

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
8th CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY
COMMITTEE MEETING**

Summary of Meeting
July 15, 2009

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

**CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
BETHESDA, MARYLAND**

Summary of Meeting

July 15, 2009

The Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) convened for its 8th meeting on Wednesday, July 15, 2009, in Conference Room 10, C-Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD from 8:00 a.m. – 2:52 p.m. Dr. John Niederhuber, Director, NCI, presided during the meeting.

CTAC Members

John Niederhuber, Chair
James L. Abbruzzese
Peter C. Adamson
David S. Alberts
Kirby I. Bland
Deborah W. Bruner (absent)
Curt I. Civin (absent)
Kenneth H. Cowan
Everett Dodson
Stephen S. Grubbs
Bruce J. Hillman
Sandra J. Horning (absent)
K. Gabriel Leung (absent)
Nancy P. Mendenhall
Heidi Nelson
David R. Parkinson
Edith A. Perez (absent)
Timothy R. Rebbeck (absent)
Nancy Roach
Carolyn D. Runowicz
Daniel J. Sargent
Richard L. Schilsky
Joel E. Tepper
James L. Wade, III

Ex Officio Members

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

Executive Secretary

Sheila A. Prindiville, NCI

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

Dr. John E. Niederhuber, Director, National Cancer Institute (NCI), called to order the 8th Clinical Trials and Translational Research Advisory Committee (CTAC) meeting. He welcomed the Committee and *ex officio* members and then reviewed the confidentiality and conflict-of-interest practices required of the Committee members during their deliberations. Members of the public were welcomed and invited to submit comments related to items discussed during the meeting in writing to Dr. Sheila A. Prindiville, Director, NCI Coordinating Center for Clinical Trials (CCCT), within 10 days of the meeting. Any written statements by members of the public will be given careful consideration and attention.

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

II. DIRECTOR'S UPDATE—DR. JOHN NIEDERHUBER

American Recovery and Reinvestment Act of 2009 (ARRA) Update. The National Institutes of Health (NIH) is fortunate that the Act recognized the importance of investment in science and technology. NIH plans to use ARRA support to significantly change the science base in 2011 and 2012 by stimulating investment in new science and technology that will make a difference for patients. ARRA funds can help change the course of disease in the future. Of the \$10.4 billion of ARRA funding provided to NIH, NCI will be directly allocated \$1.26 million. New grant applications related to ARRA funds will undergo peer review in the near future. Mechanisms for obtaining NCI ARRA funds include Grand Opportunities (GO) grants, Challenge grants, training grants, competitive revisions, administrative supplements, and activities to promote research collaborations.

In addition to the ARRA funds being distributed to the NIH Institutes and Centers (ICs), NIH has already awarded additional ARRA funds to support extramural construction and shared instrumentation. NIH has also been given \$400 million in ARRA funds to support comparative effectiveness research (CER); NCI's experience in using new knowledge to inform patient care will facilitate the use of these funds. Stimulus money is also being invested in technology development. Ken Buetow has been effective in leading NCI information technology development and explaining the Institute's progress in IT and bioinformatics (such as caBIG and the new BIG Health initiative) to the Department of Health and Human Services (DHHS) and congressional leadership.

As a member of a committee tasked with managing NIH CER programs, Dr. Niederhuber became aware that the Government needed to reach agreement on a definition of CER. The Federal Coordinating Council (FCC) for Comparative Effectiveness Research, which was established by the DHHS Secretary, was asked to develop a definition of CER. Dr. Elizabeth Nabel of the National Heart, Lung, and Blood Institute represents NIH on the FCC.

In its June 30, 2009 report, the FCC recommended investment in dissemination of results of CER focused on priority populations and high-impact health areas. The report also stressed the need to invest in data infrastructure (e.g., large databases and electronic health records). Also on June 30, the Institute of Medicine (IOM) released a report with recommendations on CER. The report suggests 100 high-priority health topics for which Federal CER projects should identify the most effective health care services.

It should not be forgotten that ARRA is primarily intended to protect existing jobs and create new employment opportunities. It is not designed to make up for recent budget deficits. The infusion of one-

time funds into the NIH budget presents problems in managing out-year obligations of new 2-year to 5-year grants. NCI is devoting a great deal of thought to softening the long-term impact of temporary increases in funding for research grants, as well as future increases in grant applications as unsuccessful applications for ARRA support are revised and resubmitted as requests for appropriated funds. There are also increased administrative costs associated with reviewing and managing larger numbers of applications.

NCI has increased the 2009 Research Project Grant payline from the 12th to the 16th percentile using appropriated funds. ARRA funds will be used to fund the first half of 4-year grants scored between the 16th and 18th percentiles, to be followed in out-years by support using appropriated funds. A mix of 2-year and 4-year grants scored in the 18th to 25th percentile range will also be funded using ARRA funds for the first 2 years. If the NCI budget for the next few years remains flat, the Institute will incur deficits due to obligations represented by increased numbers of grants. Leadership remains hopeful that at least inflationary increases in the NCI budget will be requested by the President.

Plans for the distribution of ARRA funds to categories such as research project grants, GO and Challenge grants, supplements, infrastructure, cohort studies, and other priorities remain flexible. Final decisions will depend in part on the quality of applications received. Since ARRA funds must be spent by the end of FY2010, NCI has hired a number of experienced grants specialists as contractors to help process ARRA applications.

NCI Budget Update. NCI's operating budget for FY2009 represents an increase of more than \$138 million, which is 2.9 percent more than the FY2008 budget. For FY2010, the President has proposed an increase for NCI of approximately \$181 million, or about 3.5 percent. The President proposes to invest over \$6 billion for cancer research across NIH in FY2010, reflecting the first year of an 8-year strategy to double funding for cancer research. The goal is to increase the NIH budget to approximately \$32.3 billion and increase NIH spending on cancer research to \$11 billion by FY2017. The House Appropriations Committee has drafted a bill that includes a 3.1 percent increase for NIH in FY2010.

NCI Update. Dr. Niederhuber and Dr. Stephen Katz of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) co-chaired a committee that recently developed a trans-NIH strategic plan for cancer research. Each Institute and Center involved in cancer research assigned an individual to participate in this process. The committee created a format for seeking information from ICs about their support of cancer research, specific research interests, and grant portfolios; they responded thoroughly and in a very timely fashion. The committee's report was submitted to NIH on June 30, 2009. A team of NCI staff then developed a document that merges the ICs' input into several themes. The plan outlines how cancer research could continue to move forward at NIH with the leadership of the NCI.

The ICs that contributed to the strategic plan placed an emphasis on preventing cancer and developing novel therapies. One of the goals outlined is to understand the dependence of cancer cells and cells in the microenvironment on genes that are amplified, translocated, mutated, or epigenetically altered. NCI hopes to build on the sequencing of tumor DNA to elucidate the functional implications of those alterations and begin to design targeted molecules and biologics as well as identify informative biomarkers. NCI has begun to perform some of the translational research that will help move from genomics to therapies through programs such as The Cancer Genome Atlas (TCGA), the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program, and the Cancer Genetic Markers of Susceptibility (CGEMS) initiative. The trans-NIH strategic plan for cancer calls for conducting these types of translational studies on 20 to 25 major cancers, as well as rare but highly lethal diseases, such as pancreatic and esophageal cancers.

These activities will require well-annotated biospecimens. NCI has been working for a number of years to develop criteria and standard operating procedures for collecting and sharing specimens. This has led to development of the Cancer Human Biobank (caHUB) to develop new biological resources and make them available to the research community.

The intellectual “horsepower” for work in the realms of functional and chemical biology is provided by the extramural research community. In addition to supporting this effort through the traditional grant process, NCI plans to create consortia of laboratories throughout the academic community to carry out highly targeted projects with specific metrics, deliverables, and time frames. GO grants and other ARRA-supported mechanisms will play an important role in scaling up this effort.

Dr. Niederhuber explained that he sees NCI as an “enabling partner” that creates a safe harbor between the academic and private sectors to foster progress in development of personalized and highly targeted therapies. It has become clear that this process will require large cohorts of well-characterized patients. Recently, the TCGA oversight committee stressed the need for creation of a patient and tumor characterization center to serve as a data resource for the cancer research community. NCI is planning to pilot this type of center to find out how it can be done effectively. Among other things, advancements in applied computing will be needed to manage large data sets and create safety monitoring systems that ensure information is made available only to the appropriate people at the appropriate time. It will also be important to develop ways to translate the collected data into reports that will be informative and easily utilized by practicing physicians.

NCI has begun increasing the involvement of experts in disparate fields such as chemistry, physics, and mathematics in discussions about the future of cancer research. These discussions have led to novel ideas about the evolution of systems and communication. This process has resulted in receipt of a number of applications to create “virtual centers” bringing together scientists at multiple institutions to provide fresh approaches to addressing cancer-related issues. NCI is currently evaluating the scores these applications received in peer review and considering how such centers or teams could be formed and supported.

There is evidence that between 18 and 24 percent of all cancers have some level of infectious etiology. NCI is planning a series of workshops for the fall of 2009 to obtain the input of experts in infectious diseases regarding ways to study the contributions of these diseases to cancer.

Questions and Discussion

Dr. Richard Schilsky, Associate Dean for Clinical Research at the University of Chicago, asked whether the proposed tumor and patient characterization center would be based on the NIH campus and whether NCI-designated Cancer Centers would be involved. Dr. Niederhuber replied that NCI envisions providing core operating and support activities in a central location but that technology and expertise would be widely dispersed. Both intramural and extramural programs and resources would be part of this effort. Advances in the creation of new technologies can often be achieved more efficiently within NCI than through the competitive environment. The extramural community is essential to the process of learning how best to use those technologies.

Dr. David Alberts, Director of the Arizona Cancer Center at the University of Arizona, noted that sequences of development in intraepithelial neoplasias—for example, from colonic adenoma to cancer, ductal carcinoma in situ to invasive breast cancer, or CIN3 to cervical cancer—are not being addressed by the TCGA project. Dr. Niederhuber explained that the next-generation sequencing technologies that will

facilitate such studies are still being developed. Acquisition of high-quality specimens that can be characterized in large numbers is also critical to progress in this area. caHUB will play an important role in that endeavor. Geographic location may also be a factor.

Dr. Joel Tepper, Hector MacLean Distinguished Professor of Cancer Research at the Lineberger Comprehensive Cancer Center at the University of North Carolina, asked for more information on plans to reengineer clinical trials. Dr. Niederhuber commented that NCI and its advisors have dedicated a great deal of effort to learn how to make the clinical research process more efficient. Advances in molecular targeting of therapies make this an even more complex issue. The characterization of large numbers of patients throughout the country is expected to make it possible to test new therapies more quickly by identifying the often small numbers of patients needed for specific studies rather than waiting for them to present themselves. NCI's Cancer Centers, including the new Community Cancer Centers, are an essential link in bringing these new therapies into practice. Dr. James Doroshow, Director of the NCI Division of Cancer Treatment and Diagnosis (DCTD), added that coordination is also critical to creating efficiency in clinical trials. Specialized Programs of Research Excellence (SPORES), Cancer Centers, and other groups must be brought together into an integrated clinical and translational research system.

III. LEGISLATIVE UPDATE—MS. M.K. HOLOHAN

Ms. M.K. Holohan, Deputy Director, Office of Government and Congressional Relations (OGCR), NCI, reported on the status of appropriations, highlighted several pieces of legislation, and provided an outlook for the 111th Congress.

FY 2010 Appropriations Status. The President's budget for FY 2010 was released on May 7, 2009; it included \$30.8 billion for NIH, with \$5.15 billion for NCI and \$6 billion for NIH to devote solely to cancer research. The Administration has made a commitment to double funding for cancer research over an estimated period of 8 years. However, appropriators in Congress have made it clear that this commitment should not be viewed as a mandate and that Congress will ultimately decide funding amounts. The House hearing on the NIH budget took place on March 26, 2009, and the Senate hearing took place on May 21, 2009.

On July 24, 2009, the House plans to vote on FY 2010 Labor, Health and Human Services, Education, and related agencies appropriations. There is no date set for the Senate vote, but the Chairman stated intention to pass all 12 appropriations bills before the end of the fiscal year.

Legislation. The 21st Century Cancer ALERT (Access to Lifesaving Early Detection, Research and Treatment) Act was introduced by Senators Kennedy and Hutchison on March 26, 2009, and referred to the Senate HELP (Health, Education, Labor, and Pensions) Committee. Provisions of this bill related to NCI include the enhancement and improvement of cancer research conducted and supported by NCI and the National Cancer Program; an increase in focus on biospecimen resources; and enhanced reporting on cancer, especially rare cancers and cancers with low survival rates. The emergence of health care reform as a high priority has stalled progress on the ALERT bill, and it is unlikely that the bill will undergo markup before the August recess.

Several pieces of legislation pertaining to comparative effectiveness research have been introduced. The Comparative Effectiveness Research Act was introduced by Representative Schrader on May 19, 2009. This legislation would establish a private, nonprofit organization, the Health Care Comparative Effectiveness Research Institute, which would be required to disseminate findings to clinicians, patients, and the general public. Another bill, the Healthy Americans Act, was introduced by

Senator Wyden on February 5, 2009, and Representative Eshoo on March 5, 2009; among other things, this bill would establish a Comparative Effectiveness Advisory Board. Lastly, the Patient-Centered Outcomes Research Act of 2009, introduced by Senator Baucus on June 9, 2009, would establish a private, nonprofit corporation to identify national research priorities relative to patient-centered outcomes research. The movement of these bills will depend on the outcome of the health care reform debate.

Senator Specter introduced the Cures Acceleration Network and NIH Reauthorization Act of 2009 on April 28. This bill would establish an independent agency—the Cures Acceleration Network (CAN)—outside of DHHS to promote the translation of scientific discoveries from bench to bedside. This legislation would also raise the NIH authorization to \$40 billion and elevate the National Center for Minority Health and Health Disparities to institute status.

On June 22, 2009, President Obama signed the Family Smoking Prevention and Tobacco Control Act into law. This legislation grants the U.S. Food and Drug Administration (FDA) authority to regulate manufacturing, marketing, and sale of tobacco products. This bill restricts advertising and promotions by requiring warning labels to occupy 50 percent of the front and back of packages, as well as banning misleading claims, such as “light” and “low tar.” User fees paid by tobacco companies will help support the new FDA activities related to tobacco regulation.

Outlook – 111th Congress. The Senate HELP Committee is set to vote on the Healthcare Reform Bill on July 15, 2009. The Senate Finance Committee must also mark up and vote on the bill; no date has been set but the goal is to vote before the August recess. Three committees in the House—Energy and Commerce, Ways and Means, and Education and Labor—all have jurisdiction over the Healthcare Reform Bill. These committees’ deliberations started on July 15, all with the goal of finishing the process before the recess.

IV. GENITOURINARY STEERING COMMITTEE (GUSC) UPDATE—DR. GEORGE WILDING

Dr. George Wilding of the Carbone Cancer Center at the University of Wisconsin reported that the CTAC Genitourinary Steering Committee (GUSC) has been operational for approximately 1 year. The GUSC’s co-chairs, in addition to Dr. Wilding, are Dr. Eric Klein of the Cleveland Clinic and Dr. Anthony Zietman of Massachusetts General Hospital. The more than two dozen GUSC members include representatives of SPOREs, experts in community medical and radiation oncology and urology, Cooperative Group disease chairs, extramural statisticians, NCI intramural and extramural staff, translational scientists with R01 and P01 grants, and patient advocates. A variety of institutions and cooperative groups are represented on the GUSC.

The GUSC decided to become familiar with concept evaluation as a full committee before considering the establishment of task forces. To date, six concepts have been evaluated; two have been approved, one has been revised and resubmitted, one has been disapproved, and two are in progress.

One of the approved concepts, RTOG 815-A, is a Phase III prospective randomized trial of dose-escalated radiotherapy with or without short-term androgen deprivation therapy for patients with intermediate-risk prostate cancer. Androgen deprivation therapy will be of 6 months duration with LH/RH agonists and anti-androgens. Patients will be randomized with or without androgen deprivation therapy and stratified according to number of risk factors, comorbidity status, and modality of radiation therapy (i.e., external beam treatment alone or with low dose rate or high dose rate brachytherapy).

The second approved concept, CALGB 90802, is a randomized Phase III trial comparing everolimus plus placebo versus everolimus plus the VEGF inhibitor bevacizumab for advanced renal cell carcinoma progressing after treatment with tyrosine kinase inhibitors (TKIs). In recent years, a number of drugs aimed at angiogenesis have proven to be effective agents in this disease. The challenge in kidney cancer is how to use those agents. This study will randomize patients with advanced disease who are coming off VEGF/TKI treatment, stratify them according to how long they were on that treatment, and randomize them between the mTOR inhibitor plus or minus bevacizumab.

Given the number of patients seen with prostate cancer and the number of prostate cancer studies that can be expected to come forward in the near future, a Prostate Cancer Task Force was formed in February 2009. The co-chairs of this Task Force are Dr. Michael Carducci of Johns Hopkins University, Dr. Deborah Kuban of the MD Anderson Cancer Center, and Dr. Andrew Stephenson of the Cleveland Clinic. An important aspect of this Task Force is the inclusion of representatives from the Prostate Cancer Clinical Trials Consortium, whose 13 member institutions are all NCI-designated Cancer Centers.

The Prostate Task Force has worked with the NCI Investigational Drug Steering Committee (IDSC) and the Investigational Drug Branch of the Clinical Trials Evaluation Program (CTEP), providing advice on several prostate-specific agents targeting the androgen receptor or androgen metabolism or production. The Task Force hopes to continue working with CTEP in evaluating drugs targeting genitourinary diseases. A working group is being established to convene an androgen receptor clinical trials planning meeting; another working group will work with caBIG on case report form (CRF) harmonization.

The GUSC believes that Cooperative Groups submitting concepts aimed at a particular disease state should develop a degree of consensus to bring forward a shared concept. The Steering Committee has developed a reconciliation process to be followed when duplicate concepts do not represent a consensus.

Challenges faced by the GUSC include improving accrual to Cooperative Group trials by urologists who treat prostate cancer patients; increasing cooperation among the various groups currently competing for grants to conduct Phase III genitourinary (GU) cancer studies on similar topics; and building Cooperative Group confidence of positive grant review for participation as well as leadership on shared concepts.

New clinical opportunities in genitourinary oncology include androgen receptor targeting and multiple new therapies for prostate and renal cancers. These opportunities will require evaluation in combination or in sequence. Future plans for the GUSC include convening a planning meeting within the next year on androgen receptor clinical trials and forming task forces on renal and bladder cancers.

Questions and Discussion

Dr. James Abbruzzese, Chairman of the Department of Gastrointestinal Medical Oncology at the MD Anderson Cancer Center, asked whether Cooperative Groups involved in GU research are open to working with GUSC task forces to collaborate in creating trials that represent the work product of all of the groups involved; he noted that the Gastrointestinal Steering Committee (GISC) has been successful in this regard. Dr. Wilding indicated confidence that this type of collaboration will be feasible in GU oncology. The GUSC recently received a prostate cancer concept from one Cooperative Group that incorporated a commitment from two other Groups that they will support and participate in the study. Setting expectations for consensus in concept development and guiding Cooperative Groups in following

them is not a smooth process; however, the GUSC is sending the message that concept approvals will be contingent on evidence of collaboration and consensus.

Dr. David Parkinson, President and CEO of Nodality, Inc., asked whether tumor heterogeneity in prostate cancer is being addressed by the Prostate Cancer Task Force. Dr. Wilding replied that a number of recently completed, ongoing, and upcoming Phase III trials are addressing heterogeneity in prostate cancer.

Dr. Tepper asked whether, like the Gastrointestinal Steering Committee (GISC), the GUSC has had difficulty bringing basic and translational science into clinical studies. Dr. Wilding cited the example of the Prostate Cancer Clinical Trials Consortium, which includes institutions (including prostate cancer SPOREs) that are conducting numerous early Phase I/II prostate cancer studies with laboratory correlates. Many of these institutions are also represented on the GUSC and the Prostate Cancer Task Force. This creates a promising opportunity for development of future Phase II studies.

Ms. Nancy Roach of the Colorectal Cancer Coalition stated that the GISC, of which she is a member, has involved community oncologists and patient advocates in concept review and asked whether the GUSC has involved these groups. Dr. Wilding responded that these groups have been active in recommending treatments, alerting the committee to concerns about side effects, and commenting on the feasibility of moving specific regimens into practice. Although the Prostate Cancer Task Force does not have an advocate member, an advocate member of the GUSC participates in Task Force conference calls.

Dr. Niederhuber stressed the importance of Dr. Tepper's recommendation that correlative science must be incorporated into clinical trials.

Dr. Sheila Prindiville, Director of the NCI Coordinating Center for Clinical Trials, noted that only two steering committees—the GUSC and the Gynecological Steering Committee—have been in existence long enough to begin showing the impact of their efforts on the quality of clinical trials and learning how well correlative science is being incorporated. She added that not only molecular markers but also markers associated with quality-of-life measures should be integrated into trial design.

Dr. Tepper observed that GISC task forces provide an opportunity for trading ideas back and forth and fostering collaboration. This is less likely to occur during steering committee meetings that focus more on review and approval of individual protocols.

Dr. Stephen Grubbs, Chief of Oncology at Medical Oncology Hematology Consultants, asked whether GUSC Task Forces have had any effect on the timeliness of getting trials started. Dr. Prindiville noted that the CTAC Operational Efficiency Working Group (OEWG) has addressed the time lag between concept approval and protocol activation and is preparing recommendations. Dr. Doroshow added that a preliminary report on the Working Group's findings will be available in November 2009.

Dr. Doroshow commented that the steering committees and task forces are enhancing communication among parties within the cancer clinical trials community that have historically worked together with varying degrees of efficiency. Although the reconciliation process for developing consensus concerning concepts may be frustrating today, it is expected to enhance communication throughout the clinical trials enterprise.

Dr. Alberts asked whether the Prostate Cancer Task Force has the resources needed to help determine which men need to be treated for prostate cancer. Dr. Wilding suggested that a more important question is whether individuals conducting trials have the necessary resources to perform ancillary studies to answer such questions.

Dr. Abbruzzese observed that CTAC steering committees are leading to reduction in duplication of effort in clinical trials, which should save in the expenditure of resources.

Dr. Alberts asked how the GUSC has addressed the need for establishing timelines for its work. Dr. Wilding replied that the Steering Committee has concentrated on keeping to a tight timeline for review of concepts; however, progress on duplicate concepts is slowed because they are sent back to Cooperative Groups for reconciliation. He agreed with Dr. Prindiville that the crucial concern in terms of timeliness is the gap between protocol approval and the start of accrual.

Ms. Roach suggested that the value of the OEWG and the steering committees will not be demonstrated until data are available to show trials are moving through the system more quickly, patients are being accrued more rapidly, and more important questions are being answered.

Dr. Kenneth Cowan, Director of the Eppley Cancer Center at the University of Nebraska, stressed that guidelines must be developed concerning how collaboration is rewarded when Cooperative Groups develop consensus on how to collaborate on shared concepts. Investigators who are accustomed to sole leadership of trials need a clear understanding of how participation in collaborations will be rewarded.

V. RECOGNITION OF RETIRING MEMBERS—DR. JOHN NIEDERHUBER

Dr. Niederhuber acknowledged the contributions of five CTAC members who are leaving the Committee and presented them with plaques in appreciation of their service. Dr. David Alberts is a Regents Professor of medicine and pharmacology, nutritional science, and public health at the University of Arizona College of Medicine and the Director of the Arizona Cancer Center's Cancer Prevention and Control Program. Dr. Kirby Bland is Chair of the University of Alabama Department of Surgery. His service to NCI has also included membership on the Board of Scientific Advisors (BSA). Dr. Bruce Hillman is a professor of radiology in the Department of Health Evaluation Science at the University of Virginia and former Chair of the American College of Radiology Imaging Network (ACRIN). Dr. Heidi Nelson is a professor in the Department of Surgery at the Mayo Clinic. Dr. Tim Rebbeck (not present) is a professor in the Department of Biostatistics and Epidemiology at the University of Pennsylvania School of Medicine.

VI. NCI SYMPTOM MANAGEMENT AND QUALITY OF LIFE STEERING COMMITTEE: CLINICAL TRIALS PLANNING MEETING ON CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY—DR. CHARLES LOPRINZI

Dr. Charles Loprinzi, Professor of Oncology at the Mayo Clinic, began by stating that chemotherapy-induced peripheral neuropathy (CIPN) is a major clinical problem that involves structural damage to epidermal nerve fibers and Meissner's corpuscles (that function as touch receptors in the skin). CIPN limits the amount of chemotherapy that can be provided to patients and can affect quality of life for years following treatment. Although promising preliminary research findings suggest that prevention and treatment of CIPN may be possible in the future, no proven effective therapies are currently available.

On March 23, 2009, the NCI Symptom Management and Quality of Life Steering Committee (SxQOL SC) held a Clinical Trials Planning Meeting (CTPM) on the topic of CIPN. Approximately 100

participants representing a wide variety of disciplines engaged in thought-provoking discussions. The meeting was summarized in a report that has been provided to CTAC members.

Presentations at the CTPM described a number of tools that have been proposed for use in preventing or treating CIPN and require further study. Further refinement is also needed in describing the various symptoms experienced by patients. It was noted that patient-reported outcomes are more useful than physicians' evaluations in assessing the impact of CIPN.

As an example of recent CIPN research, Dr. Loprinzi described a North Central Cancer Treatment Group (NCCTG) Phase III cancer control trial on Intravenous Calcium and Magnesium (CaMg) for Oxaliplatin-Induced Sensory Neurotoxicity. Oxaliplatin is used as part of the FOLFOX chemotherapy regimen. Results from this study strongly supported that the administration of CaMg was associated with a marked reduction in peripheral neuropathy.

Concurrently with the conduct of this NCCTG trial, another trial—the Combined Oxaliplatin Neuropathy Prevention Trial (CONcept)—also focused on dose limitations for oxaliplatin due to neurotoxicity. One study arm received FOLFOX (including oxaliplatin) alone for as long as it could be tolerated; the other arm received 4 months of FOLFOX alternating with 4 months of 5-fluorouracil/leucovorin therapy (i.e., a stop-and-go strategy). A second study question in this trial involved randomizing all trial participants to receive CaMg or placebo to determine whether CaMg could prevent CIPN. Slow accrual led to cancellation of the CaMg versus placebo part of the study; all patients in the study arms receiving continuous or stop-and-go oxaliplatin were then given CaMg. Subsequently, preliminary findings from a Data Monitoring Committee review of the placebo study seemed to indicate that CaMg was associated with reduced effectiveness of the chemotherapy. Based on this observation, both the CONcept and the NCCTG CaMg trials were abruptly stopped.

Later, independent radiologists reviewing unblinded CONcept data found that chemotherapy response rates for both groups in the CaMg versus placebo study were quite similar. This discrepancy is thought to be caused by the fact that the initial Data Monitoring Committee review included newly accrued patients (all of whom received CaMg after the randomization to CaMg versus placebo had been discontinued) who had not been in the study long enough to show responses to therapy. This diluted the response rate for patients receiving CaMg because these recent patients had not been on therapy long enough to have had a documented response to their treatment.

The history associated with the Data Monitoring Committee, which was reported in a letter in the *Journal of Clinical Oncology*, has caused considerable confusion in the oncology community regarding this issue. Because opinions in the oncology community on the efficacy of CaMg in preventing CIPN are resultantly mixed, a new study is planned that will again compare CaMg with placebo.

Other agents that have shown promise in preventing or treating CIPN include glutathione, alpha lipoic acid (thioctic acid), acetyl-L-carnitine, duloxetine (Cymbalta), and baclofen/amitriptyline/ketamine. In addition to studying these other agents, future trials should focus on whether calcium alone or magnesium alone would have similar effects on oxaliplatin-induced neuropathy and whether they would have similar effects with CIPN associated with other chemopreventive agents. Expanded basic research is also needed to create a better understanding of genetic variations that might be predictive for CIPN. The development and use of informative animal models would also assist in the design of future clinical trials.

Questions and Discussion

Dr. Peter Adamson, Chief of Clinical Pharmacology and Therapeutics at the Children's Hospital of Philadelphia, University of Pennsylvania, asked whether animal models have been used to study whether drugs used to treat CIPN affect the anticancer efficacy of chemotherapeutic agents. He also asked whether differences in drug exposure or pharmacokinetic differences could explain variations between patients in terms of CIPN. Dr. Loprinzi acknowledged that this recurrent question requires investigation. So far, animal studies have not found that CaMg or other anti-CIPN drugs (e.g., glutathione) interfere with the efficacy of oxaliplatin. In response to the second question, Dr. Loprinzi said that a number of clinical trials are examining whether drug exposure or genetic determinants of drug metabolism are predictors of CIPN.

Dr. Bland asked whether anyone had looked at the animal model for replacement of epidermal nerve growth factor following the calcium and magnesium to see if there is proof of principle. Dr. Loprinzi replied that, to his knowledge, such studies, which might produce interesting findings, have not been conducted. Also, there are no clinical data focused on the potential application of nerve growth factor in treatment of CIPN.

Dr. Alberts stressed the difficulty investigators face in finding agents and placebos for these types of studies when the patents of agents that appear promising have expired and no mechanisms exist for their production and distribution. Dr. Loprinzi said he shares this concern, adding that FDA regulations also present issues that affect the study of these agents. He noted that companies whose drugs cause treatment-limiting CIPN are sometimes willing to help with funding for acquiring promising agents to alleviate this toxicity since they have a vested interest in making their chemotherapy agents more clinically useful.

Ms. Roach expressed thanks to NCI and CTAC for supporting studies of the effect of FOLFOX and other cytotoxic agents on CIPN. She noted that FOLFOX is frequently used as a treatment for colorectal cancer. She also noted that, clinically, CIPN is a major symptom affecting patients receiving chemotherapy, and for months to years thereafter. She encouraged further efforts directed at alleviating this prominent clinical problem.

Dr. James Wade, Director of Medical Oncology at the Decatur Memorial Hospital Cancer Care Institute, stated that there is evidence pointing to the potential role of individual pharmacogenomic variations in predicting the likelihood of CIPN for specific patients.

VII. THE ROLE OF ECONOMIC ANALYSES IN CONJUNCTION WITH LARGE CANCER CLINICAL TRIALS—DRS. RICHARD SCHILSKY, SCOTT RAMSEY, AND JANE WEEKS

Dr. Schilsky stated that in the context of expensive new developments in cancer-related therapeutics and technologies, the recent congressional mandate to increase comparative effectiveness research, and the current debate concerning health care reform, this is an opportune time for CTAC to discuss the potential role of economic analysis in the clinical trials enterprise. Important questions include whether economic analyses should be incorporated into clinical trials and, if so, how they should be funded. He introduced Dr. Scott Ramsey, Director of the Cancer Prevention Clinic at the Fred Hutchinson

Cancer Research Center, who has a doctoral degree in economics in addition to his medical degree; Dr. Ramsey joined the meeting via teleconference.

Role of Economic Analysis in Phase III Clinical Trials. Dr. Ramsey described cost-effectiveness analysis (CEA), for the purposes of this discussion, as a standardized methodology for comparing benefits and costs of alternative strategies designed to improve health—usually new treatments compared with standard care. Importantly, cost-effectiveness depends not only on the price of a drug or treatment, but also on the cost of subsequent events. For example, inexpensive therapies can be cost-ineffective if they do not result in positive outcomes.

Outcomes of typical cost-effectiveness studies can be described using a “cost-effectiveness plane” on which the vertical axis represents treatment cost and the horizontal axis represents treatment effectiveness. Decisions about adoption of a new treatment are easiest when cost-effectiveness analysis shows that the treatment is less costly over the entire course of treatment and more effective than standard care—supporting adoption—or more costly and less effective, supporting continuance of standard care. When a treatment is less costly but also less effective, the decision is whether the savings to the health budget are justified by the reduction in outcomes using the new treatment. However, most cost-effectiveness studies find that new treatments are more effective but also more costly. In these cases, the added value of the new treatment must be considered in deciding whether the increased cost is justified.

Among several types of CEA, most health economists recommend cost-utility analysis, which uses quality-adjusted life years in measuring outcomes. This measure is based on a scale that ranges from ideal health (value = 1) to death (value = 0). Cost-benefit analysis, which measures what patients or health care providers are willing to pay for health benefits, is used less often because many people are uncomfortable with valuing life in monetary terms.

There are benefits of conducting CEA in conjunction with clinical trials. The validity of CEA can be enhanced by the high internal validity associated with randomized trials; the cost efficiency of CEA is improved (compared with that of retrospective CEA); and the impact of CEA is enhanced when presented in a timely manner along with clinical findings.

The combination of CEA and clinical research is not without limitations. External validity is affected by the fact that clinical care in trials is not representative of care provided in typical medical practices. In addition, clinical research and CEA are designed for different purposes and different audiences. The former focuses only on whether a treatment is effective, while the latter focuses on its value.

Methods for performing CEA alongside clinical trials have been standardized and refined, as described in a report of the International Society for Pharmacoeconomics and Outcomes Research’s task force on CEA for clinical trials. Consent forms must be modified to allow access to insurance data, billing records, or patient reports concerning costs. Staff time must be allocated for study design, data collection, data entry, and analysis. Because this staff time is expensive, CEA cannot be performed for all clinical trials—choices must be made to identify trials for which this type of analysis has potential significance.

As an example, Dr. Ramsey described a Southwest Oncology Group (SWOG) Phase III study comparing paclitaxel plus carboplatin (a new treatment regimen) with vinorelbine plus cisplatin for patients with advanced nonsmall cell lung cancer. The companies that manufactured the drugs contributed equally to the cost of the CEA. There was not a statistically significant difference in survival between the two treatment arms. A quality-of-life analysis found no difference in quality of life between the two arms.

A study comparing lifetime average costs of the two treatments found that paclitaxel plus carboplatin cost approximately \$10,000 more than vinorelbine plus cisplatin during a 24-month follow-up period that represented the total lifespan of 90 percent of the trial's patients.

In selecting trials for CEA, factors to be considered include the burden of disease, the known costs of new and established therapies, anticipated impact on posttreatment costs (e.g., treatment of side effects), and factors that might justify a significant difference in cost. One important outcome that could justify increased cost is improved survival.

“Value of information” analysis holds promise as a way to decide whether to perform CEA in conjunction with a clinical trial. This approach examines the potential economic value in terms of the impact on practice patterns, costs of care, and outcomes that could be achieved using information gained through the study in comparison with the cost of conducting the trial. Value of information analysis assigns a dollar value to the information gained from a trial, reflecting the fact that information from a clinical trial can increase the probability that an effective treatment is adopted; or conversely, that an ineffective treatment is not adopted.

Spending on oncology is rising at a much higher rate than on any other sector of health care. Treatments have become more expensive and are being pursued more aggressively over longer periods of time (since patients are surviving longer). Health insurers are now often charging 20- to 30-percent copays for the most expensive cancer drugs. Economists are concerned that insurers are basing these charges only on the cost of drugs and not on their value. By disconnecting out-of-pocket cost from the benefit of therapy, such policies may place undue burdens on patients or risk reducing the use of highly cost-effective therapies.

A recent Kaiser Foundation study documented the consequences of the financial costs of cancer for patients. Although the cost burden was significant for all patients, those who lost their health insurance during the cancer experience were much more likely than “always insured” patients to deplete their savings, borrow to pay for care, receive public assistance, or declare bankruptcy. In 2007, the Congressional Budget Office estimated that if costs per enrollee in Medicare and Medicaid continue to grow at current rates, spending on those programs will account for about 20 percent of the Gross Domestic Product by 2050, emphasizing the need for more evidence on whether new treatments warrant additional costs.

Dr. Ramsey addressed common fallacies concerning cost-effectiveness. Costly cancer treatments can be highly cost-effective, and inexpensive treatments can have poor cost-effectiveness. Adoption of a new, cost-effective cancer treatment often increases overall health care spending. The aim of CEA is not to reduce overall costs but to reduce the use of treatments that do not have high value.

Dr. Ramsey called attention to the United Kingdom's National Institute for Health and Clinical Excellence (NICE), a world leader in the use of CEA, which makes recommendations to the UK National Health Service on increasing the use of cost-effective treatments. NICE has conducted price negotiations with drug manufacturers to cover the costs of expensive but effective drugs. In the case of lenalidomide for multiple myeloma, it was found that the drug was very cost-effective for 26 cycles, but less cost-effective for maintenance therapy, so the manufacturer agreed to cover the cost of treatment beyond 26 cycles.

In the United States, cost-effectiveness is often bypassed because drugs are so quickly introduced into clinical practice following approval. This can result in widespread use of drugs that do not provide a benefit to patients in proportion to their high cost to patients and to society. Conducting CEA alongside clinical trials has the potential to mitigate this problem.

Economic Analyses Associated With Cooperative Group Trials: When and How? Dr. Jane Weeks, Professor of Medicine and Health Policy and Management at the Dana-Farber Cancer Institute, listed several criteria developed by the Cancer and Leukemia Group B (CALGB) for deciding whether to conduct CEA alongside clinical trials: (1) there is a reasonable possibility that the trial will influence practice; (2) a change in practice could have significant cost implications (either cost differences between experimental and standard care groups are substantial or the disease is so widespread that small cost differences per patient translate into substantial differences for large populations); and (3) expected differences in clinical outcomes are likely to be relatively modest.

The third criterion derives in part from the fact that cost-effectiveness can vary with the setting in which a therapy is used. The cost-effectiveness of a new drug may be better when it is used in the adjuvant rather than in the metastatic setting, because even a small increase in the cure rate results in substantial added quality-adjusted life years. It makes sense to pay particularly close attention to cost-effectiveness in situations where high costs are associated with very modest improvement in outcomes.

Conducting CEA in the metastatic setting creates special challenges. Differences in cost between study arms may be sensitive to second- and later-line therapy and to costs of care during added months of life. Quality of life during additional months of life is likely to be compromised. CEA in this context requires data collection on treatments after progression, which is not typically conducted in Cooperative Groups.

The process for targeting trials for CEA should include a systematic review of concepts to identify those that meet pre-established criteria; a decision early in protocol development to integrate CEA as a companion study; and true collaboration between the study chair and the economist conducting CEA. Data collection should focus on incremental cost and effectiveness. Information on patient resource use should be collected using case report forms and patient self-reports on other sources of support.

Conducting CEA within Cooperative Groups will require institutional commitment of time for abstracting resource use and reviewing charts and billing information; resources for statistical analysis of quality-adjusted survival; and funds to support leadership of the CEA effort, economic analysis, and the cost of patient surveys. Guidance and support from NCI will also be essential.

Questions and Discussion

Dr. Parkinson noted that there are several ways to achieve improvements in quality-adjusted life years. One is to identify patients who initially respond to a therapy and extend its use with those patients; another is to tie reimbursement to performance (i.e., the drug company is not paid if the drug is not effective). The movement toward personalized medicine also represents an opportunity to increase quality-adjusted life years by using markers to identify those likely to benefit from treatment. CEA should probably incorporate a more holistic view rather than addressing only what the average benefit is to the average person treated for the average period of time. Dr. Ramsey agreed that personalized medicine represents the future not only for delivery of cancer treatment but also for the economics of cancer treatment. Dr. Weeks added that giving therapy to patients most likely to benefit does not, in itself, guarantee favorable cost-effectiveness.

Dr. Alberts observed that oncologists and academic researchers may lose control of the decision-making process in cancer treatment if they do not incorporate CEA into their studies. Scientists need to make efforts to minimize the cost of conducting CEA studies. He asked whether it would be feasible to

collect a minimal data set for each trial and then conduct CEA when circumstances require it. Dr. Weeks suggested that data collection should focus on trials for which there is some probability that the data will be useful, but agreed that it may not be worthwhile to spend the resources analyzing the economic data if the clinical results are unlikely to change clinical practice.

Dr. Nancy Mendenhall, a professor in the Department of Radiation Oncology at The University of Florida Health Center, asked whether existing utility measures are sensitive enough to address quality-of-life issues. She also asked how CEA takes into account costs other than those billed to insurance companies; for example, over-the-counter drugs taken by patients or treatment of side effects using resources received from other sources. In addition, she questioned how CEA can take into account the changing costs associated with a treatment or drug over time (e.g., when generic alternatives become available). Dr. Weeks responded that the measures described in her presentation are designed to detect differences in costs that are great enough to influence cost-effectiveness ratios. They are not presented as an alternative to more complete quality-of-life analysis. Dr. Ramsey added that costs borne by patients should be included in CEA when examining the total costs associated with cancer therapy.

Concerning the CEA criterion that a trial's findings should be likely to influence practice, Dr. Adamson noted that Phase III trials should not be conducted if they do not have a reasonable chance of influencing practice. Dr. Weeks said that most trials do have a good chance of influencing practice, yet occasionally during the course of a trial something changes. For example, she cited a trial that was closed early due to low accrual but was accompanied by a CEA that, based on patient follow-up, indicated a high cost-benefit ratio.

Dr. Wade pointed out that CEA should focus on all costs associated with cancer treatment, as well as regional variations in facility costs and health plan coverage, rather than limiting its focus to hospital and physician charges that are reimbursed. Drs. Ramsey and Weeks agreed that CEA should include all costs by collecting data on all resources utilized. Dr. Ramsey added that CEA uses reimbursement rather than charge data, since reimbursement is never 100 percent of charges.

Dr. Daniel Sargent, Director of Cancer Center Statistics at the Mayo Clinic Foundation, suggested the possibility of collecting utilization data on subsets of patients. He asked whether electronic medical records and supplemental data sources can make it possible to collect needed data after a trial has been completed. Dr. Weeks noted that selective data collection would not be likely to produce high-quality CEA findings due to concerns about statistical power. She added that collecting data from all patients is not difficult if the trial is designed so that resource utilization data are obtained from patient charts concurrently with clinical data and minimal incentives are provided for timely data collection and reporting. Supplemental information can be collected selectively.

Dr. Hillman commented that ACRIN has an economics committee and incorporates CEA into trials when it is appropriate and feasible. He stressed that the most appropriate measure of costs for NCI-sponsored trials should be based on a societal perspective. Referring to Dr. Ramsey's slide on the cost-effectiveness of several treatment modalities, Dr. Hillman asked why the costs per quality-adjusted life year for annual CT to monitor Hodgkin disease patients in remission are so high. Dr. Ramsey replied that the high cost-effectiveness ratio is due to small differences in terms of outcomes.

Dr. Abbruzzese offered two suggestions. First, the oncology community needs to do a better job of translating the findings of CEA into practice; and second, NCI, possibly in collaboration with the Centers for Medicare & Medicaid Services (CMS), should develop resources to support integration of sophisticated CEA studies into clinical trials. He asked for comments on the difference between the NICE approach to retrospective CEA and the prospective approach advocated by the presenters, and the possibility that the NICE approach would be less costly than prospective CEA, given the lack of funding

to conduct CEA for all trials. Dr. Ramsey stated that NICE uses a mixture of approaches; some studies are prospective and others are based on modeling and retrospective data. He noted that a technology appraisal in the United Kingdom can take 39 to 52 weeks, a timeframe that would not be acceptable in the United States. It would be more useful to have the economic data available at the same time the results of trials are being used to make decisions about FDA approval.

Dr. Grubbs noted that many patients are beginning to show signs of what he calls “patient fatigue.” They are confronted with consent forms for surgery, clinical trial participation, and quality-of-life studies, as well as other forms of red tape. Asking patients to participate in CEA may present an additional barrier to participation in clinical research. Dr. Weeks suggested that consent for quality-of-life studies and CEA should be included in a clinical trial’s consent forms if these analyses are being conducted as part of the trial.

Dr. Nelson asked about barriers and incentives for encouraging CEA in conjunction with clinical trials. Dr. Weeks replied that there must be a predictable and timely process for approving and supporting CEA in order to motivate economics experts to become involved in cancer research. Faced with a lack of public funding, many experts in this field have found employment in the pharmaceutical industry.

Dr. Niederhuber asked Dr. Martin Brown, an economist with the NCI Division of Cancer Control and Population Sciences, to make a final comment on NIH discussions related to the interactions of CEA, comparative effectiveness research, and health care reform. Dr. Brown stated that NCI’s efforts to track reimbursement for cancer care over time have shown a remarkable stability in those costs in comparison with overall health care costs. However, there are signs that the costs of cancer care are beginning to increase sharply; for the first time, oncologists are becoming concerned about cost as an aspect of cancer care. There is a growing interest in the oncology community for collection of information to support decision making.

The impending crisis in health care financing has been a prime factor in increasing interest in comparative effectiveness research. In developing coding criteria, NCI has been informed that cost analysis and economics should not be considered part of CER. This may be the result of congressional concern that using cost to help determine comparative effectiveness might lead to rationing of medical care.

NCI is addressing questions about the difference between efficacy research and CER. The former focuses primarily on technical attributes of a therapy, whereas the latter focuses on the effects of a therapy, in combination with other factors, on the totality of the experiences of the patient, the physician, and the health care system. Many of the issues relevant to CEA, such as resource utilization and the effect of costs on patients and providers, are also relevant to CER even if dollar amounts are never mentioned.

Dr. Schilsky closed this session by suggesting that CTAC should consider formation of a working group to address issues related to cost-effectiveness analysis and make recommendations to NCI.

VIII. GUIDELINES HARMONIZATION WORKING GROUP UPDATE—DR. JAMES ABBRUZZESE

Dr. Abbruzzese discussed the work of the Guidelines Harmonization Working Group of the CTAC Ad hoc Coordination Subcommittee. The Guidelines Harmonization Working Group was created with the goal to promote collaborative team science by ensuring that the guidelines of different clinical trial funding mechanisms are aligned and eliminate redundancy. The Working Group is also striving to

develop incentives to foster collaboration among all components of the NCI-supported clinical trials infrastructure.

Dr. Abbruzzese thanked the Working Group—in particular, Ms. Anna Levy—for their significant contributions to the report.

The Working Group's overall purpose is to provide guidance on the integration of NCI's clinical trials system, resulting in the facilitated movement of ideas from early translation through early clinical trials and into Phase III studies. Their approach was first to define collaboration, identify three model collaborative efforts, and then review the current guidelines of all mechanisms that support clinical trials, paying particular attention to apparent disincentives to collaboration. From this review, the Working Group developed the draft vision document with specific recommendations that is being presented to CTAC today.

The Working Group initially focused on the Cooperative Groups, SPOREs, and Cancer Centers, but later included Phase I U01 grants, N01 contracts, Community Clinical Oncology Programs (CCOPs) and Minority-Based Community Clinical Oncology Programs (MB-CCOPs), and clinically oriented P01s and R01s. The Working Group believes that its recommendations are relevant for all of these mechanisms.

The Working Group's initial survey of clinical trial mechanism guidelines related to collaboration included the review of program objectives, specific application and scientific review criteria, incentives and disincentives for collaborative research, and the movement of concepts from early translation through late-phase clinical trials. As a result, the Working Group found a number of disincentives for collaboration, including limited reimbursement for patient accrual, lack of incentives for collaboration, inconsistent incentives for resource sharing, variability in collaboration across the translational and clinical spectrum, and a need for guidelines and review criteria to be harmonized, strengthened, and implemented across funding mechanisms.

The Working Group developed two sets of recommendations: one set focuses on revisions of guidelines across programs, while the other focuses on general areas for greater incentivization across funding mechanisms. In the vision document, the Working Group outlined a number of specific recommendations to eliminate disincentives to collaboration, develop new incentives and rewards for stimulating collaboration, and implement program and reviewer guidelines to facilitate collaboration, as well as potential new mechanisms to facilitate the flow of ideas and information across translational and clinical programs into later-phase and Phase III trials. Recommendations that address the need to revise guidelines across programs include: provide meaningful and specific guidance on what is needed to receive credit for active collaboration across translational and clinical trials infrastructures; incentivize trans-mechanism collaborations to facilitate transition from preclinical and early clinical development to Phase III trials; revise program goal statements and guidelines to emphasize collaborations across funding mechanisms; review program leadership based on facilitation of trans-mechanism interactions; review credit for inter- and trans-mechanism collaborations; and encourage SPORE participation in trans-mechanism Phase II trials utilizing the Cancer Trials Support Unit (CTSU) and, in some cases, Cooperative Groups. Also, the Working Group recommended that grant applications include a discrete section that would emphasize collaboration and encourage applicants to describe and discuss plans for trans-mechanism collaboration. It was agreed that the inclusion of this section should receive a rating that would impact the overall priority score.

Additional recommendations are to provide supplemental funding for Phase III studies in Cooperative Groups based on early clinical results from other NCI funding mechanisms; review credit for NCI mechanisms where early results lead to Phase III Cooperative Group trials; provide incentives to

enhance collaborations between CCOPs/MB-CCOPs, Cancer Centers, and Cooperative Groups to accelerate transfer of knowledge from trials to community practice; credit Cancer Centers based on the level of externally peer-reviewed trials rather than investigator-initiated trials; support pilot projects for multidisciplinary and translational collaborations; and highly reflect credit for collaboration in priority scores.

The first of multiple recommendations that address the need to develop incentives and rewards for collaboration is salary support and investigator recognition, which should include institutional principal investigators (PIs) through the Cooperative Group mechanism and can be accomplished in a number of ways: establish a "Chair's Fund"; increase the number and budget for institutional U01s; support PIs who collaborate across programs/mechanisms on common scientific questions; and utilize K-awards for senior investigators to facilitate collaborations. Other recommendations for incentives include enhancing recognition and career development for contributors to collaborative clinical trials who are not currently PIs; establishing performance criteria and designations—"Scholar" or "NCI Quality Investigator"—and creating new awards (i.e., the "Cancer Clinical Investigator Team Leadership Award") to recognize investigators who have provided an extraordinary service.

Another important recommendation is to enhance patient accrual, which could be achieved by increasing per-patient reimbursement; reviewing consideration for significant accrual to non-Cooperative Group, non-endorsed CTSU studies; and expanding the capacity of CTSUs to accommodate patients in large Phase II studies. Additional recommendations are to formalize a process to facilitate development and conduct of collaborative clinical trial concepts from investigators not currently engaged in NCI-funded clinical trial mechanisms and provide access to resources—CTSUs, data coordination, and accrual reimbursement—across NCI clinical trials mechanisms.

Lastly, the Working Group recommended building on the Recovery Act Grand Opportunities Grants for clinical and translational research. Depending on the success of these grants, NCI might also examine developing a new mechanism to move exciting, clinically applicable ideas through the clinical trials system based on collaborations among Cancer Centers, SPOREs, Cooperative Groups, and P01s. On a basic level, this process would present a funding mechanism that can take an idea, provide resources to an investigator to move the idea into the clinic, and then move the project into the Cooperative Groups for comparison with the existing standard of care.

The Working Group also discussed outcome measures that can be used to evaluate the effects of changes implemented based on these recommendations. The existing CTWG/TRWG evaluation process will be used to measure progress in collaboration. The Working Group will examine whether guidelines that promote collaboration are consistent across mechanisms; reviewer credit is clearly reflected in priority scores and emphasizes collaborative activities between programs; there are more Phase III trials based on early-phase studies; and contributions by program leaders across the translational and clinical trials system have increased.

If CTAC accepts the vision document, the Working Group will continue to meet and provide input as NCI staff revise the guidelines and outline plans for inclusion of incentives, which will then be presented to the Clinical and Translational Research Operations Committee (CTROC) and the NCI Executive Committee for final approval within the next 12 months.

Questions and Discussion

Ms. Roach asked for clarification of the incentive recommendation to review consideration for significant accrual to non-Cooperative Group, non-endorsed CTSU studies. Dr. Abrams explained that this recommendation refers to the potential for non-Cooperative Group investigators to link with a Cooperative Group or other NCI mechanism to move their studies to the CTSU, thereby making the study available to other investigators in the national network.

Dr. Alberts also commented on the need to ensure that cancer prevention clinical trials are well represented in the vision document. Dr. Abbruzzese assured Dr. Alberts that prevention will be included in the language of the next version of the document, along with a recommendation for a specific area of grant applications that scores the applicant's plans for collaboration.

Dr. Sargent emphasized the importance of increasing per-patient reimbursement as an incentive. Reimbursement has been fixed for approximately 10 years, which is hindering Cooperative Groups' efforts to enroll patients in their clinical trials.

Dr. Schilsky commented that the credit provided for demonstrable collaboration across mechanisms must translate into something tangible (e.g., more money or additional years of funding). Credit alone will not help investigators expand or enhance the quality of their research.

Dr. Cowan suggested that NCI provide assistance and recognition to junior investigators at the institutional level within the Cancer Center structure. Rewarding junior investigators who participate in the CTSU would be an effective incentive for collaboration. Dr. Hillman agreed that nonmonetary incentives, such as recognition, can be quite helpful in promoting collaboration and should be emphasized along with funding. Dr. Abbruzzese will incorporate these suggestions into the final vision document.

Ms. Roach commented that it will be helpful, in terms of feedback, to measure both the positive and negative impacts that implementation of the recommendations is having on collaboration. She also added that implementation of the recommended changes needs to occur as quickly as possible. Dr. Abbruzzese responded that this process needs to proceed carefully so that NCI does not unintentionally hinder collaboration rather than promote it.

Motion. A motion to accept the Guidelines Harmonization Working Group Report, Part I – July 2009, with a modification to include language regarding trans-mechanism collaborations, prevention trials, and nonmonetary incentives was approved unanimously.

IX. PROCESS TO ACCELERATE TRANSLATIONAL SCIENCE (PATS) WORKING GROUP UPDATE—DR. LYNN MATRISIAN

Dr. Lynn Matrisian, Special Assistant, Office of the Director, NCI, provided an update on activities related to the implementation of the Translational Research Working Group (TRWG) initiatives. The TRWG recommended a new process for accelerating early translational cancer research, the Translational Research Acceleration Initiative. Based on the TRWG's portrayal of translational research along various developmental pathways, a process was designed to ensure that the most promising concepts enter a defined developmental pathway and then advance to the clinic (or reach productive failure) in a rapid, efficient, and effective manner. The process was envisioned as having three steps: information gathering (identification of translational opportunities by selection of several projects ripe for

translation); determination of how to prioritize these opportunities; and development of a funding plan capable of accelerating prioritized opportunities. The acceleration process was not designed to impact basic (discovery) research, which occurs prior to the TRWG developmental pathway, nor was it meant to replace infrastructure or mechanisms currently used for translational research.

One of the first steps of the translational research acceleration process—information gathering to identify opportunities—included the NCI Translational Science Meeting (TSM), <http://ncitranslates.nci.nih.gov>, held in November 2008 in Washington, DC. At this meeting, investigators chosen by NCI program staff were invited to present their work within the context of the developmental pathways. This process will continue with TSM2, to be held November 5-7, 2009, in Vienna, VA. NCI expanded the range of participants at this second meeting by inviting more junior investigators and investigators from Cancer Centers and other specialized programs. The goals of the TSMs are to enhance scientific collaborations across NCI and assist NCI in identifying the most promising scientific opportunities ripe for translation through the new Process to Accelerate Translational Science initiative. The information gathered at the first TSM is being developed as a translational research opportunity—an idea or project that focuses on a specific clinical goal, describes scientific validity, and provides information on feasibility—and piloted using one of the TRWG developmental pathways.

The Immune Response Modifier (IRM) pathway was chosen to pilot the translational research acceleration process due to its complexity and the fact that the immunotherapy community had previously prioritized components of the IRM pathway in 2007. The PATS Working Group was able to build upon this expertise to pilot the acceleration process in two phases. The first phase of the pilot project focused on developing a well-vetted, ranked priority list of cancer vaccine target antigens based on predefined and preweighted objective criteria. This process was carried out through Web-based and face-to-face interactions among experts in the field. The resulting report of ranked antigens was submitted and accepted by the journal *Clinical Cancer Research*. The second phase of the pilot was to build on the priority list of the first phase and broaden it to encompass the entire pathway. The PATS Working Group developed a list of "ideal" criteria/characteristics for IRM Pathway Translational Research Opportunities—antigen, formulation, immune modifier agent, combination regimen, assay for immune response, assay to select patient population, and availability of patients for trials. The scientific validity and feasibility of each of these characteristics will be considered when making prioritization decisions. Dr. Matrisian anticipates fewer criteria for the other pathways, which are less complex than the IRM pathway.

The Request for Information for the IRM Translational Research Opportunities—another approach for identifying opportunities—was released on July 10, 2009, and submissions are due August 21, 2009. Once opportunities are submitted, the IRM Subgroup of the PATS Working Group will use a Web-based version of the Analytical Hierarchy Process (AHP)—a structured technique for complex decision making—as a prioritization tool. AHP provides a comprehensive framework to structure a problem, represent and quantify key elements, relate those elements to overall goals, and evaluate alternative solutions. Input will also be solicited from extramural investigators to help the Subgroup determine the adequacy of each submitted opportunity.

After the prioritization process is complete, the opportunities will go to NCI leadership, which will consider clinical need and appropriateness for NCI investment. The funding and management of selected opportunities will be conducted through a new funding strategy, the Special Translational Research Acceleration Projects (STRAPs), which are envisioned as functioning through many different mechanisms, depending on the needs of the particular opportunity. To be suitable for a STRAP, projects will be required to have: a goal of completing early-stage human studies; a project management plan; specific developmental milestones and timelines; and a development/commercialization strategy. Project management, which is a critical part of this funding strategy, will link new and existing teams/projects

and facilitate handoffs between groups. It is envisioned that funded STRAPs for the IRM pathway will occur in FY2010.

The Working Group will begin the process for the next two pathways, biospecimen-based assessment devices and lifestyle alterations, over the summer. The agents pathway, which will be developed in conjunction with the NCI Experimental Therapeutics Program, will be followed by pilot projects with the imaging and interventional devices pathways in the fall of 2009.

Questions and Discussion

Dr. Adamson questioned why the IRM pathway—the most complex of the pathways—was chosen to pilot the PATS initiative. Due to the complexity of this pathway, it may not be a guaranteed success, which is needed for the research community to become interested in the PATS. Dr. Matrisian explained that selecting the IRM pathway is a test, but there is sufficient evidence that it will be a success. Dr. Cowan added that at this stage of the PATS development, understanding why certain aspects of this pilot process fail could be just as beneficial as experiencing success.

X. NEW BUSINESS—DR. SHEILA PRINDIVILLE

Updates. Dr. Prindiville reminded CTAC members that the CCCT Web site, <http://ccct.nci.nih.gov>, has a lot of useful material, including information on the Clinical Trials Working Group, translational research activities, and steering committees. In particular, she receives many questions about steering committee membership, and she encouraged those present to access the site for current membership information. Dr. Prindiville also reported that there was a consensus to form an Economic Analyses Working Group and that she would be in touch with CTAC members regarding their willingness to participate.

Future Agenda Items. Dr. Prindiville stated that informal teleconferences with CTAC members will be arranged to plan the agenda for the November 4, 2009 meeting.