DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
15th CLINICAL TRIALS AND TRANSLATIONAL RESEARCH
ADVISORY COMMITTEE MEETING

Summary of Meeting

November 9, 2011

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

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
BETHESDA, MARYLAND
Summary of Meeting
November 9, 2011

The 15th meeting of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) was convened on Wednesday, November 9, 2011, at 9:00 a.m. in Conference Room 10, C-Wing, 6th floor, Building 31 on the National Institutes of Health (NIH) main campus in Bethesda, MD. The CTAC Chair, Dr. James L. Abbruzzese, Chairman, Department of Gastrointestinal Medical Oncology, The University of Texas M.D. Anderson Cancer Center, presided. The meeting was adjourned at 3:18 p.m.

Chair
James L. Abbruzzese

CTAC Members
Peter C. Adamson
Susan G. Arbuck (absent)
Monica M. Bertagnolli
Curt I. Civin
Kenneth H. Cowan (absent)
Kevin J. Cullen (absent)
Olivera J. Finn (absent)
Scott M. Lippman
Lisa A. Newman (absent)
David R. Parkinson (absent)
Nancy Roach
Daniel J. Sargent
Mitchell D. Schnall
Peter G. Shields
Joel E. Tepper

***Ad Hoc* Members**
Nancy E. Davidson
J. Phillip Kuebler
Mary S. McCabe
George Sledge (absent)
Gillian Thomas (absent)
Miguel A. Villalona-Calero
George J. Weiner

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

Executive Secretary
Sheila A. Prindiville, NCI

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WEDNESDAY, NOVEMBER 9, 2011

I. CALL TO ORDER AND OPENING REMARKS—DR. JAMES L. ABBRUZZESE

Dr. James Abbruzzese called the 15th CTAC meeting to order. He then welcomed new members to the Committee: Dr. Nancy Davidson, Director, University of Pittsburgh Cancer Institute; Dr. J. Phillip Kuebler, Principal Investigator, Columbus Oncology Associates, Inc.; Ms. Mary McCabe, Director, Cancer Survivorship Program, Memorial Sloan Kettering Cancer Center; Dr. Miguel Villalona-Calero, Professor of Medical Oncology, The Ohio State University; and Dr. George Weiner, Director, Holden Comprehensive Cancer Center. Dr. Abbruzzese mentioned that five additional colleagues are pending appointment to the Committee. He then reviewed the confidentiality and conflict-of-interest practices required of Committee members during their deliberations. He asked CTAC members to review their signed conflict-of-interest statements and submit them to Dr. Sheila A. Prindiville, Director, Coordinating Center for Clinical Trials (CCCT), NCI. Members of the public were invited to submit written comments related to items discussed during the meeting to Dr. Prindiville within 10 days of the meeting. Any written statements by members of the public will be given careful consideration and attention. Dr. Abbruzzese reminded members that the meeting was being videocast by NIH Events Management and that the videocast would be available for review following the meeting at: http://videocast.nih.gov/.

Motion. A motion was made to approve the minutes of the July 13, 2011, CTAC meeting. The motion was seconded, and the minutes were approved unanimously.

II. NCI UPDATE—DR. JAMES H. DOROSHOW

Dr. James Doroshow, Deputy Director, Clinical and Translational Research, NCI, gave an update on the current fiscal situation and programmatic activities at NCI.

Dr. Doroshow discussed the impact of the 1 percent funding cut to the overall NIH budget for fiscal year (FY) 2011. This reduction in funding was reflected by a decrease in R01 grant support—1,106 R01 grants were funded in FY 2011, about 100 less than were funded in FY 2010. The 1 percent reduction in NIH funding also resulted in a 1 to 5 percent cut in funding across all NCI Divisions and Programs. For example, the Division of Cancer Treatment and Diagnosis (DCTD) received a 5 percent reduction in its base budget, translating to a $25 million cut in funding to the Division. There is currently a continuing resolution in place to fund the government through November 18, 2011, which has a 1.5 percent decrease in funding for NIH. It is not yet known how much of a decrease will be allocated for FY 2012 funding. The real concern is what will happen to funding levels in 2013. NCI conducted some planning exercises to determine what will happen if NCI experiences a major reduction (i.e., 20 to 25 percent) in funding in FY 2013. Instead of across-the-board cuts, it is possible that some major programs will have to be eliminated.

Dr. Doroshow went on to discuss current programmatic activities at NCI. The Provocative Questions Initiative, which will be discussed later in greater detail, has about $15 million allocated to the project for grant support. A total of 24 Provocative Questions posed during the nationwide Provocative Questions workshops and from Web site submissions were selected for inclusion in a Funding Opportunity Announcement (FOA) “Research Answers to NCI’s Provocative Questions.” More than 700 letters of intent have been submitted in response to the request for applications (RFA).

President Obama released an Executive Order on October 31, 2011, to reduce prescription drug shortages. Cancer treatments are one category of medicines affected by the drug shortage—data indicate that the use of sterile injectable cancer treatments has increased by about 20 percent over the past five

years, without a corresponding increase in production capacity. The Assistant Secretary for Planning and Evaluation (ASPE) within the Department of Health and Human Services (HHS) released an economic analysis on the drug shortage. An important point raised by this report is that unless there are additional incentives for drug producers, it is going to be difficult to get more injectable generic cancer treatments produced.

NCI leadership has decided to release an NCI-wide announcement for R21 grants. NCI will accept R21 grants on any research subject that any principal investigator (PI) wants to propose, whether it is a clinical trial, a preliminary set of translational studies, etc. It is anticipated that these grants will be reviewed by NCI study sections. This new, unsolicited mechanism to accept R21 grants should help both the clinical trial and translational research communities.

The Clinical Investigator Team Leadership Awards, an initiative called for in the Clinical Trials Working Group (CTWG) report, are focused on recognizing investigators who do not have their own sources of funding. These awards enhance recognition and career development for individuals who make substantive contributions to clinical trials efforts. Thirty-four awards have been made in the three years of the program's existence (FY 2009-2011). The award provides recipients with $50,000 per year for two years. Thirty to 40 applications are received per year from NCI-designated Cancer Centers; however, no one Cancer Center can have more than one individual supported at one time through this grant program. A new funding announcement will be available in January 2012. NCI is developing a process to evaluate the program.

Another initiative that was called for in the CTWG report is the Cancer Trials Support Unit (CTSU) Support for Collaborative Multicenter Phase II Trials. This initiative encourages collaborations and "hand-offs" (bench to bedside and back) between Cooperative Group, Cancer Center, and Specialized Programs of Research Excellence (SPORE) investigators through Steering Committee (SC) discussions on clinical trial concepts. Since its inception a little more than a year ago, four submissions have been received from investigators. Investigators bring ideas for clinical trials or components (e.g., biomarkers) to SCs for input and collaborations. If the proposals are approved by the SCs and the Clinical and Translational Research Operations Committee (CTROC), support for CTSU services for Phase II treatment trials is provided. Under the FY 2012 program announcement, support services available include: regulatory support; Web site document hosting; protocol coordination; patient registration; study coordination; clinical database development; data management and processing; information technology; and capitation. Investigational New Drug (IND) application and statistical support, data safety monitoring, and auditing services are not available through the CTSU. This CTSU support has been particularly useful for the area of rare diseases.

Questions and Discussion

Dr. Abbruzzese asked Dr. Richard Pazdur, Director, Division of Oncology Drug Products, U.S. Food and Drug Administration (FDA), to clarify FDA's response to the drug shortage. Dr. Pazdur explained that the FDA has a separate division that handles drug shortages and that the oncology division is not directly involved. However, Dr. Pazdur has had conversations with those in charge of handling the drug shortage problem. Many of the drugs that are in short supply are not profitable and, therefore, the pharmaceutical companies are not investing a great deal of resources into manufacturing and keeping manufacturing techniques up to a minimum standard. Problems with bacterial contamination would not generally occur with more profitable drugs. Dr. Pazdur expressed his opinion that these issues must be addressed with incentives rather than punitive mechanisms. The FDA recently received additional resources to form a team to investigate the drug shortage issues.

Ms. Nancy Roach, Consumer Advocate, C3: Colorectal Cancer Coalition, asked whether there is any indication that Congress is moving toward a constructive solution for the drug shortage problem. She noted the attention that the advocacy community is paying to this issue and that there does not seem to be any indication of movement.

Dr. Peter Adamson, Chief, Division of Clinical Pharmacology & Therapeutics, The Children's Hospital of Philadelphia, asked Dr. Pazdur whether he has any sense of the possibility of the United States running out of one or more life-saving drugs in the upcoming year. Dr. Pazdur replied that he has no knowledge of any impending disaster. Both the FDA and the pharmaceutical companies manufacturing the drugs in short supply are now in the spotlight to sufficiently address this problem. One short-term solution is earlier notification of drug shortages to allow for foreign outsourcing.

Dr. Doroshow asked how the drug shortage is affecting accrual in the Cooperative Groups and the Cancer Centers. Dr. Adamson responded that it is difficult to quantify the effect of the drug shortage on Children's Oncology Group (COG) trials because they do not track patients who do not enroll on a trial. COG has operational rules in place that they have developed with the Cancer Therapy Evaluation Program (CTEP) that dictate the amount of drug needed to start a patient on a clinical trial protocol; if the drug is not in supply, the patient does not enroll on the trial. COG investigators have heard multiple anecdotal stories of patients not being able to enroll due to short drug supply, but there is no system in place to factually determine the effect the drug shortages are having on accrual. Dr. Monica Bertagnolli, Professor of Surgery, Harvard University, Brigham & Women's Hospital, Dana-Farber Cancer Institute, added that about one-third of Dana-Farber/Harvard Cancer Center active trials are affected by the drug shortage in some way; however, they are also unable to quantify the effect on accrual. Some new studies are not being put through the Institutional Review Board (IRB) due to the fact that drugs needed for the trials are on the short-supply list.

Dr. Villalona-Calero commented that the initial reaction to the drug shortages at The Ohio State University Comprehensive Cancer Center was to prioritize the administration of Taxol® to patients enrolling on a clinical trial. However, in some clinical trials the drug is used in an inoculative setting, and in that case, patients enrolled on a clinical trial cannot be prioritized over patients in a non-curative setting.

Ms. Roach commented that a trial for first-line treatment of metastatic colorectal cancer has been ongoing for some time and is finally close to completion. Unfortunately, they are unable to enroll new patients due to the shortage of 5-fluorouracil (5-FU). Dr. Kuebler added that his Community Clinical Oncology Program (CCOP) closed all gastrointestinal clinical trials in September due to the 5-FU shortage. The trials are now open but their active status is dependent on the drug supply.

Dr. Weiner commented on the concern about protocol violations for a patient enrolled on a trial who is due to receive a drug but does not. The drug shortage could result in confusing trial data if many patients are not receiving drugs as prescribed.

Ms. McCabe questioned whether smaller institutions, particularly minority-serving institutions, might be more affected by the drug shortage than large cancer centers, which have more purchasing power.

Dr. Abbruzzese asked Dr. Doroshow to further explain how NCI will approach large budget cuts: Are there particular programs already slated to be cut? Dr. Doroshow said that no decisions have been made on which programs to cut. Dr. Harold Varmus, Director, NCI, plans to look at every program across NCI and every new RFA and those coming up for competitive renewal to prioritize investments across

programs. One large and traditionally very productive program that will be up for recompetition in 2013 is the Phase I clinical trials program.

Dr. Villalona-Calero asked whether rules of the Clinical Investigator Team Leadership Award program will change to allow more than one investigator at an institution to be supported. Dr. Doroshow commented that this was a strong recommendation when the program was initiated; however, NCI wants the small amount of funding that exists to be available to investigators across the spectrum of institutions, large and small.

Dr. Doroshow clarified that there has not been a formal review of the SPORE program by the Board of Scientific Advisors (BSA). Many interviews related to SPOREs have taken place for an internal program evaluation, which will be presented to the Scientific Program Leaders (SPL).

III. LEGISLATIVE UPDATE—MS. SUSAN W. ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations, NCI, reported on the status of appropriations and gave an update on legislative activities.

FY 2012 Appropriations. FY 2011 ended on September 30, 2011, and FY 2012 began on October 1st; a continuing resolution is currently in place to fund the government through November 18, 2011. The Appropriations Committee typically works on individual appropriations bills May through July with the aim to pass the bills by the end of September; however, this year the Appropriations Committees worked on debt ceiling negotiations during that timeframe, which has delayed progress on all other appropriations processes.

During the Senate appropriations debate, Senator Moran (R-Kansas), offered an amendment to increase NIH funding by $190 million that would be paid for by an across-the-board cut to the rest of the bill. The across-the-board cut made the amendment unacceptable to most Senate members. Senator Moran is proving to be a strong supporter of NIH and NCI. During the appropriations debate in the House, Congressman Rehberg (R-Montana), Chairman of the House Appropriations Subcommittee on Labor, Health and Human Services and Education, introduced a bill that included higher funding levels for NIH than the Senate bill. However, the bill included provisions that prohibited funding for the implementation of health care reform, making it unlikely to be voted on. For the last few years, the Senate and House appropriations bills have been passed through a single omnibus bill. An omnibus bill allows little time for debate on individual issues. This year, the Senate and House leadership were looking for a way to cut the amount of time required to pass all of the appropriations bills while still avoiding a single omnibus bill. Leadership agreed to have the Senate group one to two bills into smaller packages called minibuses. The first minibus, which includes three bills, has been worked on over the past few weeks and is expected to be voted on November 10th. If the minibus passes, it then also needs to be passed in the House and signed by the President. The first minibus will likely include a continuing resolution that will extend government funding through mid-December. There is a second minibus in discussion; work should begin on it on November 10th. It is likely that the Labor-HHS-Education bill will be the last to be worked on.

NCI Interactions with Congress. In late September, the American Association for Cancer Research (AACR) invited members of the Republican Study Committee to hear Dr. Varmus give a presentation on cancer research. Ovarian cancer is a topic of interest to many members of Congress. The Ovarian Cancer National Alliance sponsored a briefing for congressional members and staff at which Dr. Jennifer Loud, Division of Cancer Epidemiology and Genetics (DCEG), NCI, gave a presentation on

ovarian cancer research programs. In October, the International Myeloma Foundation sponsored an event at which Dr. Ola Landgren, Center for Cancer Research, NCI, presented on the topic. Representative Jackie Speier (D-California) gave the opening remarks and participated in the briefing. Representative Speier met with Drs. Helman and Mackall, NIH Clinical Center, in late July to take a tour of the Clinical Center and discuss pediatric clinical trials. Dr. Francis Collins, Director, NIH, also met with the Congresswoman. Senator Moran also visited the Clinical Center and met with Dr. Collins. Additional congressional staff and advocates toured the NIH campus on a visit sponsored by Research!America. These visits serve to strengthen congressional support for NIH.

Legislation of Interest. The Preserving Access to Life Saving Medications Act was introduced by Representatives Diana DeGette (D-Colorado) and Thomas Rooney (R-Florida) in June. The legislation directs FDA to address drug shortages by requiring all drug manufacturers to notify FDA about manufacturing problems or when a drug product will be discontinued, requires FDA to maintain an online list of drugs in shortage situations, and institutes civil monetary penalties for manufacturers who fail to report. DHHS would need to implement evidence-based criteria to identify drugs vulnerable to shortages. The U.S. Government Accountability Office (GAO) is to study the possible causes; DHHS must then report to Congress. The sponsors of the legislation are open to discussion on how to strengthen the bill and have contacted NIH for technical assistance.

In general, there has been a great deal of congressional interest in the drug shortage issue. The House Energy and Commerce Committee held a hearing on the issue in late September; the Assistant Secretary for Health, Dr. Koh, testified and was accompanied by Dr. Kweder from FDA. Senators Bob Casey (D-Pennsylvania), Tom Harkin (D-Iowa), and Richard Blumenthal (D-Connecticut) have called upon the GAO to conduct a study on drug shortages in the United States. Senator Schumer held a press conference calling for the Federal Trade Commission to investigate pharmaceutical distributors for price gouging. Congressman Elijah Cummings, ranking member of the House Oversight and Government Reform Committee, launched an investigation of pharmaceutical distributors (those companies that sell drugs but do not manufacture them). He has requested information from five companies. The questions asked of the companies include how they obtain their drugs, how much they pay for them, and how much profit they make. Some companies have responded to the inquiry; others have not. In November, Congressman Cummings expressed concern that the companies in question were not cooperating and, consequently, plans to intensify the investigative efforts. On October 31, FDA posted on its Web site a review of drug shortages; DHHS also released an issue brief, “Economic Analysis of the Causes of Drug Shortages,” which is available on its Web site. The President has issued an Executive Order for FDA to use its authority to require drug manufacturers to provide advance notice of potential shortages, expand current efforts to expedite regulatory reviews, and work with the Department of Justice to review certain behaviors by market participants.

Questions and Discussion

Ms. Roach asked when the GAO report on drug shortages will be released. Ms. Erickson responded that her colleagues have heard that the report will be released in November but are not aware of a definitive date.

IV. TRANSFORMING NCI'S CLINICAL TRIALS SYSTEM—DRS. JEFFREY S. ABRAMS AND MARGARET M. MOONEY

Dr. Margaret Mooney, Chief, Clinical Investigations Branch, Cancer Therapy Evaluation Program, NCI, gave an overview of the NCI clinical trials program and presented the rationale for the development of a new RFA.

The Cooperative Group program has been funded by NCI for over 50 years as an infrastructure for conducting clinical trials in treatment, symptom management, cancer control, and prevention and screening. The program involves over 3,100 institutions; 14,000 investigators; and thousands of patients—around 25,000 patients are enrolled annually on treatment trials alone. The majority of enrolled patients (about 83%) are in definitive Phase III trials. A notable strength of the Cooperative Group program is its broad investigative branch comprising NCI-designated Cancer Centers, academic centers, and community hospitals across the United States, as well as international members and private practitioners.

There have been several reviews of the Cooperative Group program over the past five to six years, most notably from the Institute of Medicine (IOM) in April 2010. The consensus from all of the reviews has been that there is a critical need for a publicly funded clinical trials network. A publicly funded network is able to address research questions that may not be taken on by the private sector and industry because they would not be seen as research priorities; such research questions include issues related to integration of new agents into standard therapy; combinations of novel agents from different sponsors; multimodality therapies, screening, diagnostic, and prevention strategies; rare tumor types; and evaluation of competing therapies that have already been approved for certain indications. Publicly funded trials are usually focused on disease management. They are not as agent-specific as private-sector trials nor are they limited by marketing constraints. This allows researchers to address important ancillary research questions, including those related to correlative science, imaging, quality of life, symptom management, and special populations. Additionally, a public clinical trials network allows extensive and direct involvement of everyone in the oncology community in the design, development, and conduct of the trials. From 2005 to 2011, the Cooperative Group program has supported over 30 practice-changing clinical trials, including therapeutic agents and other modalities. Four of these trials were announced in the first six months of 2011 and are focusing on surgery in breast cancer, radiotherapy in breast cancer, use of a generic drug at a high dose for pediatric acute lymphoblastic leukemia (ALL), and use of a multimodality therapy. During the same period of time, there have been more than 10 FDA-approved indications using new oncology agents. In addition, a number of Group trials also have investigated and shown defined clinical benefits for new indications for generic agents.

Over the last 18 months, NCI has undertaken an extensive review and tried to receive as much stakeholder input as possible to determine how to best move forward with recommendations made by review committees to improve the clinical trials system. NCI also has had a professional analysis conducted by the Science and Technology Policy Institute on the operational efficiency of the clinical trials program, as well as gathering input from the general public through the NCI Mailbox and Web site. The IOM report outlined four consensus goals that a publicly funded clinical trials system must meet in order to address new and emerging scientific challenges. These goals include: improving speed and efficiency of development and conduct of trials; incorporating innovative science into trial design; improving trial prioritization, selection, support, and completion; and ensuring participation of patients and physicians in the system.

NCI has already made progress on many of these goals. The Operational Efficiency Guidelines have been implemented with the aggressive goal to reduce timelines for protocol development and

activation by over 60 percent. Initial data from the first 20 months of implementation show that timelines are being reduced by 50 percent. Implementation of a common data management system (Medidata Rave®) has begun and will be completed over the next 18 months. Data will be collected and patients will be enrolled in the same manner across the clinical trials system. The Biomarker, Imaging and Quality of Life Studies Funding Program (BIQSFP) has been implemented to include integral and integrated biomarkers, imaging, and quality-of-life studies in definitive large-scale treatment trials. Over the past 3.5 years, more than 13 Phase III clinical trials have made use of BIQSFP, with funding in excess of $22 million. Disease-specific and specialty Steering Committees were implemented between 2006 and 2011 to help prioritize large-scale Phase II and III trials. Slow accrual guidelines have also been implemented to help identify Phase III trials that are not accruing well in order to make appropriate modifications early or stop the trials. Finally, there have been several pilot initiatives to increase reimbursement for Phase II and III trials and assess physician and patient feedback on trials to enhance accrual.

As of January 2011, there were 10 funded U.S. Cooperative Groups—all organized and reviewed separately. Each Group comprised different components and there was some duplication of effort and infrastructure across the entire clinical trials system. NCI has tried to centralize many administrative and regulatory functions via the CTSU, the NCI Central Institutional Review Board (CIRB), and the disease-specific Steering Committees; however, the clinical trials system has still experienced a silo effect. NCI believes that in order to move forward and meet emerging challenges, the organizational structure and review processes of the entire clinical trials system will have to be fundamentally changed.

The new RFA for an Integrated National Clinical Trials Network (NCTN) sets out the next steps that need to be taken to transform the clinical trials system. Through the RFA, NCI is proposing that the organizational structure be consolidated, with funding for one pediatric Cooperative Group and up to four adult Groups. The review criteria will be changed to emphasize integration and collaboration for overall scientific achievement and operational efficiency. A new funding model is proposed that includes increased per-case reimbursement for "high-performance" academic and community sites. Additionally, there will be Competitive Integrated Translational Science Awards and a revitalization of the Cancer Center's role in the Network. NCI has other grant programs that are well coordinated with the programs that will be funded under the new RFA, including the Community Clinical Oncology Program (CCOP) and the Minority-based CCOP, the Cancer Diagnosis Program's tumor banks, contract programs that support the CTSU and CIRB, and advisory committees.

Consolidating the clinical trials infrastructure will allow NCI to gain efficiencies in the areas of information technology (IT), regulatory issues, administrative processes, and tissue resource management. Consolidation of imaging and radiotherapy—two modalities with limited private-sector and industry support—will allow NCI to provide core services for quality control and assessment across the National Clinical Trials Network. The integration of new components into trials will provide value-added research questions (e.g., advanced imaging, translational science). An integrated national clinical trials system will also allow NCI to integrate new agents into trials more rapidly. For example, erlotinib, crizotinib, and ipilimumab are being integrated into trials in earlier stages of lung cancer and melanoma treatment, requiring screening of large populations and combining of the agents optimally with surgery, radiotherapy, and immunotherapy. Additionally, the integrated Network will permit the evaluation of new agents in molecularly defined disease subsets. The number of molecularly defined patient subsets is increasing, and there is a need for trial prioritization and evaluation of multiple new agents with standard regimens across subsets to avoid duplication and optimize accrual.

Dr. Mooney detailed the organization of the new integrated Network. The Group Operations Centers and Statistical Centers will provide scientific strategy and goals across a broad range of diseases, with an emphasis on collaboration. The Centers will be responsible for Network administration ranging from study conception to accrual to trials and including adherence to timelines, quality assessment and

control, coordination of biospecimen collection, and compliance with FDA, Office of Human Research Protections (OHRP), and NCI/NIH regulations. The Centers will also provide statistical leadership for effective trial design and conduct, monitor data quality for primary analysis and correlative science, and support data management and analyses for studies outside the Network, as appropriate (e.g., SC-approved studies).

The way NCI/NIH conducts external peer review of the system will be reconfigured. There will be an emphasis on incentives for a national system with trials open to all qualified sites, and sites will be able to credit any Group to which they belong. Review of all network Groups and components will be done at the same time; there will be specific review panels for particular Network components. In the past, each Group was reviewed individually and at different points in time. Scientific evaluation will shift to evaluating each Group's role in the national Network, overall scientific strategy, innovation, and quality.

Lastly, review criteria will have a strong component for operational efficiency and collaborative management of the Network. This includes coordination with other Network Groups, NCI programs, and NCI investigators outside of the Groups. A new program is being initiated for lead academic participating sites. There will be multiple-PI grants for academic institutions with demonstrated scientific leadership in one or more adult Groups, substantial accrual, and excellent data quality—"high-performance" sites. These sites will be targeted at NCI Comprehensive and Clinical Cancer Centers and other leading academic centers. The review criteria for this new program are as follows: meets accrual threshold set from trials across the entire Network; has expertise and leadership role in Group(s); maintains high data quality; contributes to translational science within Group trials; and maintains scientific collaborations across Cancer Center/Institution and Network.

Another new component of the integrated Network is the Integrated Translational Science Awards. These are multiple-PI grants to support prominent researchers for their expertise and efforts in incorporating molecular studies into Network trials and enabling acquisition of preliminary data for further research. The grants will help fund laboratory-based researchers to facilitate the hand-off of early-phase clinical trial findings into later-phase, definitive trials. The review criteria will focus on peer review of quality of scientific approach and plans for integration of translational science into Network trials. The review will also look at whether the grants leverage independently funded laboratory resources with Group clinical specimens and data to benefit Group research aims. Researchers selected for these grants are likely to benefit trial efforts across the Network.

Two more components of the new Network are the radiotherapy and imaging core services, which will provide scientific leadership for incorporating quality assessment and image data management for research trials involving radiotherapy and imaging. The review criteria for these components will focus on scientific leadership and expertise for these core services across the entire Network, including integrated IT platforms for capturing and storing images, and efficient procedures for accessing site data for radiotherapy and image-related trial questions.

NCI has had a long history of collaboration with Canadian sites and nonprofit Canadian clinical trial organizations. The last component of the new RFA is a grant that could potentially fund a Canadian Collaborating Trials Network. The review criteria will focus on the ability of the Network to provide appropriate regulatory oversight for U.S. Network trials conducted in Canada, irrespective of which Group leads the trial and to be full partners in accruing patients to U.S. Network trials.

The new RFA will have four FOAs and potentially fund 43 to 58 grants. The first FOA will include the Group Operations Centers, the Group Statistical and Data Management Centers, and the Canadian Collaborating Network. The second FOA will be for the Integrated Translational Science

Awards. The Radiotherapy and Imaging Core Services will be included in the third FOA. The last FOA will be for the Lead Academic Participating Sites.

All external reviews of the NCI clinical trials system have emphasized the need to provide increased research reimbursement to ensure continued participation of sites in the public program. The base "per-case" reimbursement for patient enrollment in the program has remained fixed at $2,000 per patient in treatment trials for over a decade. In 2006, the estimate for average per-patient cost in industry trials was $4,700 for Phase III trials and $8,450 for Phase II trials—some industry trials provided more than $15,000 per patient. A survey of Group sites in 2009 found that of those sites planning to limit participation in the program (32% of respondents), 75 percent cited inadequate reimbursement for the decline in their levels of participation. "High-performance" sites incur additional infrastructure costs due to the numbers of patients they accrue. Additional funding is especially needed to compensate these sites for their large patient follow-up burden. An additional $2,000 per patient is proposed for these sites, for a total reimbursement of $4,000 per patient.

Funding for the program has remained essentially flat over the past six years. It was noted that there was a budget cut in FY 2011. Level funding means that there has been a decrease in the purchasing power devoted to the program over the past decade. Cooperative Group obligations have deflated in the past decade using the Biomedical and Research Development Price Index (BRDPI). In order to provide increased reimbursement, the new RFA is proposing an increase in funding for the Network in the amount of $25.6 million; $21 million of that will go directly to the Group sites to increase per-case reimbursement. The additional $4 million will be spent to increase funding for integral and integrated biomarkers, quality-of-life, and imaging studies. Along with the increased funding, there will be a 20 percent reduction in accrual (from about 25,000 patients/year to 20,000 patients/year).

Moving forward, it will be challenging to balance accrual and scientific priorities. Treatment trial accrual has been dominated by breast and gastrointestinal cancer trials, especially large adjuvant trials, over the past decade. The new funding model will require Network organizations and Steering Committees to monitor the balance of trials that are prioritized for development and aid in the formulation of a strategic consensus related to the diseases in which to encourage more trials as scientific opportunities arise. The new review criteria should facilitate more trials in disease areas that have been typically underrepresented, relative to their incidence. The portfolio balance will be monitored closely by CTAC's Ad hoc NCTN Strategic Planning Subcommittee to ensure that scientific opportunities in less-common tumors are not overlooked.

The new RFA was approved by the Board of Scientific Advisors during their concept review on November 7, 2011. Between November 2011 and July 2012, NCI will be developing the FOAs and guidelines that will need to be reviewed by the Division of Extramural Activities (DEA) and NIH. The goal is to release the FOAs and guidelines in July of 2012. Receipt of competing new applications is anticipated in the winter of 2012 with the scientific review scheduled to occur in the of summer of 2013. The National Cancer Advisory Board (NCAB) will review the applications in December of 2013. The roll-out of the new awards for the integrated Network will begin in March 2014.

Questions and Discussion

Ms. Roach asked Dr. Mooney to describe the BSA's reaction to the new RFA. Dr. Mooney said that the concept was met favorably by the BSA, who unanimously approved the RFA. The BSA appreciates that it is structured as an integrated Network and that institutions will be rewarded for their participation across the Network. An important issue brought up by the BSA is data sharing, which is

essential in a publicly funded system. The BSA agreed that the public should be given access as quickly as possible once primary research results are available. The BSA expressed concern about informed consent. Informed consent documents for trials across the newly integrated system need to be appropriate to inform patients, particularly about the use of tissue and other biospecimens for new scientific opportunities. The BSA also expressed concern that specialty research questions (e.g., radiotherapy, surgical, etc.) should continue to have a strong role within the new system.

Dr. Davidson asked whether all of the component pieces of the RFA (e.g., Lead Academic Participating Sites) will be submitted at the same time. Dr. Mooney said that the receipt dates will be slightly staggered because there will be different review panels with various areas of expertise for each of the FOAs.

Dr. Mooney commented that the review process for the Cooperative Groups will be completely different than it has been in the past. For example, there are new NIH page limitations, and the application will be shorter. The goal is to make sure that the entire application and review process is much more streamlined and condensed than it has been in the past.

Dr. Daniel Sargent, Director, Cancer Center Statistics, Mayo Clinic College of Medicine, asked for clarification regarding the role of single-arm trials in the new Network. Dr. Mooney explained that the focus of the new Network will be on definitive trials, which usually are randomized Phase II trials leading to definitive Phase III trials. However, that does not mean there never will be support for an early-phase trial— there always have been some earlier phase trials within the Cooperative Groups in order to get to the definitive trials. There are also some times when single-arm trials are appropriate.

Dr. Sargent questioned why the Cooperative Groups went from a six-year review cycle to a five-year cycle. Dr. Jeffrey Abrams, Associate Director, CTEP, NCI, said the recommendation from most of the external review committees was to conduct the review every five years to compare performance and appropriately redistribute funds.

Dr. Sargent commented on the review criteria. He expressed concern about the review score being split 50/50 between science and operations and that, as a strategy, science should be emphasized first. Dr. Mooney agreed that the science should come first, but a significant component of the review score also must be based on operational efficiency. Dr. Abrams added that collaboration is a significant portion of the operations part of the review, including scientific as well as organizational collaboration.

Dr. Weiner asked how the new Network will support the integration of correlative science in trials. Dr. Mooney said that one way correlative science will be integrated is through the BIQSFP. Applications for BIQSFP support will come in at the same time that a trial is being evaluated for the first time as a concept by the Steering Committee. Another mechanism by which correlative science will be encouraged is the Integrated Translational Science Awards.

Dr. Scott Lippman¸ Professor and Chair, The University of Texas M.D. Anderson Cancer Center, asked how the new Network will help support prevention trials through the CCOPs. Dr. Lori Minasian, Chief, Community Oncology and Prevention Trials Research Group, Division of Cancer Prevention (DCP), responded that it is expected that the CCOP research-based RFA will be revised to be parallel and complementary to the new Group RFA. Dr. Abrams added that many DCP cancer control studies are now listed on the CTSU (similar to treatment trials), which has opened up trial participation and increased accrual.

Dr. Adamson commented that the current clinical trials system is geared so that concepts fail late and asked whether the new Network will address this fundamental issue. Dr. Mooney said that NCI is

working on addressing this matter. The slow accrual guidelines will help to identify early on what can be done to modify underperforming trials. Many SCs have task forces, which means that people can weigh in very early in the process. Additionally, greater integration with the CTSU will facilitate monitoring and feedback on concepts early on in a centralized way.

Dr. Adamson asked whether the new Network will allow for innovations in the way science is conducted. Dr. Mooney responded that the Integrated Translational Science Awards program is one way in which investigators can bring innovative ideas to the system. The collaborative management of the entire Network will also provide opportunities to address innovations that may be beneficial to the clinical trials system.

Ms. Roach asked how the review process will be conducted. Dr. Mooney said that there will be review panels that will be able to adequately review the different components of the RFA. Preliminary discussions have taken place with the DEA to determine how to create enough review panels without any conflicts of interest.

Dr. Mitchell Schnall, Matthew J. Wilson Professor, University of Pennsylvania Medical Center, asked whether the Network will accommodate imaging work being done by the American College of Radiology Imaging Network (ACRIN) for the Cancer Imaging Program. Dr. Mooney replied that the total accrual planned for the Network will include imaging trials.

Dr. Joel Tepper, Hector MacLean Distinguished Professor of Cancer Research, University of North Carolina, Lineberger Comprehensive Cancer Center, asked how the tumor banks will be incorporated into the new Network. Dr. Mooney responded that the Cancer Diagnosis Program is discussing a new RFA to provide tumor banking support to the new Network.

Ms. Roach questioned whether the 30 to 40 Lead Academic Participating Sites will be reviewed at the same time. Dr. Mooney responded in the affirmative.

Dr. Bertagnolli acknowledged the hard work of Dr. Mooney and other NCI staff in developing the template for the new system. She emphasized that this was a collaborative effort that included NCI and the Groups and expressed her thanks.

V. CTAC CLINICAL TRIALS STRATEGIC PLANNING SUBCOMMITTEE UPDATE—DR. JOEL E. TEPPER

Dr. Tepper explained that the purpose of the CTAC Clinical Trials Strategic Planning Subcommittee, which held its first meeting on the evening of November 8, 2011, is to advise NCI on the development of a fully integrated clinical trials system. Although the Subcommittee's scope includes early-phase trials supported by CTEP and DCP, its initial focus will be on trials in the NCTN, concepts of which are reviewed by NCI's disease-specific Scientific Steering Committees and which are usually conducted by the Cooperative Groups and CCOPs.

The Subcommittee's objectives are to: (1) monitor and assess the balance, coherence, and appropriateness of NCI's clinical trials portfolio; (2) monitor and assess the scientific effectiveness of the Scientific Steering Committees; (3) recommend new strategies, priorities, and directions for clinical trials based on NCI's current portfolio, evolving clinical needs, and emerging scientific opportunities; and (4) monitor and assess other aspects of clinical trials operations across the system, including collaboration and timeliness. The Subcommittee understands the importance of determining the most appropriate ways

to measure some of these subjective criteria. Metrics developed by the CTAC Evaluation Subcommittee will be the starting point for addressing these objectives.

The Subcommittee agreed to establish a Clinical Trials Strategic Planning Working Group with 25 to 30 members to review available data and develop recommendations for review and revision by the Subcommittee. Small groups within the Working Group will be formed to address specific issues. Other Working Groups may be established as the Subcommittee's activities expand (e.g., to address early-phase trials).

Non-NCI groups that could be represented on the Working Group include Cooperative Group Chairs, Cooperative Group statisticians, Cancer Center Directors, CCOP PIs, patient advocates, translational scientists (e.g., SPORE and P01 investigators), cancer control and research base PIs, Steering Committee Chairs, and CTAC members. NCI members will include representatives from DCTD, DCP, and CCCT.

The next steps for the Subcommittee will be to formulate a function statement and select members for the Working Group. Initial Working Group activities will include reviewing its role, responsibilities and tasks, reviewing proposed measures to achieve tasks, developing a process for analyzing the clinical trials portfolio, and assessing portfolio balance based on input from the NCI. Ongoing implementation of the CTWG NCI Evaluation Plan will provide data for the Working Group to review and analyze.

Questions and Discussion

Dr. Adamson expressed support for a step-wise approach to addressing the many issues involved in the Subcommittee's scope.

Dr. Kuebler asked whether the Subcommittee is expected to play an oversight role for the Scientific Steering Committees and, if so, how it expects to impel the Steering Committees to implement any changes deemed necessary. Dr. Tepper replied that the NCI has the authority to set ground rules for the Scientific Steering Committees and that the CTAC has the responsibility of advising NCI on trial-related issues that have an impact on the work of those Committees.

Dr. Prindiville noted that in addition to broader issues such as the overall balance of concepts across Scientific Steering Committees, the Subcommittee will be looking at how well they are functioning. For example, how effective are clinical trials planning meetings in moving the scientific agenda forward within a Scientific Steering Committee?

Dr. Schnall urged the Subcommittee to move beyond the NCTN as soon as possible to ensure that the entire clinical trials portfolio receives adequate scrutiny. Dr. Tepper said that the experience of scrutinizing the better-organized part of the portfolio will prepare the Subcommittee for the more difficult task of addressing other parts of the portfolio, such as trials funded through the R01 mechanism.

Dr. Abbruzzese asked CTAC members whether they are interested in an updated presentation on the overall NCI clinical trials portfolio. The most recent presentation was based on 2006 data.

Dr. Bertagnolli commented that an update on how NCI clinical trials resources are being distributed should be an integral part of the Subcommittee's work.

Dr. Doroshow suggested that in addition to funding data, it is essential that CTAC be informed about where clinical trials are being conducted and what their goals are.

Dr. Peter Shields, Deputy Director, Comprehensive Cancer Center, The Ohio State University Medical Center, recalled that when the previous presentation was made, there was consensus within the CTAC that it should be periodically updated.

Dr. Adamson expressed agreement but argued that a new analysis should be done after the NCTN has been initiated. Dr. Lippman expressed disagreement with the suggestion to postpone the analysis because there have been many changes in cancer research since 2006. Dr. Schnall suggested that a Working Group might be needed to address strategic, operational, and organizational issues before planning a portfolio review.

Dr. Sargent asked how much effort was required to prepare the 2006 presentation. Dr. Prindiville said that the 2006 work was costly and time-consuming, yet it established the feasibility of doing that type of analysis. An update would be somewhat easier; however, the methodology will need to be fine-tuned. Dr. Judy Hautala of STPI, which conducted the 2006 portfolio analysis, expressed confidence that an update to provide data on the 35 programs that support clinical trials would not require as much effort as the 2006 review.

Dr. Bertagnolli noted that it may not be necessary to know where every dollar has been spent. She suggested that it might be most helpful to know how many Phase II trials are funded within specific disease types.

Dr. Adamson reiterated his belief that data should be collected until a strategy for managing the investment in clinical trials has been formulated. Dr. Lippman stated that it is more important to learn about support for trials that are not part of the NCTN. It might be adequate to reexamine the 2006 data and include a broad overview of major changes since that year.

Dr. Schnall proposed the formation of a Working Group to identify the types of data needed and determine what can be done with the data. Dr. Abbruzzese suggested asking the Strategic Planning Subcommittee to address this question as an alternative to forming a new Working Group.

Dr. Tepper expressed support for repeating the 2006 presentation. Dr. Abbruzzese replied that the presentation, whether repeated or updated, would be instructive even in the absence of a specific plan for what to do with those findings.

Dr. Villalona-Calero, while acknowledging the importance of long-term evaluation, stressed the importance of establishing mechanisms to address situations in which current practices within Scientific Steering Committees are shown to be dysfunctional. Dr. Tepper noted that Scientific Steering Committee Chairs conduct periodic conference calls during which they address these types of issues. Dr. Prindiville commented that communication between Scientific Steering Committee leadership and NCI has been useful in helping the Steering Committees solve operational problems.

Dr. Lippman suggested that the Subcommittee and Working Group should focus their attention on clinical trials in the area of prevention, especially in terms of improving industry involvement and increasing translational prevention research.

VI. A COMMON CLINICAL DATA MANAGEMENT SYSTEM (CDMS) FOR THE COOPERATIVE GROUPS—DR. MICHAEL J. MONTELLO

Dr. Michael Montello, Associate Chief, Clinical Trials Technology Branch, CTEP, NCI, provided a status update on NCI's initiative to modernize and standardize the CDMS for the Cooperative Groups.

A CDMS is the set of tools or processes that supports data collection (via remote data capture), data coding, data management, and preparation of data for analysis. The CDMS directly or indirectly affects the entire research organization. General areas affected include science, safety, regulatory, administration, operations, and financial management. Individuals impacted by the CDMS range from the Cooperative Group Chair to the research staff and the patient. There are two types of CDMS: paper and electronic. Paper CDMS forms can be mailed or faxed into corporate headquarters and often require double data entry. Paper forms can also be scanned into the system using Object Identifier technology. Paper CDMS also requires minimal setup time and effort; however, "dumb" forms require more time/effort to complete and there is increased risk of data discrepancy or delinquency. It is also difficult to maintain Case Report Form (CRF) version control. With an electronic CDMS, either a commercial off-the-shelf (COTS) or custom-built product is provided to the organization. An electronic CDMS requires more setup time and effort but provides simplified CRF version control, "smart" forms for data collection, and edit checks up front that reduce data discrepancy and delinquency.

At one point in time, all of the Cooperative Groups used a paper CDMS. However, there has been an incremental shift by individual Groups to the electronic CDMS (custom and COTS). Some Groups still use paper, which creates inter- and intra-Group variability in the approach to CDMS use. In 2006, the Groups agreed to work together to implement a common CDMS and performed an independent analysis of available COTS products; Medidata Rave® was selected. In 2009, the Center for Biomedical Informatics and Information Technology (CBIIT) released a request for proposals (RFP) that also resulted in the selection of Medidata Rave®. The NCI initiative to establish a common CDMS for the Cooperative Groups began in 2010.

Data management is necessary for the performance of clinical trials; however, the inefficiencies of the data management process can sometimes create a distraction to the overall scientific objectives. The use of multiple CDMSs within the Group clinical trial system results in increased training costs, increased risk of data delinquency and/or discrepancy, increased time and effort to correct/complete data, as well as longer duration of time to get to the science and safety results of a trial. The goal of NCI's CDMS initiative is to reinforce the clinical trial focus on science and the patient by optimizing the efficiency and effectiveness of the data management systems and processes. The IOM report, *A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program*, which was released in April 2010, stated that more resources for the rapid implementation and adoption of a common electronic registration and data capture system would increase consistency across trials and conserve resources by: reducing the workload associated with patient enrollment and follow-up; allowing for more timely review of data from a trial; and enhancing the knowledge gained from a trial. Additionally, standardized CRFs would ease the burden of regulatory oversight and lead to better compliance.

The opportunity to implement a common clinical data management system within the Cooperative Groups has always existed. There is a strong foundation for CDMS uniformity across the Groups. Investigators and sites are often members of multiple Groups, and through the CTSU, sites and investigators can enroll patients on each other's trials. There is now added emphasis to create a uniform CDMS. Federal funding constraints make it essential for sites to perform clinical trial functions with optimal efficiency. The transformation/consolidation of the Cooperative Groups serves as further promotion of Network collaboration. Groups must select a common CDMS as they merge. A common Group CDMS will promote efficient and accurate data entry using a common, intuitive/user-friendly

interface. The CDMS will be scalable for all Group trials (i.e., treatment, prevention, cancer control, and diagnostic) and will minimize training and implementation costs across Groups through shared training and experience. The common CDMS will also reduce data management burden and costs for the multicenter coordinating center as well as for participating sites.

There are five requirements necessary to deploy a common CDMS to the Groups. There needs to be a standardized approach to: (1) the application; (2) core configuration; (3) business practices; (4) integration with "global" applications; and (5) case report forms. The application that will be used for the common CDMS is Medidata Rave®, which has been purchased for the Groups. A common core configuration for Medidata Rave® has also been completed. The development of standardized business practices is ongoing. There are many business practices, such as data delinquency rules, within the Cooperative Groups that are tied to the CDMS. Integration with "global" applications is also ongoing. There are certain functions of the CDMS that all Groups utilize—patient enrollment, NCI accrual reports, adverse event reporting—that would benefit from having a common, one-time approach that meets all of those needs. There will be a single sign-on across the CDMS (e.g., an investigator can sign onto different Group studies using the same user name and password). The Cancer Data Standards Registry and Repository (caDSR) is being leveraged to complete the case report forms for the Group CDMS.

The CDMS initiative is taking a thoughtful approach to standardization by being respectful of the variation among Groups and the uniqueness of the science of each individual trial. The common CDMS should promote efficiency by having a common standard infrastructure while allowing the necessary flexibility (customization) required to support the differences between radiation, surgery, prevention, imaging, and pediatric trials. Successful deployment of the CDMS will entail several key concepts, including leveraging experience from Medidata and the Groups, achieving a common look and feel of the outward community-facing features, utilizing a standardized approach for standard interfaces, and having open communication. The organizations that are adopting the common CDMS include all of the NCI Cooperative Groups, the Children's Oncology Group Phase I Consortium, the Adult Brain Tumor Consortium (ABTC), Theradex (which does early Phase I trials), and the CTSU. The role of each of these organizations is to modify its internal business, operational, and technical infrastructure to support the transformation to Medidata Rave®. These organizations must participate in standards development/ adoption activities and integrate local applications with Rave®, as well as participate in "local" knowledge- or training-acquisition activities.

The CDMS initiative is a trans-NCI initiative. The role of NCI is to provide project oversight, establish overall direction and expectations, promote standardization (not standards), and allocate resources (e.g., licensing, hosting, training, etc.). A variety of contractors are providing support to the CDMS initiative. The CTSU, which is supported by Westat and the Coalition of Cooperative Groups, provides support for the CDMS Support Center (CSC), IT integration, training, funding, and logistics. Capital Technology Information Systems (CTIS) provides IT integration for CTEP applications. ESSEX provides working group leads for several committees and CBIIT coordination support. Medidata is providing hosting, knowledge transfer, and training support, as well as maintenance, help desk, and consulting services. The CSC is located within the CTSU and has representation from all of the major constituents: NCI, Westat, the Coalition, Medidata, and Group consultants. The role of the CSC is central management for NCI Rave® implementation, coordination of efforts for uniform deployment, oversight of day-to-day activities, and coordination of working groups and training services.

Working groups are being utilized to identify and develop standards and/or best business practices to balance the needs of the Network and the adopting organizations. There are three categories of working groups. Priority One working groups are required for launch of the CDMS and are focused on the following areas: core configuration; validation; data quality; data elements; study build; study conduct; user management; and integration. Priority Two working groups just started meeting in the fall

and are focused on metrics, remote data capture (RDC) training, and auditing. Priority Three working groups will commence in 2012 and focus on reporting, statistics issues, and ancillary studies. The working groups are coordinated and facilitated by co-leads (at least one is a Cooperative Group member). Each group has an individual charter to define its governance, goals, and deliverables. Each organization has one voting member in the working group to make recommendations on behalf of the organization. The membership for all of the working groups consists of at least two NCI representatives, at least two CTSU representatives, and one or more representative from each Cooperative Group. Communication on the CDMS initiative will be conducted through the working groups, the Leadership committee, trainings, face-to-face meetings, and a monthly newsletter.

Deployment of the common CDMS to the Cooperative Groups began April 1, 2011. The deployment plan was broken into three stages. Stage one was the Alpha stage—the first three sites began the one-year implementation of Medidata Rave®. The second three sites (Bravo stage) began deployment on July 1, 2011, with nine months to implement the application. The Charlie stage (the third three sites) began implementation of Medidata Rave® on October 1, 2011; these sites were also given nine months for implementation. The Alpha and Bravo sites should complete deployment by March 31, 2012; the Charlie sites should complete implementation by June 30, 2012. Beginning in summer 2012, all new Cooperative Group trials will be utilizing Medidata Rave® for data management. Medidata Rave® provides a curriculum for the application the Groups will be using. NCI is taking a "train the trainer" philosophy in that a core group of people will be identified within each Cooperative Group to be trained, and those people will then pass on the information they have learned. Through the CTSU, NCI will also provide logistical support (e.g., scheduling and invitations) and training and travel costs. About 200 individuals will receive the fundamental and mid-level Medidata training. About 100 individuals will receive advanced training. If needed, the Groups can pay for additional training sessions.

Dr. Montello provided status updates on the CDMS working groups. The Data Elements Working Group has established the CRF governance model for caDSR and conventions for computer-to-computer communications. The Group has also identified enhancements to improve communication between Medidata Rave® and caDSR. The Data Quality Working Group created a report shell for case report form (CRF) and query timeliness. It also provided recommendations for classifying standards for protocol deviations. The Study Conduct Working Group identified standard procedures and communication processes and designed standard processes for lost-to-follow-up as well as edit checks. The Study Build Working Group is designing a standard Medidata Rave®-specific study build workflow and exploring optimal methods of folder design within Medidata Rave®. The Rave Validation Working Group has written validation test cases and performed two Medidata Rave® site audits. They are also confirming Medidata's disaster and recovery and backup procedures. The Core Configuration Working Group has created and documented a standard Medidata Rave® core configuration across the system.

A number of integration activities must be completed in order for the common CDMS initiative to be a success. The Priority One integration activities are necessary for the implementation of Medidata Rave®, which includes the caDSR (case report form source) and establishment of a single sign-on for three applications: Identify and Access Management, Regulatory Support System, and Oncology Patient Enrollment Network. Priority Two integration activities will be deployed within the first three to six months of the implementation. These activities include NCI reports and a serious adverse event (SAE) reporting system. Priority Three will include auditing and further expansion of NCI reports; these integration activities will take place in 2012. SAE reporting is necessary for the Cooperative Groups. Currently, there is a disconnect between routine adverse event (RAE) and SAE reporting. RAE and SAE data are captured in separate systems—an issue that leads to double data entry. Double data entry can create data discrepancies and promote under- or overreporting. Medidata Rave® will provide an opportunity for single-source reporting of both SAE and RAE data. The adverse event would be entered one time within Rave®, reducing or eliminating data discrepancies. "Smart" CRFs can identify which

adverse events require additional information (i.e., SAEs). This method of adverse event reporting reduces training requirements for site doctors, nurses, and clinical research associates.

Once Medidata Rave® is deployed, NCI will continue to provide support and a forum to share experiences. The global library (caDSR) will continue to be maintained and expanded. Integration efforts will also be expanded. These efforts will include the new SAE and audit systems, enhancements to the NCI reports, and maintenance. NCI will continue to address procurement issues moving forward. The common CDMS project may also be expanded to adoption of additional multicenter organizations, such as DCP and CTEP Phase II contracts.

In conclusion, the modernized and standardized Group CDMS will: promote transformation of the Groups into a "network"; meet FDA requirements for electronic data capture and transfer; reduce the cost/effort for data management; improve trial management and decision making; promote data sharing; and set the stage for potential further infrastructure improvements.

Questions and Discussion

Dr. Villalona-Calero asked Dr. Montello to expand on how the data-sharing aspects of the Group CDMS will support development of reports and presentations by participating investigators. Dr. Montello explained that each Cooperative Group can decide how it plans to access the common CDMS for data-sharing activities. With the new system, data should be able to be accessed more quickly.

Dr. Adamson asked whether there are any plans to pilot the CDMS in one or more of the Cooperative Groups before full implementation. Dr. Montello confirmed that NCI is following the three-phase implementation timeline presented earlier and that Medidata Rave® was piloted with the newly merged Cooperative Groups in the Alliance, (American College of Surgeons Oncology Group, Cancer and Leukemia Group B, and North Central Cancer Treatment Group), and the National Cancer Institute of Canada.

Dr. Sargent suggested gathering baseline data (workload and time metric information) at participating sites to develop metrics of success for implementation of the common CDMS. Dr. Sargent's initial experience with Medidata Rave® is that it is taking more time to put studies into the system—three to four months with Rave® compared with four to six weeks with the old system. There is a learning curve with Rave® and the original implementation timeline may be too ambitious. Dr. Montello commented that, as of now, the initiative is on track to meet its April and June implementation deadlines. In addition, it is anticipated that, over time, the study setup times should improve dramatically as individuals become accustomed to the new software and begin to take advantage of the standardized processes and forms that have been developed.

Dr. Weiner asked if the new CDMS will be able to communicate with some of the more common electronic health record platforms. Dr. Montello explained that the CDMS does not currently have that communication function, but it has been discussed and is likely to be implemented in the future.

Ms. Roach asked whether the new CDMS is intended to be a completely paperless system. Dr. Montello commented that the goal is for the entire system to be paperless.

Dr. Sargent commented that using Medidata Rave® has resulted in fewer protocol amendments.

Dr. Curt Civin, Director, Center for Stem Cell Biology and Regenerative Medicine, University of Maryland School of Medicine, asked whether CTEP is working with the cancer Biomedical Informatics Grid (caBIG) to provide access to genomic data and other resources. Dr. Montello replied that because CDMS is a trans-NCI initiative, it is working closely with caBIG to leverage the strengths of both initiatives.

VII. CENTER FOR CANCER RESEARCH CLINICAL TRIALS PORTFOLIO AND IMPLEMENTATION OF TIMELINES TO ENHANCE OPERATIONAL EFFICIENCY—DR. LEE J. HELMAN

Dr. Lee Helman, Deputy Director, Center for Cancer Research, NCI, presented on CCR's clinical trials portfolio and gave an update on implementation of the Operational Efficiency Working Group (OEWG) timelines.

CCR's clinical vision is to improve outcomes of patients with cancer and related diseases and to be the world's leading oncology research organization. CCR achieves this vision by engaging outstanding researchers in consequential investigator-initiated clinical research in a translational research culture. CCR provides the flexible funding necessary to support innovative, high-impact, bench-to-bedside research through access to the largest publicly funded research center in the world. In addition, CCR collaborates with outstanding researchers across NIH and throughout the extramural community. The clinical research priorities of CCR are to: take discoveries from within CCR or other NIH laboratories to the point of first-in-human trials; foster the education and research of physician-scientists; design and execute novel, science-based clinical trials; focus on molecularly based, precision medicine; utilize technology and correlative science that is difficult to support elsewhere; and study rare cancers that are not being adequately studied elsewhere. Similar to the rest of NCI, CCR has been under financial pressure over the past few years. Last year, CCR had to make an across-the-board 8 percent cut to the intramural clinical trials program. Consequently, CCR must learn to do more with less. The vision for 2012 and beyond is to accelerate translational progress through flexible, targeted approaches to solve difficult and complex problems. The Center will embrace new initiatives and programs that enable significant progress in alleviating the impact of cancer. Science-based knowledge about both the disease and its progression will be used to intervene at the very earliest stages through early detection prior to invasion and metastasis. By integrating advanced biomedical technologies into every clinical trial, CCR will make significant advances toward improving cancer therapy by treating each patient and each tumor based on specific tumor and patient molecular characteristics.

The distinctiveness of CCR derives from a convergence of multiple attributes. There is sustained support for high-risk, high-impact research, which means failure sometimes occurs. If all research is successful, not enough risks are being taken. CCR has a highly interactive, multidisciplinary culture for basic and clinical scientists, resulting in efficient bench-to-bedside-to-bench translation. CCR researchers have access to the world's largest cancer-focused clinical research center. CCR is committed to rare cancers and underserved patient populations and can collaborate in joint ventures across NIH as well as in partnerships with industry and academia. If a health emergency arises (e.g., the severe acute respiratory syndrome (SARS) epidemic), CCR has the flexibility to rapidly redeploy resources.

A challenging question that has faced CCR in the past few years is how to be more efficient as costs increase and budgets grow tighter. CCR needs to maximize the impact per dollar spent in order to ensure that the most important clinical research is funded. Related challenges include determining how to measure quality and impact and deciding why a study should be done within CCR instead of extramurally. CCR's clinical protocols must: support the mission of CCR; be scientifically exciting; meet

peer-reviewed standards of scientific design; and have a high likelihood of timely patient accrual. In order to meet these challenges, CCR has developed a Strategic Alignment and Resource Planning (SARP) checklist. This is a six-section form that includes study identification, impact, demographics, utilization of unique CCR resources, resource needs, as well as additional pertinent information. Each time a study is proposed within CCR, the SARP form must be completed. Section 2 of the form, Study Impact, includes questions such as: How is this study consequential to the field? Will this study change research paradigms or clinical practice or be a significant step in doing either? Would leaders in this field consider this study to be of high impact? Why can't this study be easily conducted on the outside (i.e., at other institutions)? Is this a direct translation of CCR laboratory research and/or an extension of a prior study phase completed at CCR? Is the study part of an existing line of clinical investigation at CCR, or is the study a new clinical area at CCR that requires long-term commitment and tolerance for a lack of significant early clinical impact?

The goal of using the SARP form is to, as optimally as possible, distribute CCR resources across the current and projected portfolio of clinical trials to maximize the likelihood of achieving CCR's mission. Some basic principles that were set forth in this formal resource allocation process are transparency in decision making, a focus on impact and outcomes, and acknowledgement that some "good" research currently will not be funded.

CCR supported an evaluation of its program to determine the length of time it takes to complete studies. At the start of the evaluation, it took CCR an average of 208 days from the date of the scientific review to the opening of a study. An ambitious target of 60 days was set. In order to meet this target, an electronic system of prospective data collection was put in place to track the length of the scientific review, the time from completion of the scientific review to submission to the IRB, the length of IRB review, the length of Clinical Center approval, and time to accrual of the first patient. CCR is currently down to an average of 95 days from scientific review to study opening. Another efficiency process that CCR has implemented is a two-strike rule for scientific review. If an investigator sends a study for scientific review and it is not accepted, the investigator is allowed only one resubmission.

CCR's Clinical Research Center has a unique set of resources available to investigators. Imaging is a priority at CCR, and the resources at the Molecular Imaging Clinic will: help blur the line between imaging and pathology; develop novel imaging approaches and technology; improve imaging techniques to enhance early detection, diagnosis, and treatment; and develop novel imaging instrumentation and preemptive medicine. The Molecular Imaging Clinic is set up under the direction of Dr. Peter Choyke. The Clinic has positron emission tomography/computed tomography (PET/CT) and 3-Tesla magnetic resonance imaging (3T MRI) available to any patient on a clinical protocol. In collaboration with the NIH Clinical Center, CCR also has an NIH Center for Interventional Oncology. This Center offers new and expanding opportunities to investigate cancer therapies that use imaging technology to diagnose and treat localized cancers in ways that are precisely targeted and minimally invasive or noninvasive. Dr. Brad Wood is head of the Center for Interventional Oncology and is very interested in using interventional radiology as another modality. The Clinical Molecular Profiling Core (CMPC), directed by Dr. Paul Meltzer, provides CCR clinical investigators with ready access to genome technologies for tumor classification, cancer gene discovery, and clinical testing under Clinical Laboratory Improvement Amendments (CLIA). The CMPC operates on a collaborative model providing a fully integrated team with skills in genomics, oncology, pathology, bioinformatics, and laboratory operation. Operating in concert with the CMPC is the CCR Sequencing Facility. The Facility has Illumnia GAIIx and HiSeq instruments with a capacity of several hundred samples per year. A PacBio Sequencer has been installed in the Frederick facility, which provides rapid single-molecule sequencing for analysis of targeted regions in cancer and normal DNA, microbial genomes, etc. These resources will be used to ensure that the greatest amount of information can be derived from every patient participating in a clinical trial and to

gain the types of detailed information that could serve as the foundation to rapidly accelerate the pace of translation of basic science to clinical application.

CCR created a Steering Committee to discuss and determine major opportunities within the intramural program. The Steering Committee decided that a major clinical opportunity should address a fundamental problem in oncology, with broad applications across multiple clinical and laboratory branches, where the CCR has rare enabling expertise, capabilities, and/or direct patient populations. The opportunity should focus efforts over the next three to five years to achieve specified goals and deliverables that, when achieved, will be considered a major leap forward by the entire oncology community. By definition, major opportunities are not permanent organizational units but focused groups with time-sensitive deliverables. A major opportunity must have the following elements: a major theme; paradigm-shifting scientific and clinical goals; a rationale why the opportunity is unique and feasible at CCR; and collaboration across multiple branches.

A retreat was held about two weeks ago to discuss the major opportunities concept with the entire CCR community. Goals of the retreat were to increase communication among CCR members on clinical and basic activities, understand the importance of the major opportunities to the CCR, and provide transparency of the major opportunities selection process. Eight major opportunities under consideration were presented at the retreat: Targeting Inflammation in Cancer; Matrix Drug Screening for Combination Therapies in Cancer; Treatment of Cancers Based on Drivers of Mutations Independent of Histology or Site; Monitoring and Manipulating the Epigenome in Human Cancer; Targeted Therapy Combining Immunotherapy and Pharmacotherapy; Attacking Cancer Based on its Metabolic Basis; Rare Cancers and Genetic Tumor Predisposition Syndromes; and Characterizing the Transition from Premalignant or Smoldering Cancers to Malignant Tumors to Improve Interventions between Prevention and Treatment.

Structured discussions were held to determine perceptions from the external and internal oncology communities. Assuming scientific objectives are met in five years, how will each major opportunity "change the face of cancer"? Why should the major opportunity be addressed by CCR? Major opportunity strengths and areas for improvement, as well as integration with current research direction, were also discussed. A postretreat survey was given to participants of the retreat. Of the 99 people who responded, 31 identified themselves as basic scientists, 19 identified themselves as clinical scientists, and 49 identified themselves as translational scientists (clinical and basic). Responders felt the retreat was a good exercise and appreciated the interaction and ability to develop measures of success. The major opportunities will be presented to the Board of Scientific Counselors in November for additional input. All input collected will be provided to Dr. Bob Wiltrout, CCR Director, and Dr. Helman. Initial priorities will be discussed with Dr. Varmus and Deputy Directors. Once there is agreement on which major opportunities to pursue, the major opportunity leaders will be contacted to create a detailed schedule, budget, and resource list. An announcement will be made in January as to which major opportunities have been selected for funding.

CCR is an NCI intramural program, which accounts for about 14 percent of the overall NIH intramural program; however, CCR accounts for almost 40 percent of the NIH clinical program. Last year, CCR accounted for 37 percent of outpatient visits, 37 percent of inpatient days, and 22 percent of new patients at the NIH Clinical Center. About one-third of NCI's intramural trials are Phase I and about 50 percent are Phase II. Including Phase I-II studies, 95 percent of the trials CCR supports are early phase.

About two years ago, CCR started the Pediatric Wild-Type GIST Clinic at NIH, which is a collaborative effort between clinicians, research scientists, and advocates who share the goal of helping young patients with gastrointestinal stromal tumor (GIST). The Consortium for Pediatric and Wild-Type GIST Research (CPGR) was established to further understanding of this rare disease. The Clinic has seen

about 75 patients with pediatric wild-type GIST, and it has become clear that these patients almost uniformly have loss of the succinate dehydrogenase (SDH) gene. Methylation analysis revealed that these patients also have a hypermethylated genome. Within a year and a half of establishing the Pediatric Wild-Type GIST Clinic, metabolic pathway mutations (SDH and fumarate hydratase [FH]) were discovered in two rare tumors. Taking advantage of unique resources at the Hatfield Clinical Research Center, a novel mechanism (global hypermethylation) and potential treatment (metformin, antiangiogenic approaches) were identified. CCR was able to use both genomics and imaging to develop new approaches to treating diseases and to monitor therapy in real time. This work is likely to inform subsets of other common diseases.

CCR's Imaging Clinic offers the ability to use MRI to measure hyperpolarized C13 pyruvate in its molecular pathway. Hyperpolarized imaging shows trace differences between lactate, pyruvate, and alanine in tumors. Pyruvate is converted to lactate in malignant prostate cancer tissue, and this technology can be used to measure the conversion of pyruvate to lactate in tumor tissues in real time. The clinical hyperpolarizer can measure pyruvate as well as other metabolites within the tumor pathway.

Questions and Discussion

Dr. Abbruzzese asked when the major opportunity program will be launched and how many concepts will be supported. Dr. Helman clarified that the launch will occur in January and that the number of major opportunities to be funded depends on available resources; it will not be more than four.

Dr. Lippman asked Dr. Helman to expand on the "Characterizing the Transition from Premalignant or Smoldering Cancers to Malignant Tumors to Improve Interventions between Prevention and Treatment" major opportunity. Dr. Helman explained that this major opportunity resulted from discussions on whether there is an underlying metabolic mechanism in the premalignant state that is common among breast, lung, prostate, and colon cancers and myeloma.

Dr. Lippman asked whether CCR is conducting any early-phase trials in collaboration with DCP; for example, inference in smoldering myeloma. Dr. Helman commented that CCR is trying to do more in the field of prevention, but in terms of collaborating with DCP or DCEG, it depends on their portfolios and what would be complementary to CCR.

VIII. CTAC GUIDELINES HARMONIZATION WORKING GROUP (GHWG) IMPLEMENTATION UPDATE—MS. ANNA T. LEVY AND DR. TOBY T. HECHT

Ms. Anna Levy, Program Director, CCCT, NCI, gave an update on implementation of the Guidelines Harmonization Working Group's recommendations.

The goal of the GHWG was to harmonize program guidelines and develop incentives to foster collaboration among all components of the clinical trials infrastructure, including NCI-designated Cancer Centers, SPOREs, and Cooperative Groups. Dr. Abbruzzese chaired the Working Group, which was comprised of members from CTAC, the Cooperative Groups, SPOREs, Cancer Centers, and NCI leadership. The GHWG worked to define collaboration, identify model collaborative efforts, and examine current guidelines for clinical and translational research infrastructure and disincentives to collaboration. Some of the disincentives that were identified include inconsistencies across clinical trial guidelines, a lack of specificity in the guidelines for grantees and reviewers, differences in organizational cultures, and

fiscal challenges. Based on their work, GHWG members developed a vision document with recommendations that was presented to CTAC in July 2009. The recommendations fall into two broad categories:
(1) revise the guidelines and review criteria for the three major clinical trials mechanisms (SPOREs, Cancer Centers, and Cooperative Groups); and (2) provide incentives for collaboration across mechanisms. In December 2010, the Working Group presented a plan for implementation of its recommendations to CTAC.

Incentives to Promote Collaboration: Changes to the SPORE Guidelines. Dr. Toby Hecht, Acting Associate Director, Translational Research Program, DCTD, NCI, described the SPORE program implementation of the GHWG guideline recommendations. One of the recommendations was to describe collaborative efforts across mechanisms in a specified section of the application. The SPORE program created a new, independent section in the application called "Scientific Collaboration." This section includes a description of collaborative efforts that have as their goal moving studies of cancer therapeutics, biomarkers, prevention, or epidemiology from the discovery/laboratory phase to early clinical trials/studies and then to later-phase studies and beyond. The collaborative efforts should take place within the SPORE community, across NCI-supported clinical trials and translational science mechanisms, and with other government and non-government programs. The new section also includes a description of leadership related to collaboration, as well as a description of collaborative arrangements, where appropriate, such as separate grants, contracts, or Cooperative Research and Development Agreements (CRADAs) with industry for the continued development of concepts originating in the SPORE program.

The SPORE program defined two types of collaboration (horizontal and vertical) in order to best advance translational cancer research. Horizontal collaboration involves groups working together in a coordinated manner to accomplish a set of research aims or goals on a single level (i.e., in the laboratory, at the clinical trial stage, or as a population clinical study). This is the type of collaboration the SPOREs have traditionally conducted. Vertical collaboration involves groups working together sequentially or with some overlap to move up the translational cancer research pathway (i.e., from discovery to preclinical development, to Phase I trials or studies, to later-phase studies, and, possibly, to a final hand-off to a commercial company). Each SPORE must demonstrate a commitment to both horizontal and vertical collaboration in completing preclinical projects and moving promising results along the pathway of translational/clinical development.

Another recommendation included in the GHWG report is to reflect credit in the priority (overall impact) score. The "Scientific Collaboration" section of the SPORE application will receive an independent numerical score of 1 through 9 in peer review. A new paradigm for overall impact scoring has also been established. Instead of the previous 70:30 ratio between scientific projects and procedural elements, reviewers are being asked to focus on the translational impact of the scientific research projects as they are supported by the cores and in the context of the Program Organization and Capabilities, Developmental Programs, and Scientific Collaboration procedural sections of the SPORE.

Promoting collaborative activities between programs is an additional recommendation of the GHWG. Collaborative activity has always been a key feature of the SPOREs but it was reviewed as one of seven elements in the Program Organization and Capabilities section of the application. The Scientific Collaboration section is now independently scored and will receive more weight in the overall score.

The SPOREs also have been collaborating in other ways. Most organ site groups have monthly teleconferences for sharing information and data and for initiating collaborations. Institutions with several SPOREs have initiated meetings across organ site groups where signaling pathways common to several organ sites and technologies (e.g., oncolytic viruses) are shared.

A final guideline recommendation in the GHWG report is to incentivize transmechanism collaborations that will move novel interventions from preclinical to early clinical to Phase III trials. Only Phase I and early Phase II trials (less than 100 patients) may be supported by the SPORE program. Once a trial is successfully completed, it could be handed off to clinical trials Cooperative Groups. For collaboration (with other SPOREs, Cancer Centers, and other NCI grant mechanisms) on randomized Phase II therapeutic trials (greater than 100 patients), SPOREs are being advised to use the appropriate NCI disease-specific Steering Committee and its Task Forces and work together to develop clinical concepts from early SPORE trials that could move forward to the Cooperative Groups. These collaborations may include correlative studies. An alternative, but limited collaborative opportunity for large Phase II trials is to access CTSU resources on recommendation of a Steering Committee when it is not possible to use the Cooperative Groups. Additional information and instructions for all of the discussed changes are included in the new SPORE guidelines.

The SPORE program released its implementation timeline last December. Writing and approval of the new guidelines were completed in August 2011. An amended program announcement was completed in September 2011. The application receipt date is January 2012; Letters of Intent are due December 2011 for funding in FY2013.

Organ Site Workshops. Organ site workshops were established as incentives for collaboration across NCI-supported clinical trial mechanisms. The goal of the workshops is to provide a venue for investigators working in all areas of cancer translational research to come together in small groups to focus on new goals in translational science. The workshops serve to facilitate investigator-initiated interactions, foster collaborations across grant mechanisms, and forge new collaborations or consolidate ones that are in place. The conditions for holding the workshops are strict. There must be co-chairs from more than one NCI-supported mechanism (active funding required); a unique collaborative purpose, with follow-up; and stated objectives and outcomes aligned with the scientific priorities of the specific organ site disease. No similar meetings can have been scheduled for that organ site in the past or in the near future, and outcomes must be reported to the NCI by co-chairs.

Over the past year, 10 applications to hold workshops have been received. Three have been approved for support: the Prostate Cancer Genetics Workshop (November 2010); Targeting Lymphoma Metabolism and Oncogenic Pathways (July 2011); and Novel Neoadjuvant Therapy for Bladder Cancer (September 2011). The Prostate Cancer Genetics Workshop was chaired by William Catalona and William Isaacs. The purpose of the Workshop was to bring together experts in the field of prostate cancer genetics to develop a strategy to study the genetics of aggressive prostate cancer and discuss consistency in specimen and data collection. Participants came from varied backgrounds and included urologists, medical oncologists, geneticists, epidemiologists, statisticians, and NCI staff. Funding sources for participating investigators also varied and included SPOREs, the National Human Genome Research Institute, the Early Detection Research Network, the Strategic Partnering to Evaluate Cancer Signatures program, the International Consortium of Prostate Cancer Genetics, the Prostate Cancer Foundation, and MADCap. The outcome of the Workshop was a plan for multi-institutional collaboration for acquisition and analysis of data for a case-to-case association study to identify single nucleotide polymorphisms (SNPs) associated with aggressive prostate cancer. The meeting report on the Workshop was published in *Cancer Research* on May 10, 2011. Follow-up activities include the formation of a Genetics Working Group; collection of 23,000 cases (enough for analysis of Caucasians and African Americans); identification of 35 SNPs; and ongoing analysis.

Grand Opportunity "GO" Grants: A Model Mechanism for Team Science Research. The GHWG report recommended building on the Grand Opportunity grants program for clinical and translational research if evaluation found the mechanism to be effective. The "GO" grants pilot was

intended to be used as a model to develop a new mechanism to move exciting, novel, clinically applicable ideas from bench to bedside through the clinical trials system—transcending cultural barriers and research silos. The "GO" grant program had strict qualifications. An application had to include PIs from different institutions with diverse expertise who were already supported by different NCI/NIH funding mechanisms (e.g., SPOREs, P01s, R01s, Cooperative Groups, Cancer Centers, etc.) to form a team that could perform intensive, high-impact, and, if possible, paradigm-shifting studies associated with clinical trials. The PIs needed to propose translational cancer research projects of significant scope and consequence that, nonetheless, could be completed within two years. They had to propose focused, evidence-based, hypothesis-driven correlative studies associated with either an ongoing clinical trial or a new (ready to proceed) clinical trial in a multi-institutional setting. Industrial and foundation partners were allowed to participate in the research but did not receive government support for these studies.

The results of the "GO" initiative were that 32 applications were submitted and 9 were funded. The funded applications included projects from several NCI Divisions, programs, and diseases (pancreatic cancer, childhood ALL, oral cancer, melanoma, lung cancer, and prostate cancer, among others). Each of the nine funded grants has been active for two years and has been given a one-year no-cost extension. Progress reports are due after the end of that year. A full evaluation will be conducted once the grants are completed. Dr. Hecht provided a short synopsis of a few of the nine supported grants.

Dr. Timothy Triche—Translation of Predictive Cancer Biomarkers into Clinical Practice. The goal of this study is to develop diagnostic gene expression profiles from formalin-fixed paraffin-embedded (FFPE) tumor tissues for the clinical classification of childhood rhabdomyosarcoma (RMS) in order to determine treatment options, as conventional pathology and clinical criteria fail to predict outcome in most patients, particularly those classified as intermediate risk. So far, Dr. Triche and colleagues have analyzed outcome versus 1.4 million RNA transcript expression values in 167 childhood RMS cases from Children's Oncology Group intermediate-risk treatment protocols. They have derived a multigene ("metagene") biomarker profile that predicts outcome better than the standard method of prediction. The microarray-based prognostic profile has been successfully translated to a cheaper, faster platform that works well on routine FFPE specimens. The NanoString platform was selected as the best technology to translate the prognostic signature to a clinical assay. Excellent correlation was shown between data generated at the Children's Hospital of Los Angeles and the National Children's Hospital in Ohio. An application for CLIA certification is being done at both labs. Dr. Triche will assess RNA expression in 400 corresponding FFPE tumors from the COG protocol of intermediate risk; the prognostic profile will be refined by dropping underperforming RNAs. A prospective validation will be conducted on RMS patients in COG low-, intermediate- and high-risk therapy protocols.

Dr. Bruce Trock—Biomarker Prediction of Gleason Upgrading. This study aims to develop a new biomarker-based diagnostic model to improve the diagnostic accuracy of prostate biopsies—a critical need to increase the safety of patients who choose active surveillance and are determined to be Gleason grade 3, but may be Gleason 4. Biomarkers that are being looked at include: molecular indices of chromosome instability, mitotic spindle checkpoint integrity, centrosome function, proliferation, hypoxia, and epigenetic/DNA damage response. A predictive model will be proposed and validated in an independent cohort. So far, 200 radical prostatectomy specimens (Gleason scores 3+3, 3+4, and 4+3) have been accessioned and 106 biopsy cores (Gleason score 3+3) with corresponding prostatectomy tissues (Gleason scores 3+3 and 3+4 or 4+3) have been obtained. Tissue microarrays are complete. Biomarker analysis is being performed in five different laboratories to find markers that discriminate Gleason grade 3 from Gleason grade 4. Biomarker assay optimization is complete. Analysis is continuing and will be completed by the end of the no-cost extension.

Dr. Steven Grant—Proteasome/HDAC Inhibition in Leukemia/MDS: Phase I Trial and Correlative Studies. Dr. Grant is studying the antitumor activity of the combination of a pan-HDAC

inhibitor (belinostat) and a proteasome inhibitor (bortezomib)—drugs that have little or no activity as single agents—in a clinical trial of refractory acute myelogenous leukemia (AML), high-risk myelodysplastic syndrome (MDS), chronic myelogenous leukemia (CML)-blast crisis, and ALL patients. Correlative pharmacodynamic studies are also being conducted in bone marrow and/or peripheral blood on NF-kB activation, downregulation of NF-kB-dependent proteins, upregulation of pro-apoptotic protein Bim, and inhibition of 20S proteasome activity. It was difficult for Dr. Grant to get started on the study because of the Clinical Trials Agreement (CTA) between two companies; however, the CTA and IND approval were obtained. The clinical trial opened in May 2010. Sixteen patients have been enrolled in three different levels and are ready to be escalated to the fourth dose level. No dose-limiting toxicities have been encountered so far. There has been one objective response, four stable disease responses, and seven progressive disease responses. Dr. Grant has faced some obstacles. For example, some of the patients have not met the criterion for correlative studies or have refused a second posttreatment bone marrow sample. Three publications have already resulted from this work.

Dr. Susan Mallery—Clinical Evaluation of a Bioadhesive Gel for Oral Cancer Prevention. The goal of this study is to extend previous work to a prevention trial with freeze-dried black raspberry (BRB) bioadhesive gel in dysplastic oral lesions, which showed that one-third of participants were high responders (to anthocyanins in the preparation) and suggested that patient-specific differences in target tissue absorption, metabolic activation, and local retention of the BRB constituents affected chemopreventive response. Dr. Mallery has established the assays that identify the pharmacokinetic and anthocyanin bioactivation pathways that are active in the human oral mucosa. IND approval has been received. A study with normal volunteers supports differences among participants in gel absorption, distribution, and local retention of anthocyanins in the oral mucosa. The oral cancer chemoprevention trial is proceeding and 16 patients have been accrued. Studies to determine loss of heterozygosis indices and p16 methylation (comparing pre- to posttreatment tissues) are ongoing. The histologic and clinical results are promising. Ten additional patients are currently in varying stages of the study. One patient's dysplastic lesion has completely resolved clinically; his light microscopic diagnosis decreased two histologic grades. Dr. Mallery published one paper this year based on this work.

Dr. Jedd Wolchok—Defining the Importance of Immunity to NY-ESO-1 in Melanoma Therapy and Prognosis. Dr. Wolchok is working to establish the importance of NY-ESO-1 as a biomarker in the immunotherapy of metastatic melanoma with anti-CTLA4 (blocking antibody). All patients treated with ipilimumab (ipi) in the adjuvant setting have been accrued. In studies with advanced melanoma patients treated with ipi, patients with an NY-ESO-1 antibody response experienced more frequent clinical benefit at week 24 than did seronegative patients. Within a subset of seropositive patients, the induction in patients of specific CD8+ T-cell responses to NY-ESO-1 correlated with a better clinical response compared with patients who did not have specific CD8+ T cells. B- and T-cell responses to NY-ESO-1 may have predictive value for ipi treatment. One publication has come out of this work.

Currently, there are few, if any, research support mechanisms that require collaboration across institutions and across methods of grant/contract support. Collaboration is essential for many studies, particularly for studies of rare cancers and those that are underrepresented in the NCI portfolio. Funding mechanisms do not commonly support both clinical trials and correlative studies. The "GO" grant-funded studies can be completed in three years—less time than required for the average R01 study. The "GO" grant mechanism is a grant, not a supplement. The advantage is that supplements are only appropriate for grants with enough years left in their funding periods to include the period of the supplements. Additionally, collaborators need to be in synchrony with their funding periods, and investigators who are co-PIs (with critical expertise) cannot apply for supplements. Dr. Hecht then posed the question of whether NCI should consider using a mechanism similar to the "GO" grants in the future to encourage team science.

Questions and Discussion

Dr. Abbruzzese asked Dr. Doroshow to comment on the Grand Opportunity grants. Dr. Doroshow stated that the "GO" grant program provides a mechanism to bring successful investigators together with sufficient resources to accomplish research objectives that the investigators would not be able to accomplish otherwise. He expressed his opinion that NCI should continue supporting this grant mechanism in the future. Dr. Lippman agreed that CTAC needs to encourage the type of collaboration supported by the "GO" grants.

Dr. Lippman asked whether the new SPORE guidelines outline procedures for the hand-off of potential predictive biomarkers in early-phase trials to later-phase settings—that is: Is the development of biomarkers viewed the same way as the development of new agents? Dr. Hecht responded in the affirmative. However, a biomarker must undergo assay validation before clinical validation. Investigators can apply for access to NCI's assay development and validation resources through the Clinical Assay Development Program (CADP).

Dr. Bertagnolli added that the "GO" grant program is a wonderful mechanism—it has a lot of flexibility and allows translational researchers to think outside the box.

Dr. Tepper commented that collaboration and correlative science should not be combined into one issue.

Dr. Civin stated that one challenge with the "GO" grant program is the short duration of the grant support; it will be interesting to come back to the nine funded projects in a few years to see if the collaborations truly have been successful.

IX. PROVOCATIVE QUESTIONS INITIATIVE—DR. EDWARD E. HARLOW

Dr. Edward Harlow, Special Assistant to the Director, Office of the Director, NCI, presented an overview of the Provocative Questions Initiative, which he described as a compilation of important research questions with some thinking on how they can best be used within the scientific community.

Questions are a huge part of a scientist's daily work. Dr. Harlow said that his laboratory notebooks often start with a question that will be his focus for that day or week. Questions are part of scientific rigor and when posed after a talk are often the best part of constructive conversation or debate. For example, in the case of "GO" grant review, critical questions led to a tightening of thinking and essentially served as a push forward. This can be used as an organizational strategy for all parts of the scientific enterprise. Therefore, the focus of the Provocative Questions Initiative is to see how one might use proposed research questions to set scientific direction—something that has not been a significant part of NCI's operation in the past.

Provocative questions start with acquiring a sense of community opinion, a strategy influenced by the Gates Foundation's Grand Challenges in the Global Health Initiative. The Grand Challenges program aims to frame scientific opportunities by asking the community for its opinions on direction, key issues, and next steps necessary in terms of global health. The Provocative Questions Initiative, unlike the Gates Foundation program, uses questions as the key foundation for its thinking.

The Provocative Questions Initiative seeks to challenge NCI's scientific community to delve into research areas that are not immediately obvious, areas of research that are just now possible because of technological advancements, or, possibly, older areas of research that have been overlooked for decades. The questions need to address broad issues in the biology of cancer that have proven difficult to resolve, building forward from where we are today. At the same time, these initiatives must be achievable. Even though the community can readily think of areas that need work, the areas chosen for immediate attention must be reasonably approachable. The proposals should build on scientific advances in the understanding of cancer and cancer control, take into consideration the likelihood of progress in the foreseeable future, and address ways to overcome the obstacles that become apparent when answering a question.

Dr. Harlow expressed his opinion that the Provocative Questions Initiative is an experiment that seems to be working. The first questions were posed at a workshop held in October 2010 and asked whether useful questions that fit the goal of the Initiative could be developed. These first questions also asked whether the process could be fun for the community and interesting enough to draw participants. The answer to these questions was yes; participants were able to identify important questions and enjoyed the banter and constructive arguments that were part of the process.

The second stage of the Provocative Questions experiment involved establishing a large group of questions that would fit the high-level description. A series of workshops over the past months (three occurred in February) set out to accomplish this by dividing question groups into the disciplines of population, clinical, and basic sciences. The workshops took place on the NIH campus; participants came to converse for the duration of the day, and a collection of high-quality questions was built as a result.

In August, these workshops were taken on a tour of the west coast, with stops in San Diego, Los Angeles, San Francisco, Seattle, and Oregon. All workshops included local health professionals from those areas. Each session produced new questions and areas that had not been previously appreciated. Overall, the west coast workshops illustrated the richness of this question-building exercise.

Also in August, a workshop took place at NCI for trainees. The workshop extended the "experience net" and created new questions. As a result, an additional series of workshops is now planned. Some of the workshops will be held within the NCI community to build local recognition of the program, and also in Tucson and Houston.

Earlier this year, this experiment was expanded to include thinking on how best to drive research portfolio development. An RFA based on 24 provocative questions that met specific criteria was brought forward internally before approval through the Board of Scientific Advisors. These 24 questions covered a broad spectrum of cancer research. For each question, a portfolio review was conducted across all cancer research organizations to identify work in that particular area and ensure that only new or understudied research areas would be approached. The RFA closed November 14th, and a review process was put in place to manage the operation. The question to ask at the end of this process is whether this [Initiative] should be repeated if found successful and, if so, what the size of the program should be.

The Provocative Questions Web site (http://provocativequestions.nci.nih.gov/) includes questions from the workshops as well as from the community. The site is open for anyone to join and individuals may register questions and comments. It has grown popular, averaging about 1,800 hits a day and about 150 questions in total, along with comments that have been submitted online.

The RFA supports R21 and R01 grants with the intent of keeping the grant mechanisms simple for an initiative that is new. The R21 and R01 grant mechanisms are both well recognized among the scientific community. The R21 program provides the standard of two years of funding, and the R01

provides four years of funding. The thinking is that this is a preliminary project to build a new research setting and that sufficient data could be gathered in that timeframe to apply for the next round of funding.

The Provocative Questions Initiative has a $15 million budget, which was considered to be sufficient to show commitment from the community in tough fiscal times.

The five standard review criteria include significance, PI, innovation, approach, and environment. There is agreement that there are many new areas that need work. The review process should concentrate on the strength of ideas and less on preliminary data, since in many cases there will not be preliminary data in these areas. It is also important to ensure that the review process is not weighted solely by the strength of the PI's track record.

Dr. Harlow gave an overview of a few of the 24 Provocative Questions. Provocative Question 1 (PQ1), the most popular question in terms of Letters of Intent, is: How does obesity contribute to cancer risk? The intent of the question is not on how obesity is linked to cancer and what the risk factors are, but on the mechanism of how obesity contributes to cancer risk.

The connection between obesity and a higher risk of cancer already has been well established. Dr. Harlow highlighted a study on the increased risk of different tumors in both women and men. The study shows that certain tissues are very sensitive to risk factors involved in obesity. Obesity has shown a long-term, increasing trend in the American populace according to a risk surveillance system from 1999 to 2009. In fact, cancer is one of the diseases most dramatically affected by obesity, which almost doubles the risk of disease.

Dr. Harlow noted that this Provocative Question not only moves the obesity observation into understanding mechanisms but also connects it with the fields of risk identification and cancer biology. He suggested that this question provides an opportunity for epidemiologists and basic biologists to bridge observations of trends related to increased body mass—obesity events associated with events recognized at the beginning of cancer development.

PQ5 is: Given the evidence that some drugs commonly and chronically used for other indications, such as an anti-inflammatory drug, can protect against cancer incidence and mortality, can we determine the mechanism by which any of these drugs work? A study published in *Lancet* in January 2011 looked at several clinical observations on the relationship between long-term aspirin treatment and a dramatic change in overall cancer incidence. Depending on the site, cancer risk was reduced up to 30 to 35 percent. This observation was the stimulus for this particular Provocative Question—again, thinking about the mechanisms involved rather than attempting to replicate the observation or append it to different tumor sites. The question asks what events are driven by aspirin that are making the difference seen in cancer risk. Interestingly, some tissue sites are very sensitive to long-term aspirin use while other tissue sites are not. There is a both a tissue-specific event and a molecular event that the question seeks to identify.

Another question, PQ21, asks: Given the appearance of resistance in response to cell-killing therapies, can we extend survival by using approaches that keep tumors static? This question was developed during the last west coast trip to San Francisco, when an evolutionary biologist critiqued Dr. Harlow's basic biology perspective on selective pressures involved in the early stages of a tumor. The evolutionary biologist pointed to population dynamics. Dr. Harlow referred to a picture depicting the change in the color of the English pepper moth corresponding to the darkening of birch tree bark caused by industrial pollution. It shows a rapid, dynamic genetic selection in place to ensure that the once light-colored pepper moth would still be able to camouflage itself among the newly darkened trees.

The evolutionary biologist explained that according to first principles, if you have a dynamic cell population, a strong selective agent will automatically single out resistant populations. If the cell population is dynamic but cannot change, a long-term treatment is possible. But whatever the agent in a dynamic cell population, the laws of Darwinian selection predict that the resistant population will be selected—the metaphorical black moth. The evolutionary biologist suggested that methods that are not as strong in selection should be examined. These can be directed against the tumor in question, but at the same time one must be mindful that the majority of mutations are deleterious and the survival fitness of these mutated cells will reduce dramatically over time. Selective pressures that are not as strong could create a situation in which the tumor remains static—wild-type cells and mutated cells under selective pressure would be in competition.

PQ19 asks: Why are some disseminated cancers cured by chemotherapy alone? This Provocative Question served as an example for posing other important PQs. It relates to cases like that of Lance Armstrong, whose testicular cancer was cured with cisplatin treatment—a common procedure with an 85 percent chance of success. This cure is durable, but it is not understood how it works—why the cancer cells die, or why the treatment is so penetrant. If this can be understood, perhaps it can be applied to thinking about other treatments.

Dr. Harlow then discussed the value of the Provocative Questions Initiative. It highlights new research questions that are thought to need attention. It engages the community in discussion and good intellectual exchange about what the right questions are. It pushes research to new areas—particularly important in tight budgetary times. The process is a means of facilitating change in the research portfolio, spreading some of grants across the hottest areas of research as well as into other subject areas. When funding is tight, the tendency is to move toward the center, picking subjects that are less risky—something this Initiative can help avoid.

Evaluation for success of the program is not simple. For short-term evaluation and to determine whether it would be worth going out for another round, one can look at whether or not the program is able to stimulate excitement in the scientific community. There is evidence that the Initiative is generating that excitement; 701 Letters of Intent have been received and the Web site gets about 1,800 hits per day.

When measuring intermediate-term success, Dr. Harlow noted that if the process is done well, each applicant should be able to move immediately into and be competitive for traditional grant mechanisms. These are not renewable grants; however, if the investigator is helping to build a new research area, he/she already will be in an ideal place to write an R01. Longer term, it is expected that there will be answers to these questions. A better understanding of the research field and neoplasms will be achieved (i.e., better risk assessment, prevention, treatment, etc.) and the building of new subdisciplines will be apparent. If the program is successful, one will begin to see a filling in of the gaps in the portfolio.

Dr. Harlow suggested that if the Initiative is successful, a large portfolio of valuable questions can be put before the community. The challenge, then, will be to think about how to make this process work in the long term: Should it be repeated and, if so, what would be a reasonable fraction of the funded portfolio to dedicate to this Initiative? All of these questions and concerns will have to be addressed as the program moves forward.

Dr. Harlow acknowledged his colleagues, Drs. Harold Varmus and Doug Lowy (NCI), and Tyler Jacks from MIT, who were part of the team. Drs. Maureen Johnson and Lisa Stevens assisted with coordination and note-taking at the workshops. Dr. Samantha Finstad led the portfolio analysis, and Dr. Elizabeth Hsu, Dr. Margaret Ames, and staff from the NCI Office of Science Planning and Assessment produced a portfolio analysis quickly. Ms. Lisa Cole and Mr. Clint Malone were recognized for building

the Initiative's Web site. The RFA concept is now managed by Ms. Christine Seiman, and Drs. Jan Woynarowski and Jerry Lee, who is the Program Officer responsible for pulling together the multidivisional operation. Dr. Harlow extended his heartfelt thanks to all of these people.

Questions and Discussion

Dr. Weiner asked Dr. Harlow if he is sure the Provocative Questions are stimulating research in new areas or simply stimulating researchers to cleverly reshape the work they want to do. Dr. Harlow agreed that the program has to be very careful in making this distinction. He emphasized that the intent has been to focus on areas that are understudied or relatively unpopulated with current research proposals. He also expressed hope that the review process will weed out applications that do not fit this description, and these should not be considered. Dr. Weiner suggested adding an anonymous survey at the end of the process to ask if the applicant is posing new research or reshaping previous work. The next difficult step is to manage the review to think about whether something new is actually being done.

Dr. Bertagnolli commented that the Provocative Questions Initiative provides support in areas that are important for clinical/translational researchers to address. She added that large, science-based initiatives supporting research in clinical and translational fields are uncommon. Dr. Harlow noted that some who have read over these questions do not feel that they are original and are not enthusiastic about them. He stressed the need to find a balance that accommodates these diverse viewpoints, and that will be easier with time and experience.

X. NEW BUSINESS—DR. JAMES L. ABBRUZZESE

Dr. Abbruzzese encouraged CTAC members to participate in the meeting agenda planning process and suggested having a presentation on the status of the CTEP Phase I U01 and Phase II N01 program at an upcoming meeting. If CTAC members would like to suggest an agenda item(s) or participate in the agenda planning process, they should contact Dr. Prindiville or Dr. Abbruzzese.

XI. ADJOURNMENT—DR. JAMES L. ABBRUZZESE

There being no further business, the 15th meeting of the CTAC was adjourned at 3:18 p.m. on Wednesday, November 9, 2011.