

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
7th CLINICAL TRIALS ADVISORY COMMITTEE MEETING**

Summary of Meeting
March 4, 2009

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

CLINICAL TRIALS ADVISORY COMMITTEE
BETHESDA, MARYLAND
Summary of Meeting
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The Clinical Trials Advisory Committee (CTAC) of the National Cancer Institute (NCI) convened for its 7th meeting on Wednesday, March 4, 2009, in Conference Room 10, C-Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD from 8:00 a.m. – 4:00 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 (absent)
Deborah W. Bruner
Curt I. Civin
Kenneth H. Cowan
Everett Dodson
Stephen S. Grubbs
Bruce J. Hillman
Sandra J. Horning
K. Gabriel Leung
Nancy P. Mendenhall
Heidi Nelson
David R. Parkinson (absent)
Edith A. Perez (absent)
Timothy R. Rebbeck
Nancy Roach
Carolyn D. Runowicz (absent)
Daniel J. Sargent
Richard L. Schilsky
Joel E. Tepper
Jeffrey M. Trent (absent)
James L. Wade, III

Ex Officio Members

Anna Barker, NCI
James H. Doroshow, NCI
Leslye K. Fitterman, CMS
Paulette S. Gray, NCI
Lee Helman, NCI
Richard Pazdur, FDA
John F. Potter, DOD (absent)
Alan Rabson, NCI (via conference call)
Frank Torti, FDA, ad hoc

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 7th Clinical Trials 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 Board members during their deliberations. Members of the public were welcomed and invited to submit comments related to items discussed during the meeting in writing to Dr. Sheila A. Prindiville, Director, NCI Coordinating Center for Clinical Trials (CCCT) within 10 days of the meeting. Any written statements by members of the public will be given careful consideration and attention. Dr. Niederhuber also called CTAC members' attention to the future CTAC meeting dates, which have been confirmed through 2010.

Motion. A motion was made to approve the minutes of the 8 December 2008 CTAC meeting. The motion was seconded and the minutes were approved unanimously.

II. DIRECTOR'S UPDATE—DR. JOHN NIEDERHUBER

Dr. Niederhuber began by reporting that the U.S. House of Representatives Appropriations Committee has directed NCI to establish a fellowship in surgical pathology honoring Dr. Alan S. Rabson, NCI Deputy Director, in recognition of his 53 years of service to the National Institutes of Health (NIH).

NCI Budget Update. NCI is currently operating under a continuing resolution (CR), as Congress negotiates a final budget for the current fiscal year (FY 2009). Dr. Niederhuber noted that CRs place a heavy burden on NCI staff, who must administer grant awards cautiously to protect the Institute's budget and then adjust awards after the final budget has been approved.

The FY 2009 budget recently approved by the House of Representatives, which is likely to be approved by the Senate and signed by the President in the near future, is expected to contain the first increase in the NCI budget since 2004. The anticipated 2.9 percent increase would add approximately \$138 million to the NCI budget. This is a welcome addition to the Institute's ability to meet its scientific needs and cope with the effects of inflation. NCI is grateful that Congress did not perceive the stimulus funds being made available through the American Recovery and Reinvestment Act of 2009 (ARRA) as an opportunity to forgo a needed increase in NCI's budget.

ARRA will provide NIH with approximately \$10.4 billion to be spent in 2009 and 2010 to increase the economic and health impact of investments in biomedical and behavioral research. This allocation shows that Congress recognizes the economic impact of the creation of new knowledge in more than 3,000 research universities across the United States. Technological advances in science and health are thereby acknowledged to be important contributors to job creation and economic recovery.

Significant portions of the NIH allocation will be spent on renovation and construction projects, including NIH Clinical Center improvements, many of which have been planned but postponed in recent years. Similar extramural construction and renovation projects will be supported at universities across the country. ARRA also includes significant funds for large shared equipment grants, comparative effectiveness research projects, and Challenge grants.

NCI's Dinah Singer has been heavily involved in writing the Request for Applications (RFA) for the trans-NIH Challenge grant program. This 2-year mechanism is capped at \$500,000 and is designed to support innovative science that can be completed in a short time period. Applications will be reviewed in

May-June of 2009 by six special panels organized according to themes suggested by Institute Directors; awards will be made by the end of September 2009.

The remaining \$7.4 billion of the NIH allocation will be transferred to NIH Institutes and Centers (ICs). NCI is slated to receive approximately \$1.26 billion of ARRA funds in direct support of research activities. NCI staff have been studying the legislation to determine what can and cannot be done with these funds. A significant portion of these resources will be spent to support already-reviewed R01 grant applications that are in a position to make scientific contributions in the 2009-2010 timeframe. Another way to accelerate ongoing science is through carefully targeted grant supplements. These supplements will not be used to increase budgets for existing grant activities; instead, they will support new projects that will employ additional staff to address new scientific opportunities. It is hoped that an overall benefit of ARRA funds will be an improvement in success rates within the NCI-supported research community.

NCI is developing models for the impact of new grants on the Institute's budget for the next 4 to 5 years. NCI must decide how much "red ink" can be tolerated to support renewals for these grants if the budget does not continue to increase during those years.

The Department of Health and Human Services (DHHS) Office of the Secretary will receive approximately \$2 billion to create an Office of the National Coordinator for Health Information Technology. NCI has been actively involved in supporting the development of this Office by demonstrating its investment in caBIG7 (cancer Biomedical Informatics Grid) including the new BIG (Biomedical Informatics Grid) Health initiative, and submitting proposals at the Secretary's request. It is clear that no other federal organization has made as much progress as NCI in developing technological platforms for connectivity in health science and health care.

The Office of the Secretary has also been given approximately \$1 billion for a Prevention and Wellness Fund, part of which will support evidence-based clinical and community-based prevention and wellness strategies. Thanks to the efforts of Robert Croyle and the Division of Cancer Control and Population Sciences (DCCPS), NCI is well positioned to provide leadership in this area.

The necessity of moving ARRA projects into place at a rapid pace limits the type of competitive review that can be conducted. NCI will use a straightforward approach designed to support the very best scientific opportunities that promise a broad impact on the health of Americans and their communities.

A key concern in the administration of ARRA funds within DHHS, NIH, and NCI is accountability and transparency. Grantees will be faced with an unprecedented level of reporting requirements. A number of Web sites will be created to assist the public in learning how their tax dollars are being spent. NCI is seeking to create themes that will emphasize the impact of these efforts in ways that are easy for the public to understand.

While the slow process of filling the position of DHHS Secretary has hindered the ability of NIH and NCI to move forward with planning for the stimulus package, other decisions—such as the appointment of Dr. Eric Lander and Dr. Harold Varmus as co-chairs of the President's Council of Advisors on Science and Technology—have been positive signs of the new administration's commitment to the scientific community. The new administration is placing a priority on improving access to high-quality health care and increasing insurance coverage. The President has placed a special emphasis on science and recognizes the important role that NIH plays in advancing knowledge. The importance of training the next generation of scientists has also received renewed attention.

NCI is well positioned to address the priorities of the new administration. The Cancer Centers Program, launched by the National Cancer Act of 1971 to bring together basic research and clinical

activities, is a unique platform for reaching out from NCI into communities across the country. The pilot NCI Community Cancers Center Program (NCCCP) expands this ability to connect with cancer patients and their care providers. These programs are seen as an opportunity to foster the new administration's health-related information technology initiatives, including development of electronic health records. Other NCI programs relevant to administration priorities include caBIG7, BIG Health, and the recent emphasis on translational sciences designed to transform biological discoveries into clinical applications.

Dr. Niederhuber called the attention of CTAC members to their copies of the NCI Bypass Budget for FY2010. The intensity of NCI's effort to prepare this document was stimulated by anticipation of a new presidential administration and the difficult questions posed by Senator Specter about what actions and investments would be necessary to move the Institute's scientific agenda forward at an accelerated pace. Dr. Niederhuber congratulated NCI staff, especially Rich Folkers and Kathleen Schlom, on their efforts in producing the Bypass Budget.

NCI Update. NCI is closely involved with the private and not-for-profit sectors (e.g., the Brookings Institution and a subcommittee of the CEO Roundtable called the Life Sciences Consortium) to address issues related to translational research. NCI staff recently participated in a very productive meeting with Mark McClellan and his colleagues at Brookings as a follow-up to discussions held in September 2008.

NCI is also working with other federal agencies, including the Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services (CMS), to foster the role of cancer research and care as a model for development of clinical applications based on scientific evidence. A major trend in this arena is the movement toward targeted therapies for highly characterized patients. Progress in this area will depend on a translational structure that will allow NCI to work closely with FDA and CMS to obtain approval and reimbursement for the use of individual agents as part of combined therapies rather than as single agents with single targets. NCI believes that cancer as an arena for investigation of molecular medicine—to develop therapeutic, diagnostic, and preventive interventions as well as biomarkers for monitoring of therapy—will be a model for other diseases.

The NCI Executive Committee (EC) held its annual retreat in January 2009. Instead of focusing on a budget and stimulus package for which details were not yet available, the EC decided to engage in strategic discussions about new scientific opportunities. Lectures were replaced by panel discussions involving EC members and invited extramural scientists. Conversation focused on the intersection of different scientific disciplines and the importance of those intersections for developing new ideas and new theories. Topics that stimulated the most interest included: the role of viruses and infectious diseases and the need for vaccines in the treatment of cancer; real-time assays for stressors and responses that initiate and sustain cancer; modeling of the evolution of cancer with a focus on the alterations in the stroma (the so-called niche or microenvironment of the tumor) and the role this could play in converting cancer from a lethal disease into a controllable chronic disease; and the need to understand the epigenetic changes that control the type and number of malignant cells that the body must deal with.

Dr. Niederhuber closed by observing the passing of two important members of the NCI community: Dr. Stephen Williams, founding director of the University of Indiana Cancer Center, and Dr. Eugenia Calle, a member of the NCI Board of Scientific Counselors (BSC).

Questions and Discussion

Dr. Deborah Bruner, Independence Professor in Nursing Education, University of Pennsylvania School of Nursing, asked about the types of topics the Challenge grants would address. Dr. Niederhuber explained that the Challenge grants will focus on a broad range of research topics. Each NIH Institute was asked to submit five suggested opportunities; the combination of these suggestions will be used to develop themes that encompass the entire NIH research portfolio. Challenge grant opportunities will be posted on the NCI Web site to help investigators across the country determine where their work fits best.

Dr. James Wade, Director of Medical Oncology at Decatur Memorial Hospital Cancer Care Institute, asked Dr. Niederhuber to expand upon the opportunity for increased outreach and integration of cancer research in communities provided by the new NCCCP project. Dr. Niederhuber replied that one important opportunity offered by this project is using cancer as a model for developing a "web of connectivity" between private practitioners and hospitals based on the sharing of electronic patient records. The project also promises to improve the collection and sharing of biomedical specimens and addresses comparative effectiveness of interventions, health disparities, and screening issues. Through the project's evaluation component, NCI hopes to demonstrate the importance of leveraging small amounts of funding to bring people together with the goal of improving outcomes for patients.

Dr. Peter Adamson, Professor of Pediatrics and Pharmacology and Chief, Clinical Pharmacology and Therapeutics, Children's Hospital of Philadelphia, asked how CTAC could best advise NCI on applying part of the stimulus package to opportunities related to clinical trials. Dr. Niederhuber noted that the major challenge in using stimulus funding for clinical research is identifying opportunities that can be addressed within the legislation's short timeframe. One opportunity that has been mentioned is establishing a characterization center that could accelerate progress in addressing highly targeted therapies. Another potential use of these funds for clinical trials is to support trials that would evaluate promising agents that are ready for Phase I trials and could be performed within the required timeframe.

Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), NCI, noted that stimulus funds could be used to produce deliverables in the form of new materials that will be ready for evaluation in clinical trials within 18 months. Dr. Niederhuber added that all NCI proposals for use of stimulus funds will be subject to rigorous oversight at the NIH and DHHS levels before final decisions are made.

Dr. Frank Torti, Acting FDA Commissioner, suggested that cancer research fellowships are non-recurring commitments that are enormously useful to the cancer research community and fall within the ARRA timeframe. Dr. Niederhuber acknowledged that NCI's EC and Board of Scientific Advisors (BSA) have addressed the importance of fellowships, as well as the need to find ways to assist trainees in the transition from NCI fellowships to faculty positions at universities that are feeling the effects of the current economic crisis.

Dr. David Alberts, Director, Arizona Cancer Center, suggested using stimulus funds to build infrastructure at cancer centers to support videoconferencing and telemedicine.

III. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), NCI, reported on the status of appropriations, highlighted several pieces of legislation, and provided a follow-up and an outlook for the 110th and 111th Congresses, respectively.

FY 2009 Appropriations Status. On February 25, 2009, the House of Representatives passed HR 1105-Omnibus Appropriations; key provisions include \$30.3 billion for NIH and \$4.97 billion for NCI. The Senate was scheduled to consider the bill the first week of March and must come to a resolution by March 6, when the existing Continuing Resolution expires.

FY 2010 Appropriations Status. A general budget outline was released for FY 2010. The official President's budget will not be issued until early April. The Appropriations Subcommittees have not determined the number of hearings they will be able to schedule to inform FY 2010 Appropriations bills.

Economic Stimulus. The purpose of the American Recovery and Reinvestment Act relevant to NCI is to provide investments needed to increase economic efficiency by spurring technological advances in science and health, while also preserving and creating jobs and promoting economic recovery.

Legislation. The Pancreatic Cancer Research and Education and the National Childhood Brain Tumor Prevention Network Acts were introduced in the 110th Congress and have been reintroduced in the 111th Congress for further consideration. There have also been four bills related to health information technology introduced in the 111th Congress; it is not yet clear which, if any, of these health technology bills will have the support to move through Congress. The Access to Cancer Clinical Trials Act was reintroduced on January 27, 2009, by Representative Steve Israel of New York. This bill states that group health plans may not: deny beneficiary participation in cancer clinical trials; deny coverage of routine costs; or discriminate against patients based on participation in a cancer clinical trial. The bill amends the Public Health Service Act and the Internal Revenue Code. In addition, this bill would amend the Employee Retirement Income Security Act, which cannot be accomplished at the state level. However, many states have enacted laws that require certain types of health plans to cover patient care costs in clinical trials. Information on these state laws can be found at: <http://www.cancer.gov/clinicaltrials/development/laws-about-clinical-trial-costs>.

The State Children's Health Insurance Program (SCHIP) Reauthorization Act was passed and signed into law on February 4, 2009. This bill reauthorizes SCHIP through 2013; the expansion will be paid through an increase of cigarette taxes.

Outlook – 111th Congress. The new Chairman of the House Energy and Commerce Committee is Congressman Waxman of California. Another new ranking member is Congressman Todd Tiahrt of Kansas, ranking member of the Labor, Health and Human Services, Education, and Related Agencies Subcommittee. Congressman Tiahrt is new to this Subcommittee; it will be a good opportunity to educate him on the importance of programs at NCI.

Follow-up – 110th Congress. Two bills that passed in the 110th Congress are now in the implementation stage. Under the Breast Cancer and the Environment Act, NIH has established an Interagency Breast Cancer and Environmental Research Coordinating Committee, scheduled to first meet this spring. NCI and the National Institute of Environmental Health Sciences (NIEHS) are also continuing to fund Breast Cancer and the Environment Research Centers, as directed in the law. As part of the

Conquer Childhood Cancer Act, NCI is in the process of enhancing, expanding, and intensifying pediatric cancer research.

Questions and Discussion

Ms. Nancy Roach, Consumer Advocate for C3: Colorectal Cancer Coalition, brought the Committee's attention to another piece of legislation. On February 25, Representatives Kay Granger and Patrick Kennedy introduced legislation that would create a colorectal cancer screening program for the un- and underinsured. This program would be similar to the Breast and Cervical Cancer Screening and Prevention Program. More information can be found at: <<http://coveryourbutt.org>>.

Dr. Niederhuber inquired about the status of the FDA tobacco bill. Ms. Erickson clarified that it is still a draft bill and would be marked up by the House Energy and Commerce Subcommittee on Health in early March.

IV. COORDINATING CENTER FOR CLINICAL TRIALS UPDATE—DR. SHEILA PRINDIVILLE

Dr. Prindiville briefly discussed the five common themes described in the Clinical Trials Working Group (CTWG) report—Integrated Management, Prioritization, Coordination, Standardization, and Operational Efficiency. The first was an enterprise-wide/integrated management effort to restructure extramural and intramural oversight of NCI-supported clinical trials and translational research. The development of CTAC representing extramural trials and translational research was a result of this restructuring. The Clinical and Translational Research Operations Committee (CTROC) was established as the internal NCI oversight committee.

The second initiative is prioritization/scientific quality, which involves all stakeholders in the process of design and prioritization of clinical trials. A main component of this initiative is the development of a system of Scientific Steering Committees (SSC). Four types of steering committees have been developed: (1) the Investigational Drug Steering Committee; (2) a system of Disease-Specific Steering Committees (DS-SCs) that prioritize Phase III and select Phase II trials; (3) the Symptom Management and Health-Related Quality of Life Steering Committee (SxQOL SC) that prioritizes symptom management trials; and (4) the Patient Advocate Steering Committee (PASC) that coordinates advocate and consumer input across the SSCs. The SSCs are set up to: prioritize Phase II and selective Phase III therapeutic clinical trials; refine and collaborate on Phase III and select Phase II concepts, utilizing task forces when appropriate; and convene clinical trials planning meetings to identify critical issues and unmet needs to be addressed for future clinical trials in a particular disease area. The existing SSCs include Gastrointestinal Cancer, Gynecologic Cancer, Head and Neck Cancer, Genitourinary Cancer, Breast Cancer, and Thoracic Malignancies. Planning is under way for Hematological Malignancies Steering Committees; the DS-SC system should be complete by the end of 2010.

Dr. Prindiville reminded the Committee about the Biomarker, Imaging and Quality of Life Studies Funding Program (BIQSFP). This Program was initiated in 2008 to support Cooperative Groups and Community Clinical Oncology Program (CCOP) research bases so that biomarker, imaging, and quality of life (QOL) studies integral to national Phase III clinical trials could be pursued in a timely manner. Continued funding is anticipated at a level up to \$10 million for 2009. A change for the BIQSFP in 2009 is that the Program is now open for Phase III prevention, treatment, and symptom management

concepts. In addition, there is now a requirement for a description of the performance assay standards for proposed essential assays. There is an open submission cycle throughout the year for concepts. Additional information can be found on CCCT's Web site, <http://ccct.nci.nih.gov>. The SSC reviews concepts that have biomarker, imaging, and quality of life components. CTROC will recommend and prioritize BIQSFP concepts at regular meetings throughout the year and CTAC will make final recommendations to the NCI Director.

The third restructuring initiative of CTWG is coordination of clinical trials research through data sharing and providing incentives for collaboration. The CTAC created a Guidelines Harmonization Working Group that has been working on ways to harmonize guidelines and develop incentives for collaboration across NCI clinical trials mechanisms. Based on the feedback at the December 2008 CTAC meeting, NCI is also in the process of developing mechanisms to support multisite translational clinical trials in rare diseases and in areas not currently a major focus for Cooperative Groups. Another activity is development of the Clinical Trials Reporting Program (CTRP); a comprehensive database that includes information on all NCI-supported clinical trials. It is envisioned that Cancer Centers throughout the country would directly register their trials in the system and then the NCI Clinical Trials Reporting Office (CTRO) could extract key information from the online protocol document to support common data system (CDS) abbreviated reporting. Eventually, registered sites would provide clinical trial accrual data; those data have typically not been available other than for the Cooperative Groups. The CTRP went live on January 5, 2009, with five pilot sites entering information: Dana-Farber, Northwestern, Mayo, St. Jude, and Wake Forest. A slow phase-in approach is being taken; only new interventional trials with Institutional Review Board (IRB) approval to accrue patients as of January 1, 2009, are currently being entered into the system. It is important to note that there is no CTRP registration required for ongoing Cooperative Group trials sponsored by the Cancer Therapy Evaluation Program (CTEP) or Division of Cancer Prevention (DCP); NCI is internally transferring these trials into the reporting system. CTRP is following a staged deployment; the next stage entails soliciting "early adopter" Cancer Centers to enter new trials into the reporting system. It is hoped that CTRP will be open to all Cancer Centers by the end of 2009.

The CTWG's fourth initiative is to standardize informatics infrastructure and clinical research tools. NCI is in the process of procuring a remote data capture system for Cooperative Group trials, which would eventually be distributed to all NCI-supported clinical trial sites. Another initiative is the development of standardized case report forms (CRFs). A library of CRF "modules" is being developed that will be used in setting up a CRF and will optimize consistency. The modules that are created by a Working Group are then approved by CTROC for internal NCI review, and subsequently, circulated for wide review outside NCI (i.e., the caBIG Clinical Trials Workspace, Cancer Policy Today, and American Society of Clinical Oncology (ASCO) vehicles). Comments are received and analyzed, CTROC approves the module as an NCI standard, and each module is piloted with an "early adopter" group. The Clinical Data Acquisition Standards Harmonization (CDASH) initiative ensures that the modules being created are harmonized within industry. The first product of this process is the Demography module, which will conclude early adoption in April 2009. Module development is being phased in; other modules will include adverse events, medical history, physical exam, participant identification, registration, enrollment, and protocol deviations. A key point is that development is not sufficient; community adoption will be essential for success.

The last aspect of the standardization initiative is the development of common language or standard terms for clinical trial agreements. Negotiating clinical trial agreements is a key barrier to initiation of trials within an acceptable timeframe. In collaboration with the Life Sciences Consortium of the CEO Roundtable, Cancer Centers, and Cooperative Groups, NCI developed common language for negotiations around six key areas. These Standard Terms of Agreement for Research Trials (START)

clauses are available on the CCCT Web site, <http://ccct.nci.nih.gov>, and will be disseminated to Sponsored Research Offices at Cancer Centers.

The last of the CTWG initiatives is operational efficiency: using resources most efficiently through improved cost-effectiveness and accrual rates, and more rapid trial initiation. NCI created a CTAC Operational Efficiency Working Group (OEWG) to recommend strategies for reducing the time for activation of NCI-supported clinical trials. OEWG has 62 members and is chaired by Drs. Hortobagyi and Doroshow. The first face-to-face meeting of this working group took place in December 2008. The first phase of OEWG's mission is to develop strategies and implementation tactics for reducing the time for initiation of Cooperative Group and Cancer Center trials. The charge is to reduce study activation time by at least 50 percent and to optimize NCI, the sponsor(s), and investigator interactions in an effort to reduce delays. The OEWG meeting will take place in Spring 2009 to prioritize recommendations and identify implementation strategies. A full report from the OEWG will be presented to the CTAC, possibly at the July 2009 meeting.

Dr. Prindiville also discussed the CTWG rationale for a new financial model. In the current financial system, the large differential between NCI per-case costs and actual trial costs is not sustainable over time for the Cooperative Groups nor CCOPs. Also, sites that accrue only a few patients per year may result in a high per-case cost because of fixed costs. CTWG's recommended Trial Complexity Model will align reimbursement with trial complexity, but not impact the current \$2,000 base capitation rate. In 2008, 14 studies were deemed "complex" and received an additional \$1,000 over the \$2,000 base. Continued support is anticipated at a level of \$7.5 million in 2009.

The last initiative Dr. Prindiville discussed was the CTWG Minority and Underserved Populations Accrual Enhancement Initiative. CTWG recognized that minority and underserved populations are underrepresented in Cooperative Group clinical trials and recommended to expand current outreach programs to increase the recruitment of these populations to cancer clinical trials. In 2008, there were 12 minority clinical trial programs that were funded for a 2-year period with supplements of about \$100,000 per year to determine whether accrual could be enhanced.

Questions and Discussion

Dr. Bruce Hillman, Professor, University of Virginia School of Medicine, informed the Committee that NCI has been funding clinical trials by complexity in the American College of Radiology Imaging Network (ACRIN) for the past 10 years; the payment is tied to the average Medicare rate for the various technologies being used. This funding experiment has been successful and should be used as a model for other sites.

Dr. Richard Schilsky, Professor of Medicine and Associate Dean for Clinical Research, University of Chicago Pritzker School of Medicine, commented that implementation of the remote data capture system in Cooperative Groups is going to require substantial resources. A portion of the ARRA stimulus funds could be allocated toward this initiative.

Dr. Schilsky also inquired about the reporting capabilities of the CTRP. Dr. Prindiville said the intent is to be able to report on all NCI-sponsored clinical trials; in particular, accrual and outcomes data. Dr. Kenneth Buetow, Director, NCI Center for Bioinformatics and Information Technology, added that the goal is to make public all data that do not violate the Health Insurance Portability and Accountability Act (HIPAA) and ensure that the reporting sites will benefit from the database, using it as a management tool for their clinical trials portfolio.

Dr. Adamson questioned whether the CRF modules are more than just PDF or Word documents. Dr. Buetow clarified that the CRF modules are bound to the entire electronic data capture infrastructure and will be accessible as part of those resources. Dr. Adamson also asked how the effectiveness of clinical trial reporting will be monitored. Dr. Prindiville said it is hoped that all sites will participate in reporting, as it will be linked to terms of awards.

Dr. Daniel Sargent, Director, Cancer Center Statistics, Mayo Clinic College of Medicine, asked how CTAC would evolve to provide more effective advice to NCI. Dr. Prindiville said that accepting or rejecting recommendations from the working groups, such as OEWG, will be a critical role for CTAC. Dr. Niederhuber commented that the rich discussion and advice generated at the meetings is very valuable to NCI's deliberations regarding clinical and translational research. Dr. Doroshov added that it is critically important that the CTAC members prod, remind, and oversee, and redirect when there are other issues for clinical and translational research.

Dr. Bruner recommended that a portion of the ARRA stimulus package funds be used to increase funding for translation of study-related materials (e.g., consent forms) and patient-reported outcomes in minority-based clinical trials.

Ms. Nancy Roach noted that there are many who would like to provide feedback related to oversight and Dr. Niederhuber encouraged people to email him directly with anything that might be helpful.

Dr. Leslye Fitterman, Epidemiologist for the Centers for Medicare and Medicaid Services, asked how the NCI clinical database interacts with the National Library of Medicine's (NLM) clinicaltrials.gov, so that a trial does not have to be entered multiple times. Dr. Prindiville responded that it is designed so that investigators who report into the database will receive a file that is ready to load to the NLM database as required by law. Dr. Adamson questioned why this process would not be automatic. Dr. Buetow explained that this is a regulatory issue related to the fact that the Federal Government cannot act as a surrogate for the responsible party in the direct submission to clinicaltrials.gov.

Additionally, Dr. Buetow noted that NIH and NCI have put forward proposals for IT infrastructure for health information technology as part of the stimulus package. There is a sense among those who are working on health care reform, that in order to move forward, there is a need to put in place the infrastructure reengineering that the cancer community has been taking the lead on.

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

Dr. James Abbruzzese, Chairman, Department of Gastrointestinal Medical Oncology, University of Texas M.D. Anderson Cancer Center, discussed the work of the Guidelines Harmonization Working Group of the Ad hoc Coordination Subcommittee, CTAC. The Ad hoc Coordination Subcommittee was created to provide advice to CTAC on how to foster collaboration among the various components of the National Cancer Institute (NCI)-supported clinical trials infrastructure in order to develop a fully integrated clinical trials system, moving from translation to early-phase clinical trials and on into late phase or Phase III studies. The Ad hoc Coordination Subcommittee created the Guidelines Harmonization Working Group with the goal to promote collaborative team science by ensuring that guidelines for different clinical trials funding mechanisms are aligned and to eliminate redundancy and duplication. The Working Group is also striving to develop incentives to foster collaboration among all components of the

NCI-supported clinical trials infrastructure including Cancer Centers, Specialized Programs of Research Excellence (SPOREs), and Cooperative Groups.

The Working Group's approach was to first review current guidelines of all mechanisms that support clinical trials. The Working Group is currently developing a draft vision document with specific recommendations that will be presented to CTAC in July 2009. If the report is accepted, NCI staff will develop guideline revisions consistent with the vision document, which will then be presented to CTROC and the NCI Executive Committee for final approval.

One of the first tasks undertaken by the Working Group was to define collaboration. The definition developed contained two general concepts: (1) individuals from different institutions and across NCI/NIH programs pool knowledge and share necessary resources to formulate and address clinical and translational research questions; and (2) the ideal collaborative structure facilitates recognition of individuals based on specific contributions to core research resources and generation of new scientific knowledge. The Working Group looked at some of what were thought to be the best examples of where translation and collaboration had occurred in an effective manner. These included the I-SPY trial in neoadjuvant management of breast cancer among Cooperative Groups, SPOREs, and the NCI Center for Bioinformatics and Informational Technology (CBIIT); drug development for multiple myeloma with collaboration between industry, NCI, academic trials, and foundations; and the prevention trial, SELECT.

The Working Group has completed the initial review of clinical trial mechanism guidelines related to collaboration, including policy and guideline areas, specific application and review criteria, as well as incentives and disincentives to collaborative research and to moving concepts from early translation through late phase clinical trials. The Working Group examined the guidelines for references to inter- and intrainstitutional collaborations as well as trans-mechanism collaborations, but found few specific review criteria that address these issues or incentives/rewards for collaboration. The Working Group found a number of disincentives for collaboration, including a culture that provides more academic credit for Principal Investigators (PIs) of institutional trials—not being able to "count" collaborations on clinical trials led by other institutions; high costs of trials and low per-patient reimbursement; and competition for patients with pharmaceutical companies. Subsequent to this review, the Working Group also participated in discussions with extramural and NCI experts representing Cooperative Groups, Cancer Centers, and SPOREs.

The vision document currently defines the problem and introduces the issues of harmonization, collaboration, and goals. It outlines goals and roles of NCI clinical trial mechanisms, including SPOREs, Cancer Centers, Cooperative Groups, CCOPs/Minority Based CCOPs, and others, and provides specific recommendations to eliminate disincentives to collaboration, develop new incentives and rewards for stimulating collaboration, and implement program and reviewer guidelines to facilitate the collaborations, 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. This new mechanism would interface with the STRAP program to be described later in the agenda, which moves ideas to the initial phase of clinical trials.

Recommendations that address the need to develop incentives and rewards for collaboration include revising review criteria to reward participation in Cooperative Group and Intergroup trials versus nonproductive trials (trials that never accrue or don't move from early-phase to later phase trials), providing salary support for institutional PIs who participate in multicenter studies, designing processes to recognize clinical investigators who promote collaborative and translational science, and utilizing existing K-award mechanisms to facilitate collaborations across programs. Other incentives include developing supplemental awards for multidisciplinary and translational collaborations, expanding Cancer Trial Support Unit (CTSU) capacity for registration of patients in large Phase II trials, and providing

support for development/use of technical resources that support trans-program collaborations on common scientific questions. Recommendations for removing disincentives to collaboration include: (1) eliminating inconsistencies between guidelines; (2) providing more specificity to grantees and reviewers on issues such as collaboration; (3) addressing the academic reward system that promotes independence over collaboration; and where possible (4) correcting fiscal inequities and inadequacies within the clinical trial system.

The Guidelines Harmonization Working Group will be defining criteria and measures of success that can be used to evaluate the effects of changes made based on these recommendations. The Working Group plans to finalize recommendations and complete its draft report for presentation to CTAC in July. Dr. Abbruzzese asked for feedback from CTAC members on the approach of the Working Group and assessment metrics to be considered in order to answer the question: How do we know that we are achieving our goals in making this process of an integrated system more robust? He also asked that any additional comments be sent by email following the meeting.

Questions and Discussion

Dr. Lee Helman, Chief, NCI Pediatric Oncology Branch of the Center for Cancer Research (CCR), questioned how NCI plans to address the struggle between individual achievement and collaborative work at academic institutions. NCI has no control over a particular academic institution's criteria for tenure, which tends to be a barrier to collaboration. Dr. Abbruzzese commented that it will take time and leadership to eliminate this barrier. Leaders of Cancer Centers are better educated on the importance of collaborations to create a more integrated clinical trials system and need to impart this knowledge to individual investigators and senior professors. Dr. Alberts added that money plays a large role in this issue. For example, a Chair of a Phase III study does not receive money to support the percent effort that he/she contributes to Cooperative Group or collaborative work.

Dr. Schilsky commented that NCI cannot dictate promotion criteria at academic institutions; however, NCI could offer national recognition for a particular faculty member's work. Dr. Joel Tepper, Hector MacLean Distinguished Professor of Cancer Research, Department of Radiation Oncology, University of North Carolina Lineberger Comprehensive Cancer Center, urged NCI to consider ways to provide external validation (i.e., recognition by the larger research community) to acknowledge participation in team science.

Dr. Kenneth Cowan, Director, Eppley Cancer Center, University of Nebraska Medical Center, added that external validation is particularly important for junior faculty. One possibility would be to develop multi-institutional committees to foster relationships between various NCI-funded programs. Individuals serving on these committees, including junior investigators, would receive recognition for their contributions on an internal and national level. Dr. Alberts commented that NCI should consider using the K23 mechanism—the Mentored Position Scientist Career Development Award—to encourage participation in Cooperative Group or SPORE clinical trials. Dr. Heidi Nelson, Fred C. Anderson Professor at the Mayo Clinic Foundation, noted that junior investigators benefit from 2-year awards such as the First Investigator Awards. Dr. Cowan followed up by adding that the NIH Clinical and Translational Science Awards (CTSAs) could be a possible mechanism to provide funding support for junior faculty.

Dr. Wade asked about plans to expand the capacity of the CTSU to coordinate large Phase II trials. Dr. Jeffrey Abrams, NCI CTEP Associate Director, explained that CTEP has begun a pilot project that utilizes CTSU for its Phase II clinical trials network, particularly for trials of rare diseases for which

it is difficult to identify sites qualified to participate. If successful, it may be appropriate to expand this model.

VI. INVESTIGATIONAL DRUG STEERING COMMITTEE (IDSC)—DRS. CHARLES ERLICHMAN AND MICHAEL MAITLAND

IDSC Overview. Dr. Charles Erlichman, Professor of Oncology, Mayo Clinic College of Medicine, stated that the goals of the IDSC are to provide external strategic input into the prioritization of Phase I and Phase II trials for new agents for which the NCI Cancer Therapeutics Evaluation Program of the Division of Cancer Treatment and Diagnosis holds an Investigational New Drug (IND) application; increase transparency of prioritization processes; optimize clinical trial designs to improve effectiveness of early-phase therapeutics; increase the predictive value of early-phase trials resulting in the design of more successful Phase III trials; and develop a new forum for interaction among grant and contract holders and CTEP.

IDSC membership includes the PIs of all NCI Phase I U01 grants and Phase II N01 contracts, representatives from Cooperative Groups, liaisons to Disease-Specific Steering Committees, and subject area experts (e.g., biostatistics, imaging, radiation oncology, pharmacology, advocacy). Approximately 40 IDSC members participate in 13 task forces and working groups.

The IDSC Scientific Meeting Planning Working Group collaborates with CTEP to develop educational sessions for semi-annual Early Drug Development (EDD) Meetings.

The Biomarkers Task Force is addressing the question of whether biomarkers should be part of all early drug development trials and, if they are used, what levels of technical and clinical evaluation are necessary. The Task Force is developing recommendations to guide CTEP and individual investigators.

The Clinical Trial Design Task Force held a workshop on Phase I trial design in July 2008 and plans to publish a series of opinion papers in *Clinical Cancer Research* on a variety of Phase II study design topics based on a meeting in January 2007. Future topics for this Task Force will include tumor measurement analysis, the pros and cons of adaptive design versus frequentist approaches (based on an ongoing Phase II simulation trial), feasibility of using Cooperative Group databases as Phase II historical controls, and novel ways of incorporating imaging data in early-phase trials.

The first task of the Angiogenesis Task Force was originally developed to review CTEP's portfolio of antiangiogenic agents. Early efforts of the Task Force focused on the need to manage hypertension related to these agents. The Task Force's recommendations in this area will be summarized by Dr. Michael Maitland, Assistant Professor of Medicine, in the Section of Hematology/Oncology of the University of Chicago, in the second half of this presentation. In 2009, the Angiogenesis Task Force will address ventricular dysfunction and myocardial ischemia, evaluate the use of angiogenesis biomarkers in CTEP's drug development plans, and review imaging methods for assessing angiogenesis in cancer.

The Signal Transduction Task Force has worked with CTEP on the development plan for the IGF-1R antibody IMC-A12 and provided review and input on development plans for a CDK2 inhibitor, a cMET inhibitor, and the PI3-kinase category of inhibitors. In the coming year, the Task Force will address JAK/STAT inhibitors, newer proteasome inhibitors, and PIM inhibitors.

The PI3K/Akt/mTOR Task Force is also referred to as the PAM Task Force. Subgroups of this Task Force are reviewing CTEP plans for mTOR inhibitors, assessing the use of biomarkers and imaging

in the development of PAM targeted agents, addressing toxicity management, and identifying new agents to add to the portfolio.

The Immunotherapy Task Force was established to provide input on novel immunomodulators. This Task Force is reviewing CTEP's current portfolio of agents, making recommendations on the IL-12 development plan, and recommending new immunotherapeutic strategies.

The new Cancer Stem Cell Therapeutics Task Force focuses on identification of therapeutics that inhibit various types of signaling pathways. The Task Force has also been charged with looking at potential biomarkers for cancer stem cells, circulating tumor cells, tumor-initiating cells, and tumor progenitor cells. The Task Force also made significant contributions to the drug development plan for GDC-0449 and is involved in plans for development of a gamma secretase inhibitor.

The IDSC has developed a matrix that tracks activities of the 13 Task Forces and Working Groups and summarizes the Steering Committee's accomplishments. The IDSC has provided significant input on a number of drug development plans, provided feedback on career development track letters of intent, and reviewed eight potential agents. Eight manuscripts are in various stages of development. The IDSC has also developed an efficient mechanism for review of CTEP's drug development plans, defined productivity metrics for its task forces, assisted with educational sessions, developed a newsletter, and interacted with disease-related groups (e.g., the Prostate Cancer Task Force of the Genitourinary Steering Committee).

Challenges for the IDSC include bringing new agents into the portfolio and increasing coordination and interaction with the DS-SCs, Cooperative Groups, and SPOREs. Future directions for the Committee include increasing novel agents in the CTEP portfolio, increasing trial opportunities with agents already in the CTEP portfolio, working with NCI to address biomarker development in early clinical trials, and developing an effective communication effort in collaboration with DS-SC to inform early drug development leading to more effective Phase III trials.

Cardiovascular Toxicities Panel. Dr. Maitland described several projects undertaken by the IDSC Cardiovascular Toxicities Panel, a group convened by the Angiogenesis Task Force to address adverse events associated with the use of angiogenesis-inhibiting drugs, with a particular focus on hypertension. It was found that each clinical trial evaluating these types of drugs approached the identification and management of adverse events differently.

The Cardiovascular Toxicities Panel—with members from the Angiogenesis Task Force, the American Society of Hypertension, CONQUER (Cardiology Oncology International Quest to Educate and Research Heart Failure), and the Heart Failure Society of America—was brought together in 2006 to address these concerns, report to the Angiogenesis Task Force and the IDSC on the state of the science, recommend areas for further research, and provide guidance on standardized management of toxicities in CTEP clinical trials. The Panel's first project resulted in the August 2008 release of a Blood Pressure Consensus Report with recommendations for initial assessment, surveillance, and management of blood pressure in patients receiving angiogenesis inhibitors.

The Panel's work on the hypertension issue resulted in identification of three areas in which action is needed: (1) providing cross-specialty education on practice standards, epidemiology, and terminology; (2) alerting the cardiovascular specialties community about this increasingly critical issue; and (3) guiding oncologists in providing more attentive supportive care. The purpose of the project is not to discourage the use of angiogenesis-inhibiting drugs but to make their use as safe as possible for as many patients as possible.

Because some oncologists and patients do not understand why hypertension should be addressed when patients have more immediate health concerns, the project developed five key reasons for attentive management of hypertension: (1) serious adverse events associated with unmanaged blood pressure elevations can be prevented; (2) the magnitude of blood pressure elevation is variable and as yet unpredictable; (3) attentive comorbidity management has numerous potential benefits; (4) as the use of angiogenesis-inhibiting drugs expands to earlier disease settings, the principles for patient care are increasingly the same as for primary care; and (5) active control of hypertension should allow patients to tolerate high drug doses for longer periods, improving outcomes.

The Panel recommends that oncologists align their methods for rating the severity of high blood pressure with those used by cardiovascular medicine specialists. Other recommendations include: (1) candidates for the use of angiogenesis-inhibiting drugs should undergo a dedicated pretreatment risk assessment; (2) the appropriate goal for a patient's blood pressure should be <140/90 mmHg before and during treatment; (3) blood pressure should be measured accurately, early, and often; and (4) while most patients' blood pressure elevations can be managed by their oncologists, some will require care from a cardiovascular specialist. The Panel's report also contains guidance for oncologists in selecting appropriate antihypertensives and other aspects of managing high blood pressure.

Challenges the Panel faces include the "orphan" nature of this area of study, which makes it difficult to get study proposals and manuscripts through a review panel or editorial board; the voluntary nature of participation in the project, which has slowed progress; and the lack of data on the risks for hypertension and associated complications in cancer patients.

Findings from the Panel's first report are being integrated into CTEP-sponsored trials of angiogenesis-inhibiting drugs. The Panel is developing a second consensus report on vascular dysfunction and myocardial ischemia, expanding its group of expert advisors, and exploring new ways to support cross-discipline collaboration.

Questions and Discussion

Dr. Niederhuber asked whether genetics had been discussed as a factor in the issues addressed by the Cardiovascular Toxicities Panel. Dr. Maitland acknowledged that unpublished data shared by Panel members have suggested that possibility; some variability in blood pressure responses seems to be independent of the pharmacokinetics of the drugs.

Dr. Alberts suggested investigating the potential association between the scheduling of antiangiogenic agents and their toxicity.

Dr. Schilsky asked whether other efforts within NCI, such as ongoing efforts to implement the recommendations of the TRWG, are benefiting or could benefit from the expertise of the IDSC to avoid duplication of effort. Dr. Erlichman replied that he and many other IDSC members had participated in the 2008 NCI Translational Science Meeting and that Dr. Lynn Matrisian, Special Assistant to the NCI Director and TRWG Co-Chair, had attended an IDSC meeting to talk about the TRWG developmental pathway, especially related to novel therapeutic agents.

Dr. Schilsky noted that the NCI Board of Scientific Advisors recently heard a presentation from Dr. Doroshow about a proposed immunotherapy trials network. Dr. Schilsky asked whether there had been discussion with the IDSC in developing that concept. Dr. Doroshow reported that there is good communication between the IDSC Immunotherapy Task Force and the group that suggested the

immunotherapy trials network concept. Dr. Matrisian added that many of the potential immunotherapy trials network members participated in a pilot project for the TRWG prioritization process. Dr. Schilsky stressed the importance to CTAC members of learning as much as possible about how various aspects of the NCI portfolio are interrelated.

Dr. Alberts suggested that the increasing numbers of drugs available for evaluation through CTEP may require expansion of the NCI-funded Phase I centers to increase the involvement of Cancer Centers in Phase I programs.

Mr. Everett Dodson of the Lombardi Comprehensive Cancer Center commented that addressing the issue of hypertension could have the beneficial effect of reducing a comorbidity-related barrier to accrual of minorities into clinical trials.

Dr. Curt Civin of the University of Maryland School of Medicine noted that the IDSC could be of great assistance to experts in the various "omics" fields who are involved in the identification of new therapeutic targets but are not familiar with the world of drug development.

Dr. Richard Pazdur of the Food and Drug Administration asked about the extent of the IDSC's interactions with companies involved in development of *in vitro* diagnostics. Unlike large pharmaceutical firms, these companies have limited budgets and could benefit from federal guidance and assistance in bringing their markers into early-phase drug trials. Dr. Erlichman noted that the IDSC Biomarker Task Force is addressing the issue of building diagnostics into early drug development. He agreed that drug companies and diagnostics companies operate in two different worlds. Dr. Erlichman added that there are no appropriate funding mechanisms to support diagnostic development early in the drug development process. This gap in funding mechanisms should be considered an opportunity for development of centers with a focus on *in vitro* diagnostics relevant to signaling pathways being targeted by drug development groups.

Dr. Joel Tepper of the Lineberger Comprehensive Cancer Center asked about the IDSC's experience in forming relationships with other Steering Committees. Dr. Erlichman observed that many IDSC members are members of other entities such as Cooperative Groups, but it is unclear whether they communicate with those other groups about the IDSC's activities. Forming relationships is a two-way process; he acknowledged that greater efforts are needed to encourage and track the sharing of information between groups.

VII. GASTROINTESTINAL STEERING COMMITTEE (GISC) UPDATE—DR. JOEL TEPPER

Dr. Tepper presented a brief summary of the operations of the Gastrointestinal Steering Committee and listed some of the strengths and weaknesses of what the Committee has done so far. GISC has been in full operation for approximately 3 years. The Committee represents nine Cooperative Groups and has seven task forces: Esophagogastric, Pancreatic, Hepatobiliary, Colon, Rectal/anal, Neuroendocrine, and GI Stromal tumors. The task forces, which include representatives from Cooperative Groups and at least one liaison from the GISC, work on concept development. The Scientific Steering Committee devotes most of its time to concept review; it initially rejected a large number of protocols but is now accepting a higher percentage.

The GISC has sponsored a few Clinical Trials Planning Meetings (CTPM). The last meeting was held in November 2008, with a focus on hepatocellular carcinoma. This meeting was more effective than

the previous meeting on pancreatic carcinoma due to the fact that there was a stronger focus on clinical trial development than on the state of the science. As a result of the November meeting, directions for future clinical trial work were created, guidelines for clinical trials development were formulated, and critical endpoints were established. Some specific recommendations from the meeting were in regard to the issue of orthotopic liver transplantation; it was decided that randomized trials focused on liver transplantation as a modality should not be developed. However, an area ripe for development is the use of adjuvant therapy after either orthotopic liver transplantation or hepatic resection. Attendees of the CTPM also discussed having small meetings of 10-15 people to address specific critical issues in protocol development that cannot be resolved via conference call.

The Neuroendocrine Task Force is planning the next CTPM, which will take place late this fall. The meeting development process was time-intensive and required weekly or biweekly conference calls for almost a year. Some of the topics that will be discussed at the meeting are: grades of neuroendocrine tumors that can be included in a single study; agreement on parameters for tumor grading; relevant endpoints for slow-growing tumors; promising new agents; trial design for screening new agents; and appropriate patient subsets for liver-directed therapy.

After 3 years in operation, strengths and weaknesses of the GISC process have become apparent. GISC has improved interaction and cooperation among Cooperative Groups. The Committee has also allowed rapid action on critical issues and facilitated Cooperative Group science to support other group trials. However, it is important that the SSC address its weaknesses, which include inefficient translation of ideas from the lab to clinical studies and difficulty in defining and advancing novel ideas. GISC is actively working to eliminate these weaknesses. The Steering Committee has established a working group to help further incorporate science into task force operations, as well as a working group to help evaluate more formally the operations of the Steering Committee and task forces. There is also a continuing effort to expand representation of community physicians and advocates on task forces.

Questions and Discussion

Dr. Adamson questioned whether the SSC is disapproving full protocols or just protocol concepts. Dr. Tepper clarified that the failing protocols are only concepts. Dr. Sandra Horning, Professor of Medicine, Stanford Comprehensive Cancer Center, asked whether disapproval of concepts takes place at the task force level. Dr. Tepper explained that there is no formal approval or disapproval of concepts at the task force level. If a protocol concept is not reviewed favorably in a task force, it will likely not be presented to the SSC. However, a concept does not need to obtain task force approval, although it does need to be presented to the task force. Dr. Adamson added that there is potentially a systems problem with many SSCs; the system is not designed to facilitate early failure of concepts.

Dr. Alberts expressed concern that the task forces are only adding an extra step in the concept approval process. Dr. Tepper stated that the task forces have enhanced collaboration between Cooperative Groups. Dr. Abbruzzese added that GISC's vision was that the development of concepts would take place at the task force level, which allows for input from Cooperative Group members, advocates, and other NCI scientists.

Ms. Roach, an advocate on the GISC, commented that the two advocates on the Committee created an advocate roles and responsibilities document. The document has helped bring new advocates up to speed on the work of the Committee and helped investigators understand the role of patient advocates.

Dr. Hillman suggested that GISC hold a focused meeting involving the radiology community to develop standardized protocols for use of imaging to collect endpoints for clinical trials of GI tumors. Use of imaging endpoints is particularly difficult for patients receiving targeted agents, and numerous approaches are being used across study protocols.

VIII. COMMITTEE DISCUSSION—DR. JAMES DOROSHOW

Dr. Doroshow facilitated a Committee discussion on ways to increase coordination and collaboration within the clinical trials infrastructure. He noted that the reason that the preceding presentations were grouped together was to focus attention of the members on activities that would better coordinate across all of NCI's efforts to support clinical and translational research. Dr. Doroshow requested input from the group on what types of incentives would facilitate this type of coordination and collaboration.

Ms. Roach commented that National Cancer Institute needs to enhance communication with the advocacy community so that advocates understand the goals and initiatives being pursued. Dr. Niederhuber agreed that there is a huge disconnect with the outside community despite the vast resources NCI devotes to communication and education.

Dr. Helman noted that an additional strength of the GISC is the fact that interaction with and collection of input from CTEP is occurring earlier in the protocol development process.

Dr. Helman commented that there is a shared frustration over the inefficiencies in translating ideas from the lab to clinical studies and that increased interaction among the various groups that are organized or supported by NCI is needed. Dr. Tepper stated that much of the interaction that currently occurs is by chance (i.e., because individuals happen to be involved in multiple areas); however, a more formal process for exchanging information should be established. Dr. Helman suggested perhaps an increase in interaction would accompany implementation of the TRWG initiatives.

Dr. Abbruzzese commented that the translation of ideas from labs to clinical studies is particularly problematic for pancreatic cancer research, in part because there are relatively few translatable ideas. Clinical investigators studying pancreatic cancer rely on pharmaceutical companies for trial ideas. Dr. Heidi Nelson, Fred C. Anderson Professor at the Mayo Clinic Foundation, commented that translation would be facilitated if translational scientists were more engaged in the conversations at the SSC or task force level. Ms. Roach added that people involved in the development of diagnostic tests and devices also need to be involved in the early phases of development. Dr. Doroshow indicated that individuals with the desired expertise can and should be invited to be involved in the activities of the SSCs and/or task forces.

Dr. Alberts suggested that the SSCs require investigators to identify biomarkers that might be useful for monitoring response to therapy or provide mechanistic insights. This would force researchers to think about biomarkers early in the process.

Dr. Nelson inquired about the charge of the GISC, noting that the Committee seems primarily concerned with approval/disapproval of proposals rather than helping to develop innovative ideas for trials. Dr. Doroshow emphasized that the charge of the SSCs is to do whatever is necessary to advance science in their respective areas. Dr. Tepper replied that discussions, particularly at the task force level, are helping to refine proposals. Some proposals are assigned to a "pending" category; investigators of these proposals are given the opportunity to revise and resubmit their proposals based on input from the

task force. Dr. Nelson replied that investigators tend to view the SSCs as a hurdle rather than a resource. It is important that the SSCs and task forces provide something of value to investigators. Feedback from reviewers is one example of value added; it would also be useful if the SSC helped link potential collaborators. Dr. Nelson suggested that efforts be made to determine whether this type of value is being added to the clinical trials process.

Dr. Civin asked whether the Disease-Specific SSCs could issue the equivalent of an RFA to identify areas in which research is needed. Dr. Tepper answered that a similar approach has been used for some of the very uncommon diseases because the research community is relatively small and the task forces perform duties similar to those of a Cooperative Group. Dr. Adamson commented that all Disease-Specific SSCs could benefit from a database of phenotypic data (e.g., outcome of therapy), which could inform the design of future Phase III trials.

Dr. Bruner stated that many Cancer Centers have relatively low accrual rates for their clinical trials. She wondered if the efforts of the SSCs could actually have a detrimental effect on patient accrual and stated that accrual should be used as one of the metrics for measuring success of the changes in the clinical trials process. Dr. Kenneth Cowan added that completion rates should also be measured.

Dr. Doroshov reiterated that incentives must be meaningful. It is insufficient to merely state in review guidelines that collaboration is desirable; collaboration must be rewarded in the review and funding process. Dr. Schilsky commented that there are only three meaningful incentives to collaboration: money, resources (e.g., CLIA-certified laboratory), and time (e.g., shortened review process).

Dr. Matrisian explained that the TRWG envisions a paradigm in which researchers are linked in a project-specific manner rather than the creation of an overarching infrastructure to promote collaboration. The TRWG pathways can be used as a tool to create incentives—if one step of the pathway is successfully carried out, then the researchers would be provided with incentives to identify the next set of collaborators to take another step in the pathway. Study success can be measured by the number of steps taken in a given pathway. Dr. Cowan observed that if a limited number of projects are coming out of a prioritization scheme, project management should be used to efficiently facilitate these projects from startup to completion.

Dr. Sargent commented that the most effective incentive for collaboration would be the reduction of disincentives. Researchers want to collaborate but are often deterred by existing barriers in the system. Dr. Adamson mentioned that the CTSA approach, which forces collaboration, is another model to consider.

Dr. Niederhuber stated that he was hearing increasing support for the idea that NCI should play a central and significant role in coordinating clinical trials. He likened it to NCI support for the Cancer Genome Project, which involved creation of resources for data acquisition and data management. An NCI system could help control costs, increase standardization, and ensure equal access to resources. NCI will likely need to be an important driving force in the development of targeted therapies and biologics. This will require drawing from knowledge generated by genetics/biology as well as the expertise of chemists to identify drugable targets. Greater collaboration among NCI, the academic community, and the private sector will be needed to do this. Dr. Doroshov added that NCI has helped investigators of early-phase trials develop assays to measure the effect of drugs on their intended targets and provided support for correlative studies. Dr. Hillman added that equal access to resources is key. Informative clinical achievements can be made by utilizing databases that link tissue specimens, targeted imaging data, and clinical data.

Dr. Pazdur inquired how the efforts discussed during the meeting relate to the concept of comparative effectiveness that is being promoted by the Obama Administration. Dr. Niederhuber stated that this represents an effort to increase the use of knowledge management in medicine, which should help decrease health care costs. One possibility would be to use available stimulus money to establish virtual centers to determine how comparative effectiveness research should be done (i.e., what types of questions should be asked). Dr. Pazdur stated that decisions must often be made on the individual patient level. It would be positive if these discussions could be converted into research that would help determine which drugs or interventions would be best for individual patients. Dr. Wade added that these types of decision-making criteria should include quality of life and pharmacogenomics.

IX. MINORITY AND UNDERSERVED ACCRUAL IN CLINICAL TRIALS—DR. WORTA MCCASKILL-STEVENS

Dr. Wort McCaskill-Stevens, Program Director, Community Oncology and Preventive Trials Research Group, DCP, NCI, noted that the 1993 NIH Revitalization Act mandated that women and minorities, including minority subpopulations, should be represented in all clinical research. The purpose of this mandate was not only to promote justice but also to ensure that in Phase III trials, valid analyses could be done for intervention effects. The Act stipulated that the cost could not be used as justification for excluding minorities and required NIH to initiate programs for outreach, recruitment, and retention of women and minorities in clinical trials.

The NCI Cooperative Group mechanism and database includes the following populations as underserved: the elderly, African Americans, Hispanics/Latinos, Asian Americans, Native Americans, adolescents, individuals of low socioeconomic status (SES), and those who live in rural areas. The last three categories present unique difficulties for the cancer research community. Some adolescents are treated in pediatric settings while others are seen in adult clinics. Descriptions of socioeconomic status and definitions of rural areas vary widely.

The NCI Clinical Trials Network includes 64 NCI-designated Cancer Centers, 47 institutions in the CCOP, 13 in the Minority-Based Community Clinical Oncology Program (MBCCOP), 5 in the Cancer Disparities Research Partnership Program, and 16 in the NCI Community Cancer Centers Program. The Cancer Disparities Research Partnership Program, which was originally designed to take radiation protocols into underserved communities, has been substantially expanded to include surgical and medical trials. The NCCCP is a pilot program whose mission is to take multi-specialty care and early-phase trials into the community as well.

The presentation of data on minority participation in the Clinical Trials Network is organized according to guidelines published by the Office of Management and Budget in 1997. These guidelines created racial and ethnic standards for federal statistical and administrative reporting and made it possible for individuals to self-identify with more than one racial classification.

Between FY 2000 and FY 2008, overall minority enrollment in NCI trials has averaged approximately 15 percent, with less than 1 percent reporting more than one race. In FY 2007 and FY 2008, there was a slight increase in the percentage of minority participants, while total enrollment showed a slight decrease.

Data on enrollment by race for the same time period show that African Americans are the minority with the highest number of participants. There are significant deficits in the numbers of Native Americans and Native Hawaiians enrolled in NCI trials. Data on ethnicity for the same period show a

steady increase in enrollment of Hispanics/Latinos. These data are problematic due to the failure of many sites to report ethnicity and the tendency of health care providers to make decisions about their patients' ethnicity rather than asking patients to self-report.

The NCI Cancer Trials Support Unit was created to facilitate general accrual to NCI trials. Data on CTSU accrual to CTEP Phase III treatment trials between FY 2000 and FY 2008 show a pattern similar to the overall pattern for all NCI trials.

Data on enrollment of minorities over the age of 70 show lower percentages than for the general population because earlier mortality and more advanced disease are more prevalent among underserved populations and these patients do not meet eligibility criteria for trials enrollment.

Minority enrollment in trials conducted in catchment areas of MBCCOPs between FY 2000 and FY 2007 ranged from 51 to 75 percent, compared with 8 to 10 percent for the CCOPs. Increased participation of minorities in cancer control trials suggests that members of underserved populations are becoming more receptive to addressing questions related to symptom management either in the cytotoxic agents or newly studied targeted agents.

The clinical trials component of the NCI Community Cancer Centers Program is designed to increase accrual to all trials, with a special focus on minorities and underserved populations and on multimodality and early-phase trials. Two NCCCCP sites primarily serve rural Native American populations. Collection of overall data on recruitment into NCCCCP trials is incomplete; however, trends indicate an increase in minority recruitment along with an increase in overall recruitment. A breakdown of data on NCCCCP accrual to NCI Cooperative Group trials shows a trend toward increasing minority recruitment to cancer control and prevention trials.

One of the most serious barriers to improving minority recruitment to clinical trials is concomitant comorbidities, specifically in older patients, but across all age groups. Two approaches to addressing this issue are refining tools to better assess patients who have comorbidities and expanding trials to include patients with comorbidities. For trials involving large numbers of participants with comorbidities, studies must focus on research questions such as how comorbidities affect treatment, how comorbidities affect adherence, and whether the sensitivity of assays to determine who would benefit from an intervention varies between community and academic settings.

Institute of Medicine studies and the trans-DHHS Health Disparities Progress Report Group, among others, have suggested that SES affects outcomes, but data on the few existing surrogates for detecting SES are not routinely collected. Educational level, ZIP code, and insurance coverage are often used as a surrogate for SES. Another potential surrogate is census tract information. One advantage of census tract data is that there are no HIPAA concerns with such information. Collecting these data would also help investigators become more familiar with the communities in which their patients live.

An important lesson learned by the NCI Clinical Trials Network is the need to reinforce and enhance the workforce. Physicians who are new to enrolling patients into clinical trials need mentoring in managing data and working with IRBs, as well as assistance in handling increased work loads. Other important lessons are to keep the community informed about risk and develop strong recruitment plans before accrual begins.

Addressing disparities in clinical trials recruitment requires a collaborative effort among partners such as the Clinical Trials Network, the Center to Reduce Cancer Health Disparities (including its patient navigation and community networks programs), ENACCT (the Education Network to Advance Cancer Clinical Trials), and the Trans-NCI Clinical Trials Accrual Working Group (CTAWG). The CTAWG is

an internal NCI working group intended to foster collaboration and information sharing across the Institute, including development of initiatives that promote successful clinical trial accrual practices. CTAWG members are planning an interactive workshop in 2010 on clinical trial recruitment strategies and investigating the use of an interactive Web site to disseminate evidence-based accrual strategies.

Programs that enroll minorities and underserved populations into cancer clinical trials can serve as a training ground for young investigators; identify relevant basic science, clinical, and behavioral issues; collect important data on populations with significant comorbidities; and enrich the literature on research recruitment, retention, and overall improvement in cancer clinical care in this population.

Questions and Discussion

Dr. Bruner, observing that the increase in minority recruitment into cancer control trials has not been matched by an increase for treatment trials, asked what the future might hold in terms of improving minority accrual into treatment trials. Dr. McCaskill-Stevens acknowledged the lack of information that could be helpful in determining what steps should be taken. Improvements in the translation of information about treatment trials into appropriate languages and reading levels have not made significant impact on accrual. Changes that might enhance progress include improvements in reporting on health status in communities, access to information on availability of trials, communication about risk of participation in trials, and education for practitioners on working with minority populations in clinical research.

Dr. Bruner noted that recruitment is a behavioral issue that encompasses both communication and trust among patients, scientists, and providers. Most behavioral studies are small and the majority of their findings are never published. Dr. Niederhuber stated that behavioral research, in terms of both ethnicity and socioeconomic status, is a key focus of the NCCCP.

Dr. Timothy Rebbeck of the University of Pennsylvania School of Medicine stressed the need for accurate metrics to determine the sample size required to make valid inferences about how treatments affect specific minority or underserved populations. Small increases in minority participation in trials are not a measure of success if the numbers needed for valid findings have not been achieved. Dr. Wade highlighted the MBCCOPs as an example of how investigators can achieve high percentages of minority accrual into clinical trials. Dr. McCaskill-Stevens added that the outcomes from multi-institutional collaborative studies often are sufficient when addressing questions related to minorities and underserved populations. Dr. Horning noted that the underrepresentation of individuals 65 or 70 years or older in trials is striking and suggested that new programs such as the NCCCP would have a real opportunity to address that area. Dr. Niederhuber noted that the Challenge grants being released in conjunction with the Recovery Act also provide opportunities for support in these areas.

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

Dr. Matrisian provided an update on activities related to the implementation of the TRWG initiatives. The TRWG recommended a new process for accelerating early translational cancer research. 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.

Specifically, the TRWG proposed the selection of several projects ripe for translation each year as well as provisions to support the acceleration of these projects through the relevant TRWG developmental pathway(s). The translational research acceleration process was envisioned as having three components: gathering information to identify translational opportunities; determining how to prioritize these opportunities; and developing 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.

The NCI Translational Science Meeting, <http://ncitranslates.nci.nih.gov>, held in November 2008 in Washington, DC, was the first attempt to gather information on current translational research opportunities. Invited participants presented a total of 513 abstracts. The abstracts provided a representative (not comprehensive) view of NCI-supported translational research. Abstracts were organized by the TRWG pathways to clinical goals. This process resulted in the definition of a translational research opportunity. A translational research opportunity focuses on a clinical goal, describes scientific validity, details clinical need, and provides information on feasibility. One such research opportunity acknowledged at the meeting is the development of an agent with the potential to block the Wnt signaling pathway in colorectal cancer. Translational Research Opportunity Informational Guides for each of the six TRWG pathways were distributed at the meeting and are available on the meeting Web site: http://ncitranslates.nci.nih.gov/Developmental_Pathways.htm. The Information Guides serve as educational tools for the research community to outline the information that would be required to evaluate and prioritize a translational research opportunity.

At the December 2008 CTAC meeting, the Committee recommended that NCI proceed with establishing a process to accelerate translational cancer research. In order to accomplish this, CTAC created the Process to Accelerate Translational Science Working Group. This Working Group is charged with determining a format for translational research opportunities, determining pathway-specific prioritization criteria, and advising on cross-pathway criteria. The PATS Working Group first met on February 16, 2009, via webinar. The first face-to-face meeting took place on March 3, 2009, to initiate criteria setting. It is envisioned that the PATS Working Group will divide into subgroups with specific expertise in each of the six TRWG developmental pathways.

Identified tools needed to go through the prioritization process include a translational research opportunity template, and a pathway-specific criteria and rating scale. The PATS Working Group is in the process of transforming the Translational Research Opportunity Informational Guides into useful templates to be used during the prioritization process. The Working Group is proposing that the Analytical Hierarchy Process (AHP)—a structured technique for complex decision making—be used 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. This process was piloted with the immune response modifiers pathway in Fall 2008 to identify the characteristics of an ideal cancer antigen. In its entirety, the prioritization process will require the development of both intrapathway and interpathway weighted criteria, which will then be used by NCI leadership to make executive prioritization decisions.

In addition to the prioritization process, NCI concurrently needs to develop customized funding strategies and project management capabilities. The NCI Clinical Trials and Translational Research Operations Committee is charged with identifying funding mechanisms and sources that are dependent on project specifics. This will require extraordinary coordination and will range from an expansion of existing activities to the creation of new ones. The proposed new funding strategy will be a Special Translational Research Acceleration Project, which will require projects to have: a goal of completing early-stage human studies; a project management plan; specific development 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. Project management capabilities are currently being developed by the NCI Coordinating Center for Clinical Trials.

The PATS Working Group has an aggressive timeline to implement the prioritization process. Another NCI Translational Science Meeting is planned for November 2010; the call for STRAP proposals and funding requests will take place by Spring 2010.

Questions and Discussion

Ms. Roach asked whether the purpose of the next NCI Translational Science Meeting will be to link collaborators for concepts developed from the summer Request for Information. Dr. Matrisian clarified that the November 2009 NCI Translational Science Meeting will be in preparation for the next call for concepts.

Dr. Schilsky commented that it would be useful to include feedback on clinical need when prioritizing translational research concepts for acceleration.