSA), improvements in early detection, and concerns about

overdiagnosis. Although the rates are very different across population groups, they are decreasing. Liver is one cancer site that is increasing among all population groups. Incidence and mortality in cervical cancer have greatly decreased over time in all populations; however, there is still a large disparity in rates, with Hispanic women having the highest incidence rate and black women having the highest mortality rate compared with other groups.

While the *Report* provides data for all cancers, the focus in 2009 was colorectal cancer, which is the second leading cause of cancer death in the United States and the third most commonly diagnosed cancer in men and women. Again, although incidence and death rates are declining overall, there is a growing disparity in terms of mortality between the black population and the white population. It will be important to better understand what is driving these patterns. SEER also collects information on cancer staging. This is a challenging task, as staging criteria can change over time. Overall, there is a decrease in incidence in localized, regional, and distant disease. The SEER database also provides estimates of survival, which has increased within each of the stages for colorectal cancer.

One goal for the annual *Report* was to determine whether these colorectal cancer rates could be explained. Analysis from CISNET has provided a working model, called the MISCAN-Colon model, or Micro-Stimulation Modeling Projections of Colorectal Cancer Rates, which is being used as a tool to interpret changes in risk factors, screening, and treatment that affect colorectal cancer rates. It is clear that screening and treatment are working; however, there are some factors that actually increase the risk of colorectal cancer. The goal is to use the CISNET model to better understand the contribution of these components to trends that are affecting colorectal cancer at the macro level. So far, CISNET researchers have found that over half of the reduction in mortality is attributed to screening; about one-third, to risk factor change over time; and about 12 percent, to treatment. The model also predicted that declines in mortality could be accelerated if all three contributory components were pushed forward. The hypothesis is that there could potentially be a 50 percent reduction in colorectal cancer death rates by 2020 compared with 2000.

One of the challenges of the SEER Program is capturing data on comorbidity, recurrence, prognosis, biospecimens, medical management, and delivery of care. These data are retrieved from medical records within facilities. Currently, efforts are being made to auto-populate SEER data from electronic medical records; one method is linking SEER with the Medicare database. It is important that the focus of the program stay grounded in understanding not just the population in general, but populations defined by race, ethnicity, geography, or other attributes.

Dr. Edwards posed the question of how NCI can provide data in a way that is more meaningful to researchers and the work that they are doing. She also suggested that it would be valuable to compare data from biospecimen facilities with population-based or cancer registries to determine population trends and representativeness. Additionally, Dr. Edwards challenged the members to think about the best ways to go about putting the data together from the perspective of whether there should be more focus on details, more focus on broad generalities, or, again, focus on the sources of the data.

Questions and Discussion

Dr. Peter Adamson, Chief, Clinical Pharmacology and Therapeutics, Children's Hospital of Philadelphia, commented that decreases in mortality are almost less than decreases in incidence. He asked if it can be determined, by looking at the data, how much is solely driven by changes in incidence versus improvements or lack of improvements in treatment. Dr. Edwards replied that when you are examining risk factors, you are also looking at what drives incidence and mortality. Screening is also a factor,

because it can change the pool of people who will have a cancer diagnosis. Ultimately, all three factors are used in the prediction models.

Dr. Curt Civin, Director, Center for Stem Cell Biology and Regenerative Medicine, University of Maryland School of Medicine, asked if it would be helpful to determine what the limits of risk and screening are for impacting incidence and mortality. For example, what would be the outcome if smoking were eliminated [as a factor] from lung cancer? Dr. Edwards replied that CISNET has a group focused on lung cancer and is working to determine the impact of smoking rates, as well as policies on smoking, on lung cancer rates. There are also CISNET grantees that focus on breast and prostate cancer.

Ms. Roach commented that there is information on decreasing colorectal cancer mortality on http://coveryourbutt.org/, which urges Congress to pass legislation mandating a national screening program. She added that incidence of colorectal cancer is increasing in people under age 50. This has huge implications for screening guidelines. She asked how information from this *Report* is transmitted to committees that develop and implement national guidelines that can impact patients. Dr. Edwards replied that there is no clear process. These data have been published before, and some publications have recommended that the screening age limits be lowered. Data from SEER and researchers such as the CISNET groups have contributed to evidence-based reviews when invited.

Dr. Edith Perez, Director of the Breast Cancer Program at the Mayo Clinic Foundation, asked what accounts for the marked long-term impact of changes in risk factors on decreased incidence and mortality, given that negative risk factors such as obesity, consumption of red meat, and physical activity are getting worse. Dr. Edwards replied that reduced smoking is likely the most important factor in driving the long-term pattern changes for several cancers, including colorectal cancer. The second most important factor is a growing interest in diet. One of the points of the *Report* was to demonstrate that changes in risk factors can have an impact on cancer death rates many years after they occur.

Dr. Lippman commented that a multipronged approach is needed to control cancer—risk reduction, better screening and treatments, and prevention and early detection are all major driving factors. The colon cancer data focus only on one organ site, but are suggestive nonetheless.

VIII. CTWG INFORMATICS INITIATIVE IMPLEMENTATION UPDATE—DR. JAMES DOROSHOW AND MR. JOHN SPEAKMAN

Dr. Doroshow discussed the Clinical Trials Working Group (CTWG) initiative to establish a comprehensive electronic database for clinical trials.

Of the 50,000 patients per year accrued to treatment trials in NCI-designated Cancer Centers, at least 20,000 of those patients are not entered into any electronic database. Institution-supported investigator-initiated trials, as well as studies supported by R01s, R21s, SPOREs, and P01s, are all still reported and monitored using paper forms. The lack of a comprehensive electronic database makes it very difficult for NCI staff and investigators to identify long-term toxicity trends, monitor trial accrual, identify gaps and duplicative studies, and prioritize trials on a national basis. In response to this issue, the CTWG created the initiative to establish a comprehensive electronic database containing regularly updated information on all NCI-funded clinical trials.

In 2007, the Food and Drug Administration Amendments Act (FDAAA) was signed into law, establishing additional regulations for clinical trials. The FDAAA requires registration of all applicable trials (Phase II and III) with ClinicalTrials.gov, with penalties for nonregistration, including large fines

and withdrawal of NIH funding. The Act also has substantive outcomes reporting requirements, and as of January 2010, it is NIH policy that Institutes are no longer permitted to register trials on behalf of responsible parties (e.g., via Physician's Data Query [PDQ]). Although the CTWG electronic database initiative was proposed before the passage of FDAAA, efforts are under way to ensure that the database complements this legislation on national NCI-supported clinical trial activities.

NCI's new Clinical Trials Reporting Program (CTRP) abstracts information from trial protocols and returns a data file to institutions for independent validation and submission to ClinicalTrials.gov. This should ease the burden of the FDAAA requirements on trial sites while adhering to the NIH policy. Additionally, the data file can be used by institutions to generate their annual Cancer Center Summary 4 table for submission to the NCI Cancer Centers Program. The CTRP is working to make its software interoperable with commercial clinical trial management systems and with systems developed in-house by Cancer Centers.

CTRP's electronic portal will meet NCI's and the cancer research community's current and future reporting needs. In addition to basic search capability for protocol information, there will be a complete listing of all NCI-supported clinical trials, accrual data, and patient-level demographic data. Plans are also in place to eventually include patient-level outcome data. In contrast, ClinicalTrials.gov only allows for basic search of protocol information. In terms of reporting requirements for CTRP, there will be no changes for Cooperative Group and Investigational Drug trials (N01, U01). Other NCI-funded grants (P01, R21, R01, Specialized Programs of Research Excellence [SPOREs], etc.) and institutional investigator-initiated and industry trials will now have to register and share accrual data. NCI will be working with the extramural community to develop business plans for the reporting of patient-level demographics and outcome data on these trials.

Pilot implementation of the new CTRP began in 2009 with registration of trials at NCI-designated Cancer Centers; attempts are currently being made to begin to collect accrual information. The pilot phase started with a group of five early-adopter Cancer Centers. It was noted that NCI has budgeted funds to support implementation of the database at all Cancer Centers. Starting in the second quarter of FY 2010, grantees other than NCI-designated Cancer Centers will be able to register existing interventional trials.

Mr. John Speakman, Associate Director of Clinical Trials Products and Programs at NCI's Center for Biomedical Informatics and Information Technology (CBIIT), discussed related CTWG informatics initiatives.

The goal of CTWG's systems interoperability and harmonization initiative is to develop an infrastructure that enables interoperability within NCI and then devise a strategy to take it beyond the Institute. The long-term goal is for all clinical trials sites either to use the caBIG architecture or develop interfaces and other required enhancements such that their IT architecture is fully interoperable with the caBIG standards-based architecture. NCI Divisions, Programs, Centers, and Offices engaged in clinical trials activities (e.g., CTEP, Division of Cancer Prevention [DCP], Office of Communication and Education [OCE]) are assembling integration plans to achieve this goal.

Another informatics initiative of the CTWG is the development of standardized case report forms (CRFs). A library of CRF modules that can be assembled into case report forms is being developed and should reduce the cost, time, and effort of the production of CRFs. The use of common data elements will standardize data capture and cross-trial analysis, maximize the capture of critically important data, and provide for a simpler regulatory review. This initiative leverages past and current NCI work and experience regarding what does and does not secure adoption of standardized elements. Efforts are being made to ensure that the modules are harmonized with industry by including elements and standards set forth by the Clinical Data Acquisition Standards Harmonization (CDASH) initiative of the Clinical Data

Interchange Standards Consortium. The first completed CRF module is the demography module. Other modules will include adverse events, medical history, physical exam, participant identification, registration, enrollment, and protocol deviations. A key point is that community adoption will be essential for success of these standardized data elements.

The fourth CTWG informatics initiative is the development of a credentialing system for investigators and sites. A credential repository would eliminate the need to reestablish credentials each time a trial is initiated (or annually in the case of CTEP). It would also facilitate rapid communication of new regulations and changes to the clinical research community and changes in the status of individual investigators and sites to sponsors. To accomplish this initiative, NCI will partner with relevant Federal agencies, professional societies, and trade associations. NCI will also leverage FIREBIRD (Federal Investigator Registry of Biomedical Information Research Data), which automates and centralizes the FDA 1572 Form investigator registration process—a key activity in the regulatory data submission process and compliance requirement for investigators participating in clinical trials. FIREBIRD is a product of the NCI-FDA Interagency Oncology Task Force.

NCI is working towards the procurement of an enterprise-wide clinical data management system (CDMS), which is critical for many of the CTWG informatics initiatives. To date, NCI has purchased licensing rights for a commercial CDMS software product. The software will be made available free of charge to all organizations in the NCI Clinical Research Enterprise (i.e., all nonprofit NCI-supported organizations conducting clinical trials). The CDMS software can be used under license terms for all cancer trials, including industry and investigator-initiated trials. However, the software cannot be used for noncancer trials under the license terms. If an organization wanted to extend the license to allow use in noncancer trials, a business discussion between the organization and the vendor (not involving NCI) would be required. Procurement of the CDMS software was in response to the need expressed by Cooperative Groups for a single remote data entry system with the intent to deliver full-function clinical data management capability to the entire NCI-supported clinical research community, irrespective of ability to pay. The license terms state that the software can be hosted locally or by NCI. It is an unlimited-user, perpetual license that includes onsite installation, administrator training, user training manuals, telephone/e-mail support, and periodic software upgrades. The license terms do not include custom integration with existing/legacy systems or migration of legacy data to the new system. A request for Letters of Intent was sent out in November 2009 and a total of 43 LOIs were received. Full implementation of the CDMS software has been delayed because of vendor protests; however, it is expected that this issue will be resolved judiciously.

Questions and Discussion

Dr. Adamson requested more information on the governance of the CTRP and who will have access to data. Dr. Kenneth Buetow, Director, CBIIT, NCI, responded that data currently available through ClinicalTrials.gov will be made publicly available and that additional discussions can be held to decide whether other types of information should be released.

Dr. Adamson also asked when the CDMS vendor protests would be resolved. Dr. Buetow said that they are in the final stages of resolution and the process should be completed within a few months.

Ms. Roach asked what barriers may be in the way of adoption of the standardized CRFs. Dr. Buetow speculated that the main barrier to adoption is changing existing data capture infrastructure at individual institutions with newly established processes and procedures. Ms. Roach also questioned whether NCI is providing any incentives for adoption of the CRFs. Dr. Doroshow commented that CTEP

has ARRA funds available for a program called ADOPT to specifically assist Cooperative Groups with initiation and integration of the remote data capture system and use of the electronic CRFs.

IX. SCIENTIFIC STEERING COMMITTEE (SSC) ANNUAL UPDATE—DRS. DEBORAH JAFFE AND MARGARET MOONEY

Dr. Deborah Jaffe, Program Director, Coordinating Center for Clinical Trials, NCI, updated the CTAC on the steering committee system and recent activities of the Scientific Steering Committees.

The steering committee system encompasses 3 of the 22 Clinical Trials Working Group initiatives. The Investigational Drug Steering Committee (IDSC) provides strategic input into the clinical development plans for new agents in early-phase clinical trials in the CTEP Investigational Drug Branch. The Symptom Management and Quality of Life Steering Committee (SxQOL) evaluates and prioritizes symptom management interventions and clinical trial concepts conducted through the CCOP mechanism in conjunction with the Division of Cancer Prevention. The Patient Advocate Steering Committee (PASC) develops and shares best practices for patient advocates and interactions across all steering committees.

The nine disease-specific cancer steering committees—Breast Cancer Steering Committee, Gastrointestinal Steering Committee, Genitourinary Steering Committee, Gynecologic Steering Committee, Head and Neck Steering Committee, Leukemia Steering Committee, Lymphoma Steering Committee, Myeloma Steering Committee, and Thoracic Malignancy Steering Committee—prioritize Phase III and large (>100 patients) Phase II concepts conducted by the Cooperative Groups. These steering committees include liaisons from the IDSC and SxQOL steering committees, and liaisons from the planned Clinical Imaging Steering Committee (CISC) will participate in the future.

There are currently four additional steering committees under development. The Clinical Imaging Steering committee (CISC) is under development and will review concepts with primary imaging endpoints and provide a forum for strategic input into imaging activities in clinical trials. Steering committees focused on brain cancer and pediatric cancers (hematologic and solid tumors) will be formed later in 2010.

PASC functions in a slightly different way than the other steering committees: all steering committee advocates on the other steering committees automatically become members of PASC, providing a true forum for information exchange among the advocates across all committees.

Transparency is an important priority of the steering committee system. The membership spans all major components of oncology, including Cooperative Group members, SPORE members, translational scientists, community oncologists, biostatisticians, advocates, and NCI staff.

Three times a year, the Chairs of the Steering Committees get together for a joint conference call. This provides an opportunity for the Chairs to share issues, barriers, and best practices, and update each other on activities.

The CTAC members were given copies of the IDSC and CCCT newsletters, a list of the concepts approved since the SSCs formed, and executive summaries/manuscripts of the clinical trial planning meetings (CTPMs) that have been published based on those meetings.

The steering committee system has been in place for 4 years. In this time, the disease-specific and SxQOL steering committees have prioritized Phase II and III trials conducted by the Cooperative Groups and run CTPMs to identify critical questions, prioritize key strategic plans for future clinical development, and discuss unforeseen implementation and accrual issues.

From 2006 to February 2010, these SSCs approved 55 of 98 concepts; 20 resulted in trials opening. In 2008-2009, approved concepts took a mean of 14-55 days (depending on the steering committee) from the time they entered the Protocol and Information Office (PIO) to final evaluation. When considering the SSCs that evaluated the most concepts (Gynecologic, 28; Gastrointestinal, 24; and SxQOL, 23), the mean time for approval from the time the concept came from the PIO to the time it was approved by the steering committee was 60, 130, and 150 days, respectively. This variation illustrates that more work must be done to meet the 90-day OEWG standard.

Nine CTPMs have been held since the inception of the SSCs. The meetings aim to identify critical questions and unmet needs in a specific cancer, foster innovation and collaboration among clinicians and scientists, and prioritize and develop key strategic priorities for future clinical trials, including developing a consensus on the most important clinical trials to conduct in the near term (6-12 months) and long term (18-36 months). Dr. Jaffe suggested that CTAC might want to consider conducting evaluations of SSCs 1 or 2 years after the planning meetings to assess whether goals and timelines related to the established priorities are being met.

This year, a new meeting series is being initiated in collaboration with the Translational Research Program (TRP). The Organ Site Specific Meetings will be convened with the goals of accelerating clinical and translational research; fostering collaborations across funding mechanisms; and meeting objectives and outcomes aligned with the scientific priorities of the specific organ site.

Dr. Jaffe noted that previous CTAC meetings have included updates and plans from SSC Chairs; she asked CTAC members what would be most useful for them at this time. Possibilities include presentations of approved CTEP or DCP concepts by program officers; presentations of successes and barriers by an extramural representative of an SSC; and written information provided in the board books.

Dr. Margaret Mooney, Branch Chief, Clinical Investigations Branch, Cancer Therapy Evaluation Program, NCI, presented two recently approved Phase III trial concepts that illustrate how the SSCs are prioritizing research and creating opportunities to immediately discuss new and emerging data.

Radiation Therapy Oncology Group (RTOG)-1010: A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2 Overexpressing Esophageal Adenocarcinoma. This trial, led by the Radiation Therapy Oncology Group, is an intergroup effort for evaluating trastuzumab in patients with resectable HER2-overexpressing esophageal adenocarcinoma.

The number of cases of adenocarcinoma of the esophagus has been increasing in the United States, particularly in men; this disease has shifted from a squamous to an adenocarcinoma histology over the past decade. Five-year relative survival rates are very poor, even for local disease. In the United States, the preferred treatment option for Stage II to Stage IVA esophageal cancer patients is surgery, with most patients receiving either pre- or postoperative chemoradiation therapy. Patients who are not candidates for surgical resection receive definitive chemoradiation therapy.

Data presented by the American Society of Clinical Oncology in 2009 indicated that patients with advanced gastric and gastroesophageal junction (GE junction) tumors that overexpressed HER2 showed an overall survival improvement when treated with trastuzumab in addition to chemotherapy. The overall survival benefit was more than 2 months, with an observed hazard ratio of approximately 7.4. In a pilot

study at Brown University, a 3-year survival rate of 47 percent was observed among HER2-overexpressing esophageal adenocarcinoma patients treated with trimodality therapy (trastuzumab, paclitaxel, cisplatin, and radiation therapy, with 1 year of maintenance trastuzumab).

Based on these data, the GE Esophago-Gastric Task Force became interested in use of trastuzumab in the adjuvant setting and a trial design was put forward for consideration. According to the protocol, potentially eligible patients will receive pathological confirmation of HER2 overexpression using either immunohistochemistry or fluorescent in-situ hybridization, and their disease will be staged using both ultrasound and PET CT. Patients in Stage II to IVA with resectable disease, a positive celiac node, and adequate cardiac function will be randomized to either Arm 1 (FOLFOX/radiotherapy followed by surgery) or Arm 2 (FOLFOX/radiotherapy with trastuzumab, followed by surgery and maintenance trastuzumab for 1 year).

It is estimated that 30 percent of esophageal cancer patients overexpress HER2. Thus, a large number of patients with a rare tumor would need to be screened in order to identify an adequate number of appropriate subjects. The current sample size of 148 patients is based on 480 patients being screened over 4 years. The primary endpoint of the trial is disease-free survival. Based on the results observed when trastuzumab was used in the adjuvant setting for breast cancer patients, it is hoped that a substantial survival benefit will be seen in this trial; the study is powered to detect a hazard ratio of approximately 0.56 with a power of 85 percent.

When this study concept was brought to the Gastrointestinal Steering Committee, several concerns were raised. The need for a clear and concise plan for toxicity monitoring was emphasized, particularly given that patients would receive trastuzumab or trastuzumab with chemoradiation therapy in the preoperative setting and then as maintenance. With the relatively small target population, many patients will have to be screened. The Steering Committee asked RTOG to have a plan in place to increase the sample size if the accrual rate and toxicity were found to be acceptable so that the study could be powered to detect a smaller hazard ratio, which could still have clinical significance. Also, eligibility considerations and surgical quality control issues were raised. A strong commitment was both requested and given for complete support across the Cooperative Groups participating in the trial, as well as a clear plan for the biomarker analysis that would be conducted for HER2. A BIQSFP application to support that analysis is in process.

This concept was approved by the Steering Committee on January 20, 2010, 83 days after submission. Roche and GenenTech agreed to RTOG's request for trastuzumab in February, with the final approval letter (clarifying the method of immunohistochemical scoring) received in March.

Cancer and Leukemia Group B (CALGB)-90901: A Randomized Phase III Study of Ixabepilone, Mitoxantrone, and Prednisone Versus Mitoxantrone and Prednisone Alone in Patients With Castration Resistant Prostate Cancer Previously Treated With Docetaxel Chemotherapy.

Dr. Mooney's second example was a study that is looking at a combination of ixabepilone with mitoxantrone and prednisone in castrate-resistant prostate cancer patients previously treated or refractory to docetaxel chemotherapy. Clinical data from early-phase single-agent and combination trials of ixabepilone, as well as a single-arm Phase II study, suggested a significant PSA decline and a promising objective response rate; although the regimen had toxicities, it was reasonably well tolerated.

Phase III trials were proposed by both the Southwestern Oncology Group (SWOG) and the CALGB; CALGB's proposal was selected to move forward. This study will involve patients who have metastatic, castrate-resistant prostate cancer and who have previously received and are refractory to docetaxel therapy. The primary endpoint is overall survival, with secondary endpoints of progression-free

survival, post-treatment PSA decline, time to treatment failure, toxicity, health-related quality of life, and correlative studies. The sample size is approximately 700 patients.

When the proposal was submitted to the Genitourinary Steering Committee, however, there were concerns regarding proceeding with a 700-patient randomized Phase III trial based on the single-arm combination study, which included a relatively small number of patients. Other concerns focused on toxicity and whether the PSA decline and response are appropriate measures for evaluation of overall survival. In order to address these concerns, the Steering Committee suggested that CALGB design the study as a Phase II/III, such that the study would proceed to Phase III only if the Phase II results looked particularly promising. The Steering Committee also suggested additional toxicity monitoring and that other information be added in terms of analyzing time to treatment failure.

This proposal was approved by the Steering Committee on August 28, 2009, over 6 months after submission. Both the drug commitment and the final CTEP approval were received in December. The approval process took a little longer than the RTOG proposal because both SWOG and CALGB were proposing similar trials and there was no task force in prostate cancer at that time to help with prioritization.

Last Friday, Sanofi-Aventis announced positive results from a Phase III trial in the same patient population using the same combination of standard therapy and one of their agents, cabazitaxel; a 3-month improvement in overall survival was seen. The Principal Investigator of the CALGB study has already contacted the Genitourinary Steering Committee. The Steering Committee will be discussing this at its upcoming meeting and will consider whether the CALGB trial should continue to move forward in light of the results of the Sanofi-Aventis trial.

Questions and Discussion

Dr. Runowicz noted that while the disease sites may differ, the biologic rationale and designs of studies could be applicable to each other. For example, it has been shown in breast cancer that the sequence of treatment is important: chemotherapy followed by radiation yields better results than radiation followed by chemotherapy. However, a study in endometrial cancer—which is biologically and histopathologically similar to breast cancer—is comparing radiation alone to radiation followed by chemotherapy. Is the steering committee process a forum in which some of those lessons could be applied to studies across disease sites and further questions could be considered? Dr. Mooney responded that there is an historical evolution for the way treatments are adopted, not always with the best evidence. It is, however, difficult to know how to translate issues across disease sites. There is certainly a benefit to being aware of different approaches and, when appropriate, making recommendations given the biology. Dr. Tepper agreed; however, it is difficult to design studies and make clinical decisions based on analogy, even though it is useful in thinking about trial design.

Dr. Lippman stated that there is a movement to design studies to detect bigger differences. Small, incremental studies may meet their primary endpoints of a few weeks or months, but they take a long time and do not result in large advances. The RTOG study was powered for a larger difference, but if accrual is good, it might look to a shorter endpoint. Is this the general direction in which research should be going? Dr. Mooney responded that, in all likelihood, the number of patients would go from 148 to only 183, due to the high numbers of patients that need to be screened. The hazard ratio might be lower, but it would still be much more aggressive than in many other studies in adjuvant settings.

Dr. Richard Pazdur, Director, Division of Oncology Drug Products, FDA, suggested opening up the RTOG study to international accrual, perhaps taking advantage of Roche's international presence to increase the chances of accrual success and decrease the time to accrual. Dr. Horning agreed that these studies should reach out to large international communities; she will take that idea to RTOG. There were also general discussions about moving into the early gastric cancer space, because gastric cancer, as the second most common cause of death worldwide, is such a large international problem.

Dr. Horning also noted that this study's hazard ratio is potentially quite remarkable. Roche's ToGA trial, an ongoing Phase III, multicenter study evaluating the efficacy and safety of trastuzumab in patients with HER2-positive advanced gastric cancer, showed that reliability of HER2 testing is important and affects outcomes. When considering sample size, it is critical to have an accurate diagnosis with targeted therapy; this should be considered when thinking about sample size. Dr. Mooney noted that samples would be located in one central laboratory and handling procedures would follow ToGA's example.

On the topic of information useful for CTAC, Dr. Abbruzzese noted that there is tension regarding some decisions that were made without CTAC consultation. For example, at the last CTAC meeting, there was a decision to move forward on the immunologic modifiers translational research pathway, although there were options to examine other pathways first through the Special Translational Research Acceleration Project (STRAP) awards. CTAC members would have liked to have some input in that decision. However, it is likely not practical for CTAC to be involved at that level; perhaps the Committee's role might be to look at the outcomes of the programs—in this case, the SSCs—at a reasonable interval (every 2 or 3 years) and make judgments about outcomes. Dr. Lippman agreed that it is not feasible for the Committee to meet frequently enough to evaluate every proposal; it might be more effective to encourage change in targeted drug development through a more philosophic approach. Ms. Roach noted that CTAC could provide feedback on Steering Committee and Task Force decisions and initiatives. Dr. Adamson added that the role of CTAC should be to consider whether the work being conducted is likely to improve outcomes; unfortunately, there are not many good surrogates to predict what is needed to improve outcomes. Presenting data on PIO, for instance, can be highly misleading, particularly when work is shifting between the Cooperative Groups and the Task Forces. For accurate interpretation, the entire timeline must be considered in context.

Dr. Adamson inquired about the wide range of approval rates (30-80 percent) in the Cooperative Groups and whether there is a correlation between the number of Cooperative Groups with activity in a particular disease area and the chance of success of a proposal in that disease area to the related SSC. Dr. Mooney replied that there is some correlation, likely because collaboration and coordination at the Task Force and Cooperative Group levels is not complete. Several groups working in the same disease area might propose similar ideas. Also, as progress is made in understanding the biology in a disease area, there may be an increase in the number of concepts approved. It is important to look at the different disease areas in context, realizing that there are differences in what is understood about the biology of those diseases. The challenge is to improve correlations between what moves forward and what is eventually approved, such that researchers can rapidly take advantage of insights.

Dr. Adamson noted that the original mission of the SSCs was to help coordinate and incentivize collaboration between Cooperative Groups. The only two metrics available to evaluate progress are timeline and quality; quality is difficult to measure, leaving timeline as the main metric. One interpretation of the SSCs is that they are a back-end fix to a front-end problem—lack of collaboration among the Cooperative Groups. Dr. Abbruzzese responded that part of the mission for the SSCs is to foster collaboration and reduce competition and redundancy in Cooperative Group trials. However, another part of the mission is to prioritize trials, which is painful and time consuming. The metrics being

used to evaluate progress—days to protocol approval, for instance—do not measure the value added with prioritization.

Dr. James Wade, Director of Medical Oncology, Decatur Memorial Hospital Cancer Care Institute, and his colleagues on the SxQOL Steering Committee recently conducted a self-evaluation, looking at the rate at which the Steering Committee approved concepts and comparing it to the approvals from Division of Cancer Control and Population Sciences (DCCPS) staff who were part of the review process. Concepts were also sent to faculty at the University of Rochester, who graded how well the Steering Committee had reviewed them compared with DCCPS. In the end, the Steering Committee and DCCPS results were almost 100 percent congruent, leading members to wonder how much extra time was being added to the process by having concepts go through Steering Committee review. Members also wondered how much the Steering Committee is helping to stimulate the science and change practice; they concluded that they are not yet interacting with the other committees or Cooperative Groups enough to push the science forward.

The SxQOL Steering Committee operates differently than the disease-based SSCs, in part because interaction on symptom management and quality-of-life issues is new. Because the disease-based SSCs have been working together in some manner for many years, an intergroup process is already in place.

It is striking that a large percentage—60 percent—of the approved studies fall into two categories: gynecologic and symptom management. Dr. Horning suggested that it would be beneficial to have metrics that describe the trials that are approved, such as targeted therapy, novel/adapted trial design, and integrated biomarkers, that would be the basis for a scientific merit score. Likewise, the characteristics and context (redundancy, prioritization issues, etc.) of rejected proposals should also be reported. CTAC could examine these metrics, with an eye toward better understanding the disparities in approval rates of the different SSCs.

One of the goals of the steering committee process is to halt trials that are problematic or likely to fail before they are begun. However, this is difficult to measure. Dr. Tepper stated that much of the determination related to the Gastrointestinal Steering Committee is done at the task force level. While formal approval happens in the SC, the task force is responsible for modification of concepts and other issues that help move a trial toward success. Also, the GI Steering Committee has been struggling with the issue of metrics. A subcommittee has been charged with developing reasonable metrics, but thus far it has not been successful.

Dr. Tepper suggested that science be strongly incorporated into the activities of the task forces and SCs. There are members with significant laboratory research being conducted, but they represent only their own areas of expertise; they do not represent the world of science.

Dr. Lippman asked whether CTAC should discuss issues of novel trial design. The need for novel and adapted early-phase designs is frequently mentioned, but many trials being approved use the same or similar designs.

Dr. Doroshow noted that CTEP is making a major effort to increase the number of smaller randomized Phase II trials with biomarker endpoints, which will raise the bar for Phase III trials as well. This policy change has not yet been presented to CTAC.

X. CCCT AND WORKING GROUP UPDATES—DR. SHEILA PRINDIVILLE

Dr. Prindiville discussed the CTWG Evaluation Working Group. The major issue at hand is how all of the changes recommended in the CTWG report will be evaluated. A report was generated a year ago that included baseline feasibility and analysis, as well as a recommended future evaluation system. An experienced evaluation specialist, Dr. Judith Hautala, and her team from the Science Technology Policy Institute (STPI) designed the system. Many of the proposed measures include qualitative and quantitative measures, as well as perceptions of experts and empirical data. This report must be reviewed to determine which of the measures should be included in the final evaluation. While many feasible measures were presented in this report, it is important to clarify which measures are desirable, what needs to be done to assess them, and how often they will be measured.

There are two types of measures: system outcome and system process. System outcome measures address whether the overall output of the NCI clinical trials system is improving. System process measures address whether the individual CTWG initiatives are having the desired effect on the performance of the NCI clinical trials system. The following system outcome measures have been proposed: quality of trials, including publications and strength of trial designs; impact of the trial (e.g., Does the trial guide new therapeutics or diagnostics development or lead to changes in patient management?); efficiency of trial development and initiation; and efficiency of trial conduct (e.g., rate of accrual, trial completion, cost-efficiency). There are 22 CTWG initiatives, with proposed system process measures for each initiative. Many of the measures proposed relate to the disease-specific steering committee processes. Some are empirical measures such as database analysis (e.g., time to initiate trials, collaborations, quality of clinical trials) and others are more qualitative, such as use of an expert panel to assess the quality of the system (e.g., How good are the trials? Are they different from previous trials? Has the clinical trial system improved?) and stakeholder interviews to assess the process and quality (e.g., How well is the process going? Does it take too long? Is the system cumbersome? Is there collaboration with Cooperative Groups?). Although Dr. Adamson and Dr. Daniel Sargent, Director, Cancer Center Statistics, Mayo Clinic Foundation, have previewed the measures, extramural input is needed to determine which of the proposed measures will be included in the final report. A CTWG Evaluation Working Group is being formed to determine which metrics should be used to select the appropriate measures, (e.g., Should a combination of expert quality assessments and interviews be used? Are these all of the measures that are feasible?).

Dr. Prindiville discussed three other working groups, the Guidelines Harmonization Working Group, the Process to Accelerate Translational Science Working Group, and the Cost Effectiveness Analysis (CEA) Working Group. Dr. Abbruzzese chairs the Guidelines Harmonization group. The goal of this group is to harmonize program guidelines and develop incentives to foster collaborations among all components of the clinical trials infrastructure. They ensure that guidelines for different clinical trials funding mechanisms are aligned and help to eliminate redundancy and duplication while encouraging collaboration. The group reviewed last year's initial report and recommendations and will develop updated guidelines and incentive plans by July 2010. The PATS working group is led by Drs. Lynn Matrisian and Kenneth Cowan. The Immune Response Modifier (IRM) Working Group report is an example of an accepted report, which will result in the first STRAP and piloting within the TRWG pathway. One of the goals of the PATS group is to determine how to move ahead with STRAPs for other TRWG pathways. They are also reviewing the immune response modifier pathway experience and assessing alternative approaches for gathering information about translational research opportunities. The CEA Working Group is chaired by Dr. Scott Ramsey. The purpose of this group is to advise CTAC and NCI on the development of a prioritization process and funding mechanism to ensure that the most important cost-effectiveness analyses can be initiated in a timely manner in association with clinical trials.

Dr. Prindiville presented additional CCCT updates. The Clinical Investigator Team Leadership Award was initiated last year to enhance recognition of midlevel clinical investigators at academic institutions who are promoting successful clinical research programs. Eleven awards were made in 2009. Additionally, the Biomarker, Imaging, and Quality of Life Studies Funding Program has been revised to include large Phase II studies. It was mentioned that this program previously supported only Phase III studies.

XI. NEW BUSINESS—DR. JOHN NIEDERHUBER

Dr. Niederhuber told CTAC members that he sees this Committee as an invaluable resource to NCI's clinical research aims. A future research aim that he hopes CTAC members will support is the investigation of infectious disease and its role in the etiology of cancer. On March 14-16, NCI is bringing together a group of individuals who are leaders in the areas of infectious disease, virology, and vaccine development to brainstorm how NCI should proceed in this field of research. Dr. Niederhuber will report back the conclusions of this meeting.

XII. ADJOURNMENT—DR. JOHN NIEDERHUBER

Dr. Niederhuber expressed his gratitude to all of the CTAC members for their participation and input.

There being no further business, the 10th meeting of the CTAC was adjourned at 3:32 p.m. on Wednesday, March 10, 2010.