DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
6th CLINICAL TRIALS ADVISORY COMMITTEE MEETING

Summary of Meeting
December 8, 2008

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 6th meeting on Monday, December 8, 2008, in Conference Room 10, C-Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD from 8:00 a.m. – 4:43 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 (absent)
Kenneth H. Cowan
Everett Dodson
Stephen S. Grubbs
Bruce J. Hillman (absent)
Sandra J. Horning (absent)
K. Gabriel Leung
Nancy P. Mendenhall
Heidi Nelson
David R. Parkinson
Edith A. Perez
Timothy R. Rebbeck
Nancy Roach
Carolyn D. Runowicz
Daniel J. Sargent
Richard L. Schilsky
Joel E. Tepper
Jeffrey M. Trent (absent)
James L. Wade, III

***Ex Officio* Members**
Anna Barker, NCI (absent)
James H. Doroshow, NCI
Leslye K. Fitterman, CMS
Paulette S. Gray, NCI
Lee Helman, NCI
Richard Pazdur, FDA
John F. Potter, DOD
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 6th 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 in writing, regarding items discussed during the meeting, 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 Board 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 25 June 2008 CTAC meeting. The motion was seconded, and the minutes were approved unanimously.

II. DIRECTOR'S UPDATE—DR. JOHN E. NIEDERHUBER

Dr. John Niederhuber, Director, NCI, began by extending an additional welcome to new CTAC members.

NCI Budget Update. Fiscal year 2008 ended on September 30 with R01 paylines around the 14th percentile, plus exceptions, continuing a trend in the R01 payline over the past several years. However, the success rate among grant applicants is a more important indicator. Approximately 20 percent of the applications submitted to NCI received funding.

Through a special funding program targeting young investigators, applications were funded at the 19th percentile, plus exceptions awarded, resulting in 234 grant awards. Based on a belief that furthering the careers of young investigators requires a partnership between NCI and the extramural community, Dr. Niederhuber has been working with Dr. Dinah Singer [Director, Division of Cancer Biology] to find ways to encourage institutions to provide mentoring programs and resources for young investigators to make them more eligible for R01 exception funding. NCI expects mentoring programs to support new assistant professors from their initial appointment to their achievement of tenure. A monitoring system is being put into place to determine whether the program is having the anticipated benefits.

NCI funded approximately 1,284 competing Research Project Grants (RPGs) in FY 2008, including some supplements. One new Cancer Center was established at the University of Maryland.

The NCI Budget Office closed FY 2008 with a balance of $3,302. This is a significant achievement, since any funds left over at the end of a fiscal year must be returned to the U.S. Treasury.

In FY 2008, the National Institutes of Health (NIH) received $150 million in supplemental funding, of which NCI received $25.56 million. Of this amount, $14 million supported 35 additional RPGs, $1 million was used for supplements to the AIDS Center, $.5 million was spent in support of clinical groups, $4.8 million was spent for research and development contracts, and $5.2 million went to enhancing the drug development infrastructure to support the extramural community. This type of supplemental funding is likely to be the primary means of obtaining incremental funding increases in the near future. It has the potential for creating problems in future years because a 1-year boost in funding, which is not part of the baseline budget, is being used to initiate multiple-year grants that will require

continued support. These concerns govern decisions on how many new grants can be added to the NCI portfolio with supplemental funds.

The Federal Government will continue operating under a Continuing Resolution (CR) until a FY 2009 budget is approved. NCI is spending at a rate slightly less than in FY 2008 rate due to the fact that the CR in place for FY 2009 could remain in effect for months and/or that the FY 2009 appropriation may be less than that for FY 2008. NIH policy is to continue funding its noncompeting portfolio at approximately 90 percent of the commitment level. It may be possible to restore that 10 percent later in the fiscal year. NCI hopes to be able to provide a 1-percent inflationary allowance for noncompeting grants. One effect of budgetary uncertainty and constraint is the increased expense involved in portfolio management.

A comparison of noncompeting grants between FY 2008 and FY 2009 shows a slight reduction in the number of grants because the budget peaked approximately 5 years ago. Spending on program evaluation and administrative adjustments will remain approximately the same in FY 2009.

For competing RPGs, NCI has developed targets for paylines and numbers of awards both for the CR and the anticipated FY 2009 appropriations based on the President's budget request. Under the CR, continuing grants will receive 3- to 5-percent increases over FY 2008 funding. Smaller new grant requests will be reduced by approximately 13 percent and larger new grants by approximately 17 percent.

In the past, NCI's budget included a separate line item for cancer control, which was mandated by Congress. The Office of Management and Budget did not want variations in line items between Institutes, so this line item has been removed from the NCI budget. Cancer control continues to be an important area for research funding, but this change in budget organization has made management of cancer control funding more difficult.

The FY 2008 NCI base appropriation was approximately $4.805 billion. The FY 2009 President's budget request is approximately $4.809 billion. This represents an increase of $4.731 billion, or one-tenth of 1 percent. The NCI budget has remained almost flat since FY 2006. Ideas for an economic stimulus package being discussed at the congressional level may or may not result in additional funding for NIH. If such funding does become available, questions remain about how best to manage funds that will not continue as part of the base for the FY 2010 budget. The NCI Executive Committee will hold a budget retreat in January to address budgetary issues. NCI leadership has significantly increased the amount of time it spends on such issues over the past several years. Much of this work involves prioritizing science within each NCI Division to ensure that each Division's programs fit well within the overall priorities of NCI and NIH.

Thoughts About the Future. Because 2009 is a year of transition in U.S. leadership, NCI needs to be ready to communicate clearly with the new administration's transition team. A small group within NCI leadership has been meeting weekly to focus attention on several programs and topics that are expected to be of special interest to the new administration. Examples include clinical research, translational research, health-related information technology, the societal costs of pharmaceuticals, cancer as a model for other diseases, and quality of care and outcomes research. White papers on these topics are under development. Members of the President-elect's transition team met on the NIH campus in November with Institute Directors and senior staff of the NIH Office of the Director. These individuals were well informed about NIH and the Directors were able to clearly articulate NIH priorities. One discussion highlighted the importance of conflict-of-interest issues within the extramural community; Congress is expected to make this a high-priority issue.

NCI has created a number of trans-NCI initiatives to take advantage of scientific opportunities in a coordinated fashion. Examples include the cancer Biomedical Informatics Grid (caBIG™), the NCI Community Cancer Centers Program, the NCI Alliance for Nanotechnology in Cancer, The Cancer Genome Atlas (TCGA), the proteomics initiative, biorepository development, and the Clinical Trials and Translational Research Working Groups.

The NIH Clinical Center is of particular interest to the CTAC. NCI is responsible for approximately 40 percent of all Clinical Center activities. Dr. Lee Helman of NCI's Intramural Research Program is a member of the new NIH Intramural Clinical Research Steering Committee. Major issues being addressed by this committee include the Center's administrative structure; its funding resources; harmonization of policies and operations; standardization of Institutional Review Boards (IRBs); consistent review of scientific protocols, especially those involving human subjects; and accrual of patients into clinical trials. It is important for the NIH to provide leadership in this area because it is difficult to recruit and maintain clinician scientists in this environment. Young clinician scientists on a tenure track at NIH are likely to focus on the laboratory rather than the clinic because the process of conducting clinical trials and publishing results is much longer than the process for making progress in the laboratory.

The NCI Cohort Consortium recently held a large meeting. This consortium, which includes 37 population cohorts with a total of 3.5 million patients, has conducted a number of significant studies over the past 35 years and is a major resource for genome association studies of breast, prostate, and colon cancers and replication studies in prostate cancer.

The Cancer Genome Atlas is also becoming extremely informative. Significant infrastructure development was necessary to begin sequencing of tumors from patients. A successful pilot study in glioblastoma, ovarian cancer, and small-cell lung cancer was made possible by investments in collection of high-quality tissue specimens and establishment of sequencing centers, tissue characterization centers, and bioinformatics infrastructure. The first publication from the pilot in *Nature* described two and possibly three genes strongly associated with glioblastoma that may open the potential for related drug discovery.

The NCI Targeted Drug Development Platform is working to bring new information from the genome to the patient. Findings from genome association studies conducted by TCGA are reviewed for their potential as novel targets. Assays are quickly developed and subjected to high-throughput screening. Targets are then transferred to the new Informed Chemical Biology Consortium, which evaluates them for possible inclusion in the RAID program and then into clinical research. This program supports both the intramural and extramural communities and has potential to also support the private sector.

This type of activity is moving cancer research from the 20th century paradigm of organ site-based, single-agent-based trials to a new paradigm of multiple, highly targeted agents matched to molecularly selected patients. NCI is making efforts to prepare for the era of translational research required to take advantage of these advances. The Translational Research Working Group has developed pathways that will be useful to scientists by providing checkpoints at which critical decisions must be made in the translational research process. Translational research will be carried out in the NCI SPOREs (Specialized Programs of Research Excellence), program project grants (P01s), intramural studies, Cancer Centers, and special initiatives designed to address specific questions. If the proposed STRAPs (Special Translational Research Acceleration Projects) program is approved, this will be another significant mechanism through which translational research will move forward. The key experimental challenge is to characterize a large enough portion of the population so that appropriate patients can be identified to help answer questions about specific targets and communication pathways.

The Life Sciences Consortium (LSC), which is a subcommittee of the CEO Roundtable on Cancer, has made significant progress in developing common ground within which academic institutions and pharmaceutical companies can expedite development of contracts for the conduct of clinical trials. In September 2008, the U.S. Department of Justice issued a statement indicating that it would not oppose the Roundtable's efforts to develop and publicize model contract language for clinical trials of new cancer treatments.

In terms of the proposed economic stimulus package, the scientific community needs to communicate to Congress that project-based funding will be less important for the expansion of knowledge than support for laboratory infrastructure and research capacity in the academic community. It should also be made clear that research and grant expenditures generate significant impact on local economies. Every dollar spent on NCI research results in almost $3 in increased economic activity. In FY 2007, NCI research awards created and supported more than 54,000 jobs in the United States.

NCI faces serious concerns in the years ahead, including the possibility that budgets will continue to be increased at less than the inflation rate. NCI also faces challenges in providing leadership to both academia and industry; attracting the best and brightest young scientists into cancer research; and building new translational research programs.

Questions and Discussion

Dr. Richard Schilsky, Professor of Medicine and Associate Dean for Clinical Research, Biological Sciences Division, University of Chicago Pritzker School of Medicine, suggested that NCI-supported Cancer Centers should develop presentations about their economic impact on their communities to educate local leaders. Dr. Niederhuber agreed, adding that NCI is engaged in collecting reliable data on the state and local economic impact levels to be shared with Cancer Centers.

Dr. David Alberts, Director, Arizona Cancer Center, observed that studies that focus on characterization of patients should also focus on lifestyle and behavioral changes that could benefit people with specific genotypes and phenotypes. Dr. Niederhuber added that pharmacogenomics can also determine which patients will benefit from interventions based on enzymatic profiles.

Dr. Niederhuber explained that NCI hopes to make a case for cancer as a model for the global impact of investment in scientific research. NCI can lead the entire scientific community as an example of how to collect tissue, conduct clinical trials, build bioinformatics infrastructure, and conduct cutting-edge studies in areas such as transcriptional regulation, methylation, heterochromatin, and signal pathways.

III. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations, NCI, reported on the status of appropriations, highlighted several pieces of legislation, and provided an outlook for the 111th Congress.

FY 2008 Appropriations Update. The HR 2462-Supplemental Spending Bill was signed into law on June 30, 2008. The bill provided supplemental appropriations to the National Institutes of Health (NIH) in the amount of $150 million, of which NCI received $25 million.

FY 2009 Appropriations Status. On September 30, 2008 Congress passed a CR included in HR 2638, which contained full appropriation bills for only three Federal agencies; all other agencies were funded at the FY08 level (including NIH). NIH received $29.012 billion and NCI received $4.805 billion. The CR is in effect through March 6, 2009, whereupon Congress' options are to devise a new appropriation bill, create an omnibus bill to fund the agencies not yet funded, or extend the current resolution for the full year.

Legislation. In spring 2008, Senators Kennedy and Hutchison announced their intention to introduce a bill. However, there is not yet a final draft and the new intent is to introduce the Kennedy Bill early in the 111th Congress. Enacted legislation of interest discussed includes: the Caroline Pryce Walker Conquer Childhood Cancer Act that has key provisions to expand and intensify pediatric cancer research and establish a national childhood cancer registry; and the Breast Cancer and the Environment Act that has key provisions to expand and intensify breast cancer and the environment research and establish a Coordinating Committee to oversee research in this area. In July 2008, Senators Specter and Harkin introduced the NIH Emergency Supplemental Appropriations, with $5.2 billion for NIH and $1.2 billion of that amount for NCI, but there has not been any further action on this bill. The Access to Cancer Clinical Trials Act, which was introduced in the House in 2007 and in the Senate in 2008, is also pending. 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 trial. While this bill did not become Federal law, it is important to note that some states have enacted laws similar to this bill that provide protections for people living in those states.

Outlook – 111th Congress. In January 2009, the majority members will change in both the House and the Senate—the Democrats will have a larger majority than in the 110th Congress. With this shift, some of the leadership positions will also change, including the Chairman of the House Energy and Commerce Committee.

Questions and Discussion

Ms. Nancy Roach, Consumer Advocate for C3: Colorectal Cancer Coalition, questioned whether the Access to Cancer Clinical Trials Act would apply to individuals covered under ERISA (Employee Retirement Income Security Act) plans. There is an issue with state plans because they cannot provide coverage of clinical trial costs under ERISA plans. Ms. Erickson said she believes that ERISA plans are covered in the Federal bill, but would research this issue and return to the Committee with a definite answer.

IV. STANDARDIZATION OF CLINICAL TRIALS AGREEMENTS: JOINT NCI-CEO ROUNDTABLE PROJECT—DR. JAMES DOROSHOW

Dr. James Doroshow, Director of the Division of Cancer Treatment and Diagnosis, NCI, discussed the initiative outlined by the Clinical Trials Working Group (CTWG) to establish a set of commonly accepted clauses for negotiating clinical trials agreements. Negotiation of clinical trials agreements between industry and academic medical centers was identified as a key barrier to timely initiation of cancer clinical trials. NCI partnered with the CEO Roundtable on Cancer's Life Sciences Consortium (LSC) to determine key contract clauses that delay negotiations and to draft standardized, common language for the identified clauses. Participants in the process included LSC pharmaceutical companies, NCI-designated Cancer Centers, and Cooperative Groups.

There was a high degree of participation from both the pharmaceutical and Cancer Centers communities to provide information upon which to base discussions. Dr. Doroshow stated that they received copies of 78 clinical trials agreements: 49 redacted final agreements and 29 templates. Of these agreements, approximately half were from Cancer Centers and half were from LSC companies and represented industry-sponsored clinical trials and investigator-initiated trials. An independent third-party group led by Judith Hautala, Research Staff Member, Science and Technology Policy Institute (STPI) analyzed the clauses in these agreements to develop a conceptual framework of key contract categories. The analysis demonstrated that two-thirds of the time, negotiators end up in the same place with respect to particular issues and there is an even greater degree of convergence pertaining to many contract terms. Using these findings, the group then drafted proposed clauses, obtained extensive input from participants and legal and business representatives, and refined the clauses based on this feedback.

In regard to *intellectual property*, Dr. Doroshow explained that if trials are company sponsored, inventions are owned by the companies and research institutions have a right to use what they have learned in a noncommercial process. In investigator-initiated trials, inventions are owned by the cancer center or research institution, which presents the company with a royalty-free nonexclusive license and an option to obtain a royalty-bearing exclusive license. With respect to study data, the research institution owns medical records and the company owns study data records and reports in company-sponsored trials. The research institution makes medical records available to the company and to regulatory authorities and the company licenses the research institution to use study data for noncommercial research, educational purposes (subject to confidentiality), and publications. For investigator-initiated trials, research institutions own their medical records and their study data, but the data need to be made available to the pharmaceutical or biotechnology company for regulatory purposes.

Dr. Doroshow stated that more than 90 percent of the time, there was agreement with respect to *publication rights*. In investigator-initiated trials, research institutions can publish study data after a 30-day company review period. The company also has the right to require removal of company confidential information other than study data and to delay publication for an additional 60 days to apply for patents on inventions. Publication rights are the same for company-sponsored trials, with the addition that individual sites in multisite studies may publish after a multisite publication or 18 months after completion, termination, or abandonment of the study, whichever occurs first.

Subject injury is an important area for developing common language. In company-sponsored trials, the company reimburses the research institution for treatment of adverse events and personal injury resulting from the study unless injury is caused by research institution negligence or failure to follow protocol/applicable law. For investigator-initiated trials, subject injury reimbursement provisions were not included in 90 percent of the submitted negotiated agreements.

There was general agreement around *confidentiality* contract clauses in terms of what is considered a company's proprietary data and what is considered new data generated in an investigator-initiated trial. Time could certainly be saved if common language were developed for confidentiality issues.

Dr. Doroshow concluded by explaining that the standardized/harmonized clauses are intended only as a starting point for individual negotiations between parties. A few months ago, Dr. Niederhuber presented the proposed clauses for common concepts to the Association of American Cancer Institutes (AACI) and Cancer Center Directors. Significant interest was expressed in this process and the next step toward implementation includes discussions with legal and business representatives of Cancer Centers not participating in the initial project. NCI will request that Cancer Centers make their home institutions aware of the proposed clauses and will discuss the project with academic medical centers. The project and

proposed clauses for common concepts will also be publicized through professional and trade associations, industry meetings, and other opportunities.

Questions and Discussion

Dr. James Abbruzzese, Chairman of the Department of Gastrointestinal Medical Oncology, University of Texas M.D. Anderson Cancer Center, asked what is happening to translate the proposed clauses for common concepts down to the level of individual investigators. Dr. Doroshow said that the best route to start with is publicity. This project has been presented to numerous company and academic leaders. However, industry help is needed; Dr. Doroshow encouraged the Committee to offer additional ideas for publicity and implementation.

Dr. K. Gabriel Leung, Executive Vice President and President, Oncology, OSI Pharmaceuticals, commented that a communication plan for the pharma-biotech side was derived at the C-Change Annual Meeting in College Station, Texas. The plan is to review the clauses with the members of the LSC and then to disseminate to other pharmaceutical and biotechnology companies to apprise them of the proposed clauses.

Dr. David Parkinson, President and CEO of Nodality, Inc., added that to successfully introduce the common language, both sponsors and institutions need to view the common language as advantageous in the negotiation process. Dr. Richard Schilsky, Professor of Medicine and Associate Dean for Clinical Research at the University of Chicago Pritzker School of Medicine, commented that it is critical that CEOs encourage the use of proposed language and send a message to their companies that it is their expectation that these clauses are going to be used with minimal revision.

Dr. Peter Adamson, Professor, Pediatrics and Pharmacology, and Chief, Division of Clinical Pharmacology and Therapeutics of the Children's Hospital of Philadelphia, University of Pennsylvania, expressed concern over communication with the academic sector. He asked whether the proposed clauses for common concepts would be published in an academic journal to inform individual investigators that the language exists. Dr. Doroshow said that there is a manuscript in preparation.

Ms. Roach asked whether the language could cover devices as well as drugs. After Dr. Niederhuber responded yes, she suggested extending outreach efforts to device companies because more and more trials are involving diagnostics. Dr. Lee Helman, Chief, Pediatric Oncology Branch, and Deputy Director, Center for Cancer Research, NCI, added that if the proposed language is successfully used in the cancer realm, it could be a model for all biomedical research.

Dr. Niederhuber asked Dr. Doroshow to make a final comment regarding the future direction of the relationship between LSC and NCI. Dr. Doroshow said that other issues of interest include the amount of data needed for clinical trials—whether there is a minimum set of less costly and more efficient data that will facilitate new drugs and treatment approaches. Material transfer agreements are also an issue for companies and cancer centers, and a similar approach to developing common terms could be undertaken.

Dr. Nancy Mendenhall, Professor, Department of Radiation Oncology, University of Florida Heath Science Center, commented that it would be useful to include a section in the manuscript that is being prepared that models potential savings from using the common language (i.e., lost time that would now be saved).

V. COOPERATIVE GROUP CLINICAL TRIALS COMPLEXITY FUNDING MODEL—DR. MARGARET MOONEY

Dr. Margaret Mooney, Acting Chief of the Clinical Investigations Branch of the Cancer Therapy Evaluation Program (CTEP), explained that the Cooperative Group Clinical Trials Complexity Funding Model is an initiative of the Clinical Trials Working Group designed to align reimbursement for Phase III treatment trials with their complexity in order to compensate trial sites for the additional expenses associated with participation in complex trials. The intent was not to reduce the base rate of $2,000 per case, but to increase funding for complex trials.

The first step was to develop a system or model for ascertaining trial complexity. A Complexity Model Working Group was organized to develop criteria for a complexity model for Phase III treatment trials. Its objectives were to identify key elements of studies thought to require additional work at participating sites and categorize those elements into three tiers reflecting work effort. Working group members included Cooperative Group members and representatives of the NCI Cancer Trials Support Unit (CTSU), CTEP, Division of Cancer Prevention (DCP), and CCCT.

The Complexity Model Working Group initially developed five primary criteria related to complexity: number of study arms, informed consent process, number of registration and randomization steps, complexity of the actual treatment, and length of treatment. Four additional elements were subsequently identified: impact of operating and monitoring the study on personnel, complexity of data collection, follow-up requirements, and ancillary studies. Finally, a 10th element was added to address participant recruitment feasibility (e.g., recruiting underrepresented patients or those who required molecular screening of their tumors). Each element can be graded at a level of low, medium, or high complexity.

During FY 2008, while the model was still being finalized, a pilot test of the draft model with the initial five elements was conducted. The test was limited to ongoing trials or trials that were about to be activated; NCI did not want to include trials nearing completion. Cooperative Groups were asked to use the model to recommend up to five Phase III trials that they considered complex enough to receive additional funding. Groups had the option to supplement the model with additional elements they considered to be important, and most did so.

NCI reviewed the recommendations of the Cooperative Groups and made decisions on how to distribute approximately $7 million of available funding. An effort was made to achieve a balance among disease types. NCI also took into consideration trial statistics (numbers of patients already accrued) and whether the trials were already being supplemented with additional funding from other sources. A large number of recommended trials focused on neoadjuvant or preoperative treatment, advanced disease settings, multimodality treatments, and hematology trials; these types of trials are often conducted in complex settings.

After reviewing the recommendations, NCI decided to increase the per capita payments by $1,000. It was also decided that additional funding should be committed for the full length of the trial by aligning the budget to targeted accrual numbers. Fund distribution has started with retroactive payments for accrual beginning on June 1, 2008. The program must remain flexible to account for the possibility that some trials will end early while others may increase their accrual targets.

The Complexity Model Working Group continues to refine the model and is developing procedures for monitoring the impact of this program. A potential framework for future years, if funds continue to be made available, would be to ask Cooperative Groups to submit a complexity score for each

new Phase III treatment trial based on the Working Group's final ten-element model. CTEP would review this scoring sheet to ensure that criteria have been applied consistently. Selection of trials for additional funding could then take place in a manner similar to that used in the FY 2008 pilot test.

Questions and Discussion

Dr. Deborah W. Bruner of the Abramson Cancer Center noted that the Radiation Therapy Oncology Group (RTOG) tried a similar approach but found that trials with accrual problems and trials with adequate accrual both scored high on complexity. Dr. Mooney replied that although improved accrual is one outcome objective for the Complexity Model Working Group program, the primary aim is to encourage site participation in labor-intensive trials. Other outcome metrics, such as timeliness of accrual and quality of data, may be needed as the program evolves. Dr. Prindiville added that this program will be part of an overall assessment of the way Cooperative Groups are funded.

Dr. David Alberts, Director of the Arizona Cancer Center at the University of Arizona College of Medicine, asked whether this program has extrapolated its work to encompass trials conducted by NCI DCP. Dr. Mooney replied that although the program currently focuses on treatment trials, the Working Group plans to expand its efforts to address complex prevention trials in the future.

Dr. Stephen Grubbs, Chief of Oncology at Medical Oncology/Hematology Consultants, P.A., asked for details on how funds flow to Community Clinical Oncology Programs (CCOPs). Dr. Mooney replied that funds will be distributed to CCOPs via "credits" for accrual in the first year of the program. For accrual beyond Year 1, distribution will be made either through CCOP grants or through CTSU.

Dr. Daniel Sargent, Director, Cancer Center Statistics at the Mayo Clinic Foundation, suggested that NCI evaluate this program by comparing accruals for trials that received supplements with those for trials recommended but not selected for additional funding.

Dr. Edith Perez, Director of the Breast Cancer Program at the Mayo Clinic Foundation, asked whether this program might be expanded to include trials conducted through the contract mechanism. Dr. Mooney replied that it may be possible to expand this program in the future to trials conducted through contracts, but a number of differences in funding and infrastructure would have to be addressed.

VI. HEAD AND NECK SCIENTIFIC STEERING COMMITTEE UPDATE—DRS. ARLENE FORASTIERE, DAVID SCHULLER, AND ANDREW TROTTI

The primary goal of the Head and Neck Scientific Steering Committee (HNSC) is to increase productivity of clinical research involving head and neck cancer patients. Productive clinical research is defined as studies that answer important clinical and translational questions, decrease time to complete trials, develop biologic correlates, and address quality of life (QOL) issues.

Dr. David Schuller, Professor, Head and Neck Surgery, and Director Emeritus, the Ohio State Comprehensive Cancer Center-James Cancer Hospital and Solove Research Institute, reviewed current clinical research challenges of interest to the HNSC. Accrual to trials is a challenge due to the relative infrequency of head and neck malignancies compared with other cancers, such as prostate, lung, breast, and colon. The relevant patient population comprises older patients with substantial comorbidities, which may be related to reduced treatment tolerance. The target population also presents numerous psychosocial

needs, often related to alcohol and tobacco use. Another challenge is associated with an emerging trend in human papillomavirus (HPV)-related malignancies in younger men.

Approximately 10 to 30 percent of all patients with upper aerodigestive tract squamous cancers have multiple primary malignancies. This suggests that prevention strategies should be integrated into therapeutic trials to improve survival. Premalignancies also present opportunities for intervention in cooperation with cancer prevention groups.

In the past, several Cooperative Groups had head and neck committees; currently, only the RTOG and the Eastern Cooperative Oncology Group (ECOG) have such committees. Nevertheless, there is a critical mass of expertise and populations available to support head and neck studies within existing Cooperative Groups. Dr. Schuller stated that the HNSC is seeking advice on expanding capacity for accrual to head and neck studies from Cooperative Groups as well as from institutions not currently involved in those groups.

Dr. Andrew Trotti, Director, Radiation Oncology Clinical Research, H. Lee Moffitt Cancer Center, presented a progress report on the HNSC, which recently completed its first full year of activities. This is the third disease-specific steering committee established as a result of Clinical Trials Working Group recommendations. The Committee's mission is focused on review and development of Phase III and large Phase II clinical trials. The HNSC has established four task forces and two working groups. Specialized Programs of Research Excellence (SPOREs), Cooperative Groups, Cancer Centers, NCI staff, advocates, and bench scientists are all well represented on the HNSC.

Two funding concepts were reviewed by the HNSC in 2008. An RTOG study, "A Phase III Study of Postoperative Radiation Therapy (IMRT) +/- Cetuximab for Locally Advanced Resected Head and Neck Cancer," was first reviewed in February and approved in August. An American College of Radiology Imaging Network study, "FDG PET/CT Staging of Head and Neck Cancer and Its Impact on the N0 Neck," was reviewed in November and its outcome is pending.

The Endpoints Working Group is developing a draft document on endpoints for local regional progression and organ preservation, which will be delivered to the HNSC in January 2009. The Expanding Access to Clinical Trials Working Group has successfully argued for a policy change that will allow Phase II trials endorsed by only one group to be listed by the NCI CTSU. This Working Group is also developing a white paper on challenges and opportunities related to access to clinical trials.

A Clinical Trials Planning Meeting (CTPM) was held in November 2008 in Washington, DC. More than 70 clinicians, translational scientists, epidemiologists, and others attended to discuss clinical trial design for HPV-related head and neck cancers. Proceedings will be published in the journal, *Head and Neck.*

Only in the last few years have scientists recognized an epidemic rise of a unique subset of head and neck cancers associated with the HPV-16 virus. The virus infects young, sexually active individuals and takes between 20 and 30 years to generate malignancy. These malignancies have a distinct survival advantage over HPV-negative disease. Oropharyngeal cancer, primarily driven by HPV infection, is on the rise, while tobacco-related (HPV-negative) head and neck cancers are decreasing.

Participants at the CTPM identified several principles for HPV trial development that will be piloted in one or two trials during the coming year. Participants concluded that HPV-positive head and neck cancer is such a sufficiently different disease that it requires separate trials. They also acknowledged that there are insufficient numbers of HPV-positive patients for a Phase III trial, but determined that a Phase II-R de-escalation trial with toxicity as the primary endpoint is feasible. Patients should be

stratified for smoking and a central reference lab with quick turnaround is needed to move HPV-positive patients into these trials.

The HNSC has developed a conceptual design for a study of locally advanced head and neck cancer that includes fractionation radiotherapy with concurrent platinum as a standard of care. The investigational arm will involve a reduction in the intensity of therapy. This is a significant paradigm shift for head and neck cancer treatment, which has historically moved toward more intensive treatment with multiple modalities, resulting in increased toxicity and reduced quality of life for patients. This will be the first systematic attempt to de-escalate treatment intensity.

Dr. Arlene Forastiere, Professor, Oncology and Otolaryngology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, described initiatives that have been proposed to overcome the challenges described by Dr. Schuller. In addition to squamous cell cancers at all stages, both alcohol/tobacco related and HPV related, the HNSC identified an unmet need associated with rare disease, including salivary gland, sinus, and thyroid cancers, especially among young people. The Rare Tumors Task Force is addressing these rare diseases.

The HNSC is uniquely structured to take advantage of opportunities to accelerate bench-to-bedside discovery. The Committee is broadly inclusive, bringing together major leaders in head and neck cancer. The Committee's task force structure is balanced, with some members focused on tumor sites and stages and others on development of standards and quality assurance. Based on access to established tissue banks and the ability to carry out prospective serial tissue sampling, the HNSC has been able to generate interest among basic scientists and the pharmaceutical industry in using head and neck cancer as a model for development of targeted agents.

The relationship established by CTEP and academic head and neck cancer programs with private industry provides HNSC with an excellent opportunity to evaluate combination regimens. Increased interest in these cancers has led to development of a full pipeline of targeted therapeutics. Working with industry improves access to infrastructure and to additional patients for clinical trials.

The HNSC plans to work with foundations and advocacy groups to help achieve its goals. These groups can assist with fundraising, provide information to their constituencies, and advocate for wider options in clinical trials to accelerate discovery of curative therapies.

The HNSC is leveraging its structure in three ways to enhance clinical research: prioritization of clinical research questions to be addressed by HNSC task forces; streamlining of communication among stakeholders to eliminate redundancy in study design; and expansion of partnerships to increase physician participation in trials, increase patient accrual, and accelerate trial completion.

The next step following the November 2008 CTPM will be to develop and submit a concept for HNSC review. This will be an opportunity for multiple stakeholders to invest in the process and outcome of a trial focusing on HPV-related head and neck cancers.

Another opportunity for head and neck cancer research is associated with a November 2008 Salivary Gland Cancer Workshop jointly sponsored by the National Institute of Dental and Craniofacial Research and the Adenoid Cystic Cancer Research Foundation, which has formed a consortium of academic centers and created a biospecimen repository. The outcome of this meeting will be another concept for HNSC review.

The current model for the HNSC prevents a variety of groups—such as the Cancer and Leukemia Group B (CALGB), Southwest Oncology Group (SWOG), SPOREs, clinical trials networks, and

foundations—from submitting research concepts directly to the HNSC. All concepts must be introduced through ECOG or RTOG. The HNSC hopes to accelerate head and neck cancer research by streamlining this model for developing new concepts. The HNSC has developed a proposal for modifying the current model to support collaborative protocol development. For concepts proposed by investigators outside Cooperative Groups, trials would continue to be activated by the NCI CTSU and supported by RTOG and ECOG statistical and operations offices, but co-investigators from outside organizations would be able to make major contributions. Per-case payment would be made to offset costs for non-ECOG/RTOG members. New authorship criteria to incorporate scientific contribution and accrual would be agreed upon by all Cooperative Groups.

Questions and Discussion

Dr. Joel Tepper, Distinguished Professor, Department of Radiation Oncology, University of North Carolina, noted that the NCI Gastrointestinal Cancer Steering Committee uses mechanisms similar to those described by Dr. Forastiere to support trials proposed by investigators not involved in Cooperative Groups.

Dr. Adamson asked why three rounds of review were required to approve the RTOG postoperative radiation therapy study proposed in 2008. Dr. Forastiere replied that HNSC asked for improvements in the correlative science associated with the proposal and clarifications of endpoint definitions.

Dr. Schilsky noted that some Cooperative Groups, such as the CALGB, do not have head and neck committees because they lack resources (e.g., travel, statistical support, reimbursement) to support trials. As Chair of the CALGB, Dr. Schilsky said that he encourages CALGB institutions to participate in head and neck trials, with the understanding that CTSU would provide reimbursement because CALGB does not have a head and neck committee. CALGB institutions registered on such protocols would be able to assign those registrations to meet their CALGB accrual requirements, but the investigators who initiated the concept would not receive academic credit through CALGB peer review because of the lack of a head and neck committee.

Dr. Jan Buckner, Chair, North Central Cancer Treatment Group at the Mayo Clinic and Co-Chair of the CTMS Steering Committee, noted that many members of Cooperative Groups that do not have head and neck cancer committees are also members of RTOG or ECOG, and thus they could participate in head and neck trials through those memberships.

Dr. Alberts stressed the timeliness of the opportunity to explore ways to prevent HPV-induced head and neck cancers.

Dr. Forastiere expressed concern that institutional resources may not be available to support a trial activated by CTSU rather than a Cooperative Group. Dr. Schilsky commented that CTSU can serve as a "matchmaker" by connecting investigators with an appropriate Cooperative Group or statistical center that could help manage trial data.

Dr. Schuller stressed that the HNSC is not lobbying for new Cooperative Group head and neck committees, but rather is seeking more flexible and inclusive mechanisms to support new concepts that come from outside RTOG and ECOG.

Dr. Doroshow stated that the HNSC proposal for inclusive support for head and neck trials can serve as a test of NCI's commitment to a coordinated approach to conducting clinical trials by bringing together SPOREs, Cancer Centers, Cooperative Groups, and other organizations to do important studies in areas that are unlikely to be supported without collaboration.

Dr. Parkinson added that improving the infrastructure for early introduction of potentially important therapeutics in head and neck cancer can serve as a model for other less common diseases that have not captured the attention of the pharmaceutical industry.

VII. BIOMARKER, IMAGING AND QUALITY OF LIFE STUDIES FUNDING PROGRAM CHANGES FOR 2009—DRS. SHEILA PRINDIVILLE AND JAMES JACOBSON

Dr. Prindiville presented an update on the Biomarker, Imaging and Quality of Life Studies Funding Program (BIQSFP). The purpose of the BIQSFP is to ensure that the most important correlative science and quality of life studies can be initiated in a timely manner in association with clinical trials. The intent is to fund studies conducted in association with Phase III trials when the cost is too high to be covered by Cooperative Group mechanisms. The highest priority studies to be funded are *integral* studies—a test that must be performed in order for the trial to proceed. Other studies to be funded are *integrated* studies—those intended to identify or validate markers and imaging tests or quality of life instruments that might be used in future trials. The funds are not available for correlative studies to develop markers, assays, or imaging tests that are performed on a retrospective basis. Three BIQSFP applications were funded in 2008.

Dr. Prindiville went on to discuss BIQSFP changes for 2009. It is anticipated that the program will have a funding level of at least $5 million for next year. Cooperative Group and Community Clinical Oncology Program Research Base Phase III trials with integral and integrated biomarker, imaging, or QOL studies will continue to be eligible for these funds, but the request for funding of the biomarker, imaging, or quality of life study must be made a the time the concept is initially reviewed. Exceptions for extraordinary BIQSFP proposals embedded in pre-existing approved concepts or protocols that are in early stages of accrual will be considered after consultation with NCI staff. Other changes for 2009 include an additional requirement for data characterizing the precision, reproducibility, and validation of the assay, test, or assessment tools involved in the BIQSFP study. There will be an open submission cycle throughout the year for studies. The Scientific Steering Committees will review the study concepts with BIQSFP correlative components. The NCI Clinical and Translational Research Operations Committee (CTROC) will recommend and prioritize BIQSFP proposals at regular meetings throughout the year and CTAC will make final recommendations to the NCI Director approximately twice a year. Dr. Prindiville concluded by recognizing that the BIQSFP is limited to Phase III studies, but as the program gains more experience it will open up to large randomized Phase II studies.

Dr. James Jacobson, Acting Associate Director, Cancer Diagnosis Program (CDP), Division of Cancer Treatment and Diagnosis (DCTD), NCI, added to Dr. Prindiville's presentation by discussing the performance standards for clinical trial marker assays. The CTWG identified the need to establish standards for the data required to support use of marker assays in Phase II/III clinical trials. The CDP was charged with documenting the levels of data required for these standards. The Strategic Group of the Program for the Assessment of Clinical Cancer Tests (PACCT) developed the Performance Standards Document, which was approved in draft form by CTAC in July 2007.

Dr. Jacobson explained that the purpose of the Standards Document is to ensure that marker assays are sufficiently validated to be used to make clinical decisions and that tests used in trials can be

rapidly translated to clinical practice to benefit patients. The Standards Document also ensures that use of precious and nonrenewable specimens collected in randomized trials leads to clearly interpretable results that move the field forward. Dr. Jacobson focused his talk on integral assays and stated that *in vitro* assays must be performed in laboratories with at least a CLIA (Clinical Laboratory Improvement Amendments) Certificate of Compliance. Required information for integral assays includes the same categories of data as required for submission for U.S. Food and Drug Administration (FDA) clearance (510k-substantial equivalence) or approval (premarket application). Other information required includes: the role the assay will play in the trial (analogous to FDA "intended use"); assay description; specimen type; measurements of precision and reproducibility; data to support cut points if assay results are not reported as a continuous variable; analytic sensitivity and specificity; accuracy measurements; the statistical design used to establish the correlation with the clinical parameter of interest; and procedures in case of assay results that are not interpretable or are discrepant. The Standards Document also covers the use of *in vivo* imaging assays in clinical trials. The information needed to support the use of imaging assays is concurrent with that needed for *in vitro* assays, with the addition of information about the implementation of standardized guidelines for image acquisition, analysis, and interpretation.

Implementation of the Standards Document for the clinical trials concept and protocol development stage is currently under way. Dr. Jacobson stated that, ultimately, they will use the information to prioritize assays for receiving support from the MoDEL system—an assay evaluation and implementation program. The Standards Document implementation plan includes a checklist that captures the data elements for concepts that are to be submitted to CTEP. The checklist is also incorporated into the BIQSFP solicitation. The Standards Document provides a basis for being able to evaluate assays and decide which are ready to move forward and which are not.

Questions and Discussion

Ms. Roach asked what the FDA's position is on the Standards Document. Dr. Jacobson said the PACCT program has FDA representation and the document was developed with their collaboration.

Dr. Adamson questioned whether the BIQSFP had any opportunity to look at integrated assays that are currently being used in the Cooperative Groups or Cancer Centers to uncover deviations from the Standards Document. Dr. Sheila Taube, formerly of NCI DCTD, stated that a systematic evaluation has not yet been done. However, they have looked at some of the assays that have been included as integral assays, and they have not had all the information needed to move those assays forward. Dr. Jacobson commented that there are a few pilot projects going forward in MoDEL that are looking at assays in clinical trials and seeing how well they perform during an independent evaluation. The results of those projects will be presented to CTAC in the future.

VIII. CMS CLINICAL TRIALS PHASE I AND II POLICY—DR. LESLYE FITTERMAN

Dr. Leslye Fitterman, Epidemiologist at the Centers for Medicare and Medicaid Services (CMS), discussed the current Medicare Clinical Trial Policy. Medicare's policy was initiated, in part, due to an impetus from the cancer community; prior to its enactment beneficiaries were not allowed to participate in clinical trials because those were considered experimental or investigational. To provide a context for the discussion, Dr. Fitterman noted that a recent search of clinicaltrials.gov disclosed approximately 3,600 open Phase I and Phase II cancer clinical trials; these were intervention studies in the United States enrolling subjects age 66 or older.

In 2000, President Clinton issued an Executive Order to establish a clinical trial coverage policy through the National Coverage Determination (based on 1862(a)(1)(E) of the Social Security Act). The policy was developed closely with the Agency for Healthcare Research and Quality and stayed in effect until 2007, when a reconsideration of the policy was opened. The reconsideration expanded coverage related to evidence development and for services considered standard of care delivered as part of clinical trials.

The goals of the Medicare Clinical Trial Policy are to: allow beneficiaries to participate in research studies; encourage the conduct of research studies important to the Medicare population; allow beneficiaries to receive care that may have a health benefit, but for which evidence of effectiveness is insufficient to allow full, unrestricted coverage; and limit coverage of costs to those studies that have the greatest likelihood of answering questions of importance to CMS.

Two major issues exist in terms of coverage of Phase I and Phase II trials. One issue is that to be considered a "trial" it must meet seven desirable characteristics of any good clinical trial. Trials funded by NIH and trials conducted under an Investigational New Drug reviewed by FDA are deemed qualified to meet the seven desirable characteristics. However, the second issue is that the trial must meet three additional Medicare requirements, one of which is "therapeutic intent." The 2000 policy states that, "The trial must not be designed exclusively to test toxicity or disease pathophysiology. It must have therapeutic intent."

One of the major goals when reconsidering the Medicare policy was to more clearly define therapeutic intent. The proposed 2007 language stated: "The clinical research study is not designed to exclusively test toxicity or disease pathophysiology. Research studies, including some Phase I trials, whose protocols commit to measuring therapeutic outcomes as one of the objectives, may meet this standard only if the disease being studied is chronic, life threatening, or debilitating." This language would have met the needs of cancer clinical trials; however, it was denied and the language established in 2000 remains.

Dr. Fitterman explained that Medicare contractors, who are located throughout the country and spend varying degrees of time reviewing trials, could interpret therapeutic intent differently. As part of the Medicare Modernization Act of 2003, contracting reforms are taking place that will help address this variability. By 2009, the number of Part A and Part B Medicare Administrative Contractors will be reduced from 40 to 15, which will allow CMS more flexibility and capability to work with them on these issues. Dr. Fitterman concluded by asking the Committee to provide any input or additional ideas they may have in regard to the issue of therapeutic intent.

Questions and Discussion

Dr. Parkinson asked Ms. Erickson whether the draft language of the Kennedy Bill addressed any of the issues regarding therapeutic intent. Ms. Erickson was not aware of the specific bill provisions or whether this was addressed.

Dr. Trotti commented that what is needed to change cancer clinical trial accrual rates is for CMS to take positive steps to reward and incrementally fund patients, through their physicians, who are placed on clinical trials.

Dr. Abbruzzese asked Dr. Fitterman whether CMS has considered focusing on the term "exclusively" rather than trying to define therapeutic intent. For example, all of the trials considered with the seven characteristics are not exclusively focused on toxicity. Dr. Fitterman agreed that oncology trials are different in terms of exclusively looking at toxicity. However, when reconsidering the language some of the medical directors relied on the FDA definitions for Phase I and Phase II trials even though they were not always applicable to trials in oncology.

Dr. Schilsky commented that the American Society of Clinical Oncology, the American Association for Cancer Research, and the AACI recently authored a letter on behalf of a cancer center that is embroiled in discussion with their local contractor about reimbursement for Phase I trials. One of the key points brought out in this letter concerned therapeutic intent. The NCI investigator's handbook definition of Phase I trials states that "therapeutic intent is always present in Phase I trials," whereas the FDA's definition states that gaining early evidence of effectiveness is among the objectives of Phase I trials. There are an increasing number of tumor responses being recorded in Phase I trials, which is a positive indicator for moving clinical trial policy forward in the right direction.

Ms. Roach asked whether Dr. Fitterman's group works with advocacy groups in their efforts to change policy language. Dr. Fitterman said she would check with their Office of Legislation but would welcome advocate input. Dr. Grubbs reemphasized that a big problem is variability among local contractors and said he shares the hope that this will improve with fewer Administrative Contractors.

Dr. Bruce Hillman, Theodore E. Keats Professor of Radiology, University of Virginia School of Medicine, suggested that CMS use the Institutional Review Board (IRB) approval or human subjects research protection that is federally legislated to prove the potential therapeutic benefit of trials. Dr. Fitterman commented that IRB approval could be used when meeting with or submitting information to Administrative Contractors. Dr. Niederhuber stated that there needs to be a meaningful discussion at the executive level about the future of clinical trials research, especially in terms of priority and allocation of resources.

IX. CTWG INFORMATICS INITIATIVES UPDATE—DRS. JAN BUCKNER AND KEN BUETOW

Clinical Trials Management Systems (CTMS) Steering Committee Report. Dr. Buckner listed four informatics initiatives that were recommended by the CTWG: (1) establish a comprehensive database containing regularly updated information on all NCI-funded clinical trials; (2) achieve industry and FDA concurrence on standard case report forms incorporating common data elements; (3) promote establishment of national clinical trial information technology infrastructures that are fully interoperable with NCI's caBIG™; and (4) develop a credentialing system for investigators and sites that is recognized and accepted by NCI, industry sponsors, clinical investigators, and clinical trial sites. To achieve these goals, the caBIG™ CTMS workspace was expanded to include these activities.

The CTMS Steering Committee has been charged with providing strategic guidance for the CTMS workspace, advising on project selection and prioritization, reviewing activities of workspace task forces, and ensuring alignment of workspace projects with broader NCI goals and objectives. Steering Committee members include clinical investigators, statisticians, data managers, nurses, informatics specialists, patient advocates, and representatives of government agencies. The Steering Committee meets on a quarterly basis to discuss implementation of CTWG recommendations and develop consensus on action items.

Dr. Buckner identified several significant strengths of the CTMS Steering Committee: (1) meaningful bidirectional communication between NCI and the extramural community, between clinical investigators and informatics specialists, and between Cooperative Groups and Cancer Centers; (2) mutual accountability and shared responsibility; (3) pragmatic prioritization; and (4) anticipatory troubleshooting. Weaknesses include: (1) lack of continuity from one meeting to the next; (2) limited input from FDA; (3) lack of representation of the U.S. Department of Health and Human Services (DHHS) Office of Human Research Protections (OHRP); and (4) incomplete implementation plans.

The most important opportunity for the CTMS in the near future is implementation of the Clinical Data Management System (CDMS) to support data sharing among Cooperative Groups. Other opportunities include: (1) implementation and integration of caBIG™ resources under development, such as adverse event reporting tools; (2) the Clinical Trials Reporting Program; and (3) the NIH Clinical Translational Science Awards program.

The CTMS faces several threats to its continued success that are currently being addressed: (1) immaturity of implementation plans; (2) unresolved policy issues (i.e., related to data sharing and intellectual property); (3) the tendency of workspaces (i.e., laboratory, pathology, imaging, clinical) to operate separately rather than interdependently; and (4) lack of internal NCI cohesion concerning policies (e.g., guidelines for protocol authoring) and development of shared research resources (e.g., use of multiple adverse event recording systems).

Questions and Discussion

Dr. Timothy Rebbeck of the University of Pennsylvania School of Medicine asked how the CTMS plans to deal with institutions that have already developed their own clinical trials databases that are not designed using caBIG™ guidelines. Dr. Kenneth Buetow, NCI Associate Director and Bioinformatics and Information Technology Chief, explained that caBIG™ has the flexibility to support interoperability with other systems. Individual databases can be harmonized with caBIG™ using "adapter" software while maintaining the "front end" part of the system that is unique to the individual institution.

Dr. Sargent stressed the importance of developing data management systems that can be utilized across all settings involved in clinical research, including Cooperative Groups, Cancer Centers, and SPOREs.

Ms. Roach asked about plans to address the CTMS weaknesses mentioned in Dr. Buckner's presentation. Dr. Buckner and Dr. Niederhuber replied that these issues are critical agenda items for meetings of the CTMS Steering Committee and the CTROC, an internal NCI committee with members representing every NCI component involved in clinical research. caBIG™ has been very responsive and has shown a remarkable ability to leverage resources through voluntary contributions of time and effort from members of the bioinformatics community.

Clinical Trials Reporting Program (CTRP). Dr. Buetow reported that beginning early next year, the CTRP will make the transition from a prototype to a fully operational system. The result will be an NCI-wide database with a complete inventory of information on all clinical trials supported by the Institute. When trials are registered, staff of the Clinical Trials Reporting Office will be able to abstract data from protocols that grantees submit as part of registration (either online or as XML uploads); this information will populate CTRP data elements that describe components of the clinical trial. Grantees will regularly upload updates of accrual information.

For 2009, the CTRP will be used only for interventional trials. Addition of observational, ancillary, and correlative studies will be deferred at least until 2010. In the first quarter of 2009, the system will be implemented at five pilot sites with diverse portfolios of clinical trials. In the second quarter, selected Cancer Centers will be asked to begin entering trials. Provisional goals include allowing all Cancer Centers to enter trials in the third quarter of 2009; allowing non-Cancer Center grantees to enter trials and begin collection of accrual data in the fourth quarter of 2009; and beginning reporting of outcomes and adverse events in the first quarter of 2010.

NCI has conducted an aggressive communication campaign to keep the entire cancer community informed about CTRP development. Presentations have been made to NCI's major advisory groups and information has been shared with NCI Program Directors, Cancer Center Directors, and a number of important professional societies. The system has been highlighted in the NCI Cancer Bulletin and an e-mail has been distributed to all NCI grantees. The NCI Office of Communication and Education (OCE) is helping with development of educational tools and instructional materials. The public can access information about the project on the Internet at http://www.cancer.gov/ncictrp.

Questions and Discussion

Dr. Adamson asked how much time will be required to enter registration information about trials. Dr. Buetow replied that 15 straightforward data fields must be completed. This can be done manually online in a small amount of time, or data can be submitted as XML files.

Dr. Adamson asked how use of this system will be managed at individual sites. Dr. Buetow explained that the system is being operationalized first at Cancer Centers because they already have centralized management of clinical trials. Other sites will vary in how they work with the system (e.g., some may work through IRBs while others may work through a formal Clinical Trials Office).

Dr. Adamson asked how labor-intensive the process of abstracting protocols will be and how many trials will be involved. Dr. Buetow said that preliminary results indicate that abstracting will take from 4 to 12 hours, depending on trial size and complexity. NCI anticipates tracking approximately 2,500 trials on an annual basis.

Dr. Alberts asked whether Phase I trials sponsored by pharmaceutical companies would be included. Dr. Buetow replied that such trials can be registered but, due to intellectual property considerations, the specific protocol information will not be submitted.

Dr. Schilsky asked about the types of reporting the system will be able to generate. Dr. Buetow explained that public reports will be similar to data currently available through the clinicaltrials.gov Web site. For sites that submit data, however, the system can serve as a portal to a comprehensive collection of information about their trials. It will help institutions keep track of the accrual for all of their trials. The system will also be a powerful program management tool for NCI.

Dr. Sargent noted that CTRP reports will only be as reliable as the data investigators give to their Cancer Center Directors or Clinical Trial Offices for submission. Dr. Buetow said that the system will be monitored and selectively audited to ensure accuracy.

X. TRWG IMPLEMENTATION UPDATE—DR. LYNN MATRISIAN

Dr. Lynn Matrisian, Special Assistant, Office of the Director, NCI, provided an update on activities related to implementation of the Translational Research Working Group (TRWG) initiatives. The TRWG recommended a new process for accelerating early translational cancer research. Based on the TRWG portrayal of translational research as a pathway, the proposed 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 selecting several projects ripe for translation each year and providing support to accelerate these projects through the applicable TRWG pathway. The translational research acceleration process was envisioned as having three components: gathering information to identify translational opportunities, determining how to prioritize those 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 pathway, nor was it meant to replace infrastructure or mechanisms currently used for translational research.

In February 2008, CTAC asked NCI to demonstrate the existence of sufficient translational research opportunities to warrant development of a new prioritization process and funding strategy. This culminated in the NCI Translational Science Meeting, http://ncitranslates.nci.nih.gov, held in November 2008 in Washington, DC. Invited participants presented a total of 513 abstracts. The abstracts provided a representative (not comprehensive) view of NCI-supported translational research. In addition to researchers, the meeting was attended by NCI staff and patient advocates. The three primary goals of the meeting were outlined.

The first goal of the meeting was to enhance the knowledge and use of the TRWG Pathways, which are flow diagrams that depict the translational research process. Six pathways were developed to illustrate different realms of translational research—Image-Based Assessment Modalities, Biospecimen-Based Assessment Modalities, Agents, Immune Response Modifiers, Interventive Devices, and Lifestyle Alterations. All of the pathways start at the end of fundamental/basic research and extend to early-phase clinical trials. The early translational research activities are divided into five domains—credentialing, supporting tools, creation of the modality, preclinical development, and early-phase clinical trials. The pathways are described in more detail in seven papers recently published in Clinical Cancer Research. Prior to the meeting, presenters were asked to code their abstracts to one of the pathways and also identify the population and/or organ site addressed by their research. This exercise helped familiarize the research community with the pathways. The pathways were also discussed during a plenary session at the meeting.

The second goal of the meeting was to use the pathways to organize selected research studies into "translational research opportunities" and determine what information would be required to evaluate and prioritize these projects. As defined by the meeting organizers, a translational research opportunity focuses on a specific clinical goal and follows the steps of one of the pathways to achieve this goal. Translational research opportunity information guides for each pathway were distributed at the meeting. Each guide provides a structured format for collecting information on a translational research opportunity. Researchers are asked to summarize data (e.g., epidemiological data, cell culture data, expression data) that support the scientific validity of a translational research opportunity and illustrate its ripeness for translation. The guides also collect information on clinical or public need (e.g., incidence, five-year survival rates, information on alternatives) to help determine whether expenditure of resources is justified. The feasibility of the opportunity is also addressed (e.g., availability of supporting tools). The information guides then move through a pathway to gauge what effort and resources would be necessary to complete each step. Finally, the guides assess whether the project is appropriate for NCI investment and whether opportunities exist for collaboration with industry or foundations. The information guides served as

educational tools for the research community to outline the information that would be required to evaluate and prioritize a translational research opportunity.

The third goal of the meeting was to demonstrate that there are compelling translational research opportunities warranting acceleration. A program committee organized the submitted abstracts by pathway and then by organ site, population, or topic of interest, resulting in 25 poster discussion sessions. Each session had two scientific and two advocate co-chairs to help facilitate discussion. The scientific co-chairs used the abstracts from their session to develop sample translational research opportunities, which were presented to session participants. One translational research opportunity example for each pathway was presented at the closing plenary session of the meeting. For the Agents pathway, Dr. Stephen Baylin presented a research opportunity to develop an agent with the potential to block the Wnt signaling pathway, which is important in stem cell regulation. For the Biospecimen-Based Assessment Modalities pathway, Dr. Joe Gray discussed four biomarkers for development as predictive for ductal carcinoma in situ and/or early-stage breast disease. The example for the Immune Response Modifiers pathway was presented by Dr. Martin Cheever, who discussed development of WT1 as a potential vaccine for ovarian cancer. For the Image-Based Assessment Modalities pathway, Dr. Sanjiv Gambhir discussed engineering antibody fragments against prostate-specific glycoprotein and labeling them for use with PET or SPECT for use in staging and monitoring therapy in prostate cancer. Dr. Gary Dorfman presented the example for the Interventive Device pathway, which involved using irreversible electroporation in combination with an imaging methodology to treat hepatocellular carcinoma. For the Lifestyle Alterations pathway, Dr. Stephen Barnes discussed looking at diet and exercise interventions in women between the ages of 15 and 20 to reduce breast cancer risk.

Next steps are to concurrently develop a process for prioritization and establish funding and project management procedures. It is envisioned that NCI would solicit concepts for translational research opportunities and a CTAC Working Group would develop criteria to prioritize the concepts both within and across pathways. The Working Group's recommendations would be presented to CTAC for concurrence. NCI leadership would then develop processes for competitive solicitation and funding. It is hoped that a proposal for a prioritization process will be presented to CTAC at its March 2009 meeting. The funding strategies and the Request for Information for concepts would be developed in summer 2009. Concepts would be prioritized and competitive solicitations released in fiscal year 2010.

Questions and Discussion

Dr. Tepper asked how prioritized projects would be deemed "productive failures" and terminated if necessary. Dr. Matrisian acknowledged that despite efforts to select the most promising projects, there would always be risk of failure. Identifying productive failures quickly and efficiently would be an important part of the process. Dr. Niederhuber commented that the expectation is to fund promising projects that have progressed part of the way through the pathway and have a high likelihood of success. He also noted that an approach similar to that used by the Small Business Innovation Research program might work for prioritized translational research projects, including leveraging funding to encourage co-support from venture capitalists.

Dr. Abbruzzese asked whether concepts for potential prioritization would be limited to those presented at the NCI Translational Science Meeting. Dr. Matrisian said that the meeting was meant only as an educational experience and would not limit the concepts considered for prioritization. Dr. Abbruzzese also expressed concern that any competitive solicitation developed would not be truly competitive because it is likely that only a limited number of individuals or programs would be able to develop effective applications. Dr. Matrisian conceded that this is at least partially true. Part of the

competitive process would occur during the concept development stage. However, while the number of investigators/programs capable of carrying out some steps of a project may be limited, there may be more flexibility/opportunity for other steps.

Dr. Bruner commented that the pathways need to be more broadly disseminated among nontraditional translational scientists (e.g., behavioral scientists), who were underrepresented at the NCI Translational Science Meeting. The pathways would be very helpful for informing symptom management and quality of life research.

Ms. Roach complimented NCI for involving patient advocates in the Translational Science Meeting in a meaningful way. She also commented that the pathways make it easier for advocates to explain translational research to Congress and illustrate how funding is used. She stated that a good credentialing process will be essential for identifying high-quality projects for prioritization.

Dr. Schilsky reported that while many in the scientific community appreciated the pathways as organizational tools and expressed enthusiasm about new funding mechanisms, there was concern about priorities being established by a small committee rather than through a traditional peer review process. He stated that it would be important that any prioritization process be palatable to the scientific community. He also said that many investigators would be wary of a two-step application process through which they would be required to develop a concept, and then, if the concept were approved, write a grant. Dr. Matrisian said the TRWG envisioned that prioritization would first be done within pathways by content experts similar to traditional peer review groups; however, prioritization between pathways would be different from what has been done in the past. It is important that the prioritization process be effectively communicated to the scientific community—it must be clear that the Special Translational Research Acceleration Projects (STRAPs) are not replacing existing programs. Also, any new translational research resources (e.g., project management, core facilities) should be accessible through multiple mechanisms (e.g., a researcher with an investigator-initiated grant should be able to apply for access to these resources). Dr. Niederhuber reminded the Committee that NCI is a translational resource platform for everyone—the private sector, government agencies, the extramural community, etc. One of the goals of the prioritization process would be to help connect all these components in order to complete a specific project and create a specific deliverable.

Dr. Kenneth Cowan, Director of the Eppley Cancer Center, University of Nebraska Medical Center, commented that early private investment in prioritized projects will be key to their success. He also said that the work of the TRWG, including the prioritization initiative, will help investigators not involved in a SPORE or other large group become aware of how to get involved in translational research and access available resources. Dr. Helman added that developing the metrics used to define success will be important. Dr. Niederhuber emphasized that overall success is achieved when patients' lives are improved. Dr. Matrisian commented that working out the details of a prioritization process would be the responsibility of the Working Group.

Motion. A motion was made to form a CTAC working group to advise NCI on the development of a prioritization process for translational research opportunities and provide input on funding strategies. The motion was seconded and unanimously approved.

XI. CTEP PROCESS ANALYSIS—DR. DAVID DILTS

Dr. David Dilts, Director, Center for Management Research in Healthcare, discussed the CTEP process flow and timing analysis of clinical trials. The current clinical trial system is broken; with diminishing funds and resources available, a dramatic change is needed to reinvigorate the system. Extensive site visits were conducted in order to create a process map for the CTEP analysis. The process map includes concept review, regulatory affairs, drug company support, the Central Institutional Review Board, new protocol development, common data elements, pharmaceutical practice, final protocol, and final study activation. The analysis counts the number of decision points and working steps at each processing phase (e.g., what is required to get the first patient on study in a Phase III Cooperative Group clinical trial). It takes over 810 steps to open a Phase III clinical trial; 652 working steps, 158 decision points, 68 potential loops, and 38 groups are involved. With this many steps, there are that many more opportunities for inefficiencies and for mistakes to be made.

The CTEP analysis also looked at accrual numbers of Cooperative Group and non-Cooperative Group trials. About 28 percent of clinical trials at four major Comprehensive Cancer Centers result in zero accrual; 59 percent of all studies result in accrual of less than five patients. These numbers are a clear indicator of wasted resources. Cooperative Group trials at these locations have about double the number of zero accruals than in-house studies. Overall, half of all Phase III clinical trials processed through CTEP and opened in an eight-year period did not achieve 25 percent of their minimum accrual; overall, two-thirds did not meet their minimum accrual goal. This problem is not unique to Phase III trials, as all phases of clinical trials have issues with accrual. Forty-eight percent of Phase I/II and 35 percent of Phase II trials sampled did not meet their minimum. Thus, 17 percent of the total patients enrolled in the trials sampled were enrolled in a trial that had underperforming accrual. Dr. Dilts pointed out that enrolling a patient in a trial that will never be published presents an ethical dilemma.

Dr. Dilts also discussed the relationship between success of a trial and the time taken to open it. For all study phases looked at by CTEP, the median time to open a trial was 18 months. If a trial was opened faster—in 9 to 12 months—the odds ratio of attaining accruals was doubled. If a trial opened in about 27 months, the odds of attaining accruals greatly dropped. The time until accrual of the first patient was a very good indicator of whether total accruals would be met—odds drop dramatically if it takes 6-12 months. If a trial met 60 percent of its accrual goal at a specific time point, it was also a good indicator that the trial would be successful. A solution to help attain accruals could be to open the study to many other institutions. However, this is not likely to work because a trial that fails at the initial institution will probably fare the same elsewhere.

Dr. Dilts concluded by informing the Committee that CTEP plans to develop an article summarizing the aforementioned statistics and will submit an article entitled "Unethical Delay" shortly.

Questions and Discussion

Dr. Niederhuber stressed that NCI will have to make tough decisions in the future about which trials warrant continued funding. Dr. Perez added that stricter timelines will be key to improving the clinical trials system. If a trial does not meet the deadline for opening or patient accrual, its funding should be revoked.

Dr. Adamson commented that there is a window of opportunity to achieve success in pediatric drug development. If these drugs do not get into early-phase clinical trials at the right time, those trials

will fail. He added that the incentives for participation in NCI-funded clinical trials are not in line with the goals of those trials, whereas in industry, incentives are better aligned and trials are more successful. Dr. Bruner agreed with the need to realign incentives in order to change the clinical trials system. She noted that the prestige of being Principal Investigator on a clinical trial prevents rational decisions on whether to continue studies with poor accrual.

Ms. Roach stated that NCI cannot eliminate the Cooperative Groups because they are a valuable resource for networking with the community. However, she recommends that NCI work with experts in the field of change management to repair the broken clinical trials system. Dr. Doroshow added that NCI should not simply focus on making the system speedier and more efficient, but rather build a system that has a wealth of support and resources so that no one would perceive a rationale for developing a parallel track for clinical trials. Such a system would involve all participants in drug research and development—a coordinated clinical trials system. Dr. Dilts commented that there is much redundancy in the current system and a more efficient and streamlined process could be created by relying on a different perspective of accountability, performance metrics, and coordination of resources.

Dr. James Wade, Director of Medical Oncology, Decatur Memorial Hospital Cancer Care Institute, commented that it could be worthwhile to have a discussion with the Office for Human Research Protections or the Data and Safety Monitoring Committee (DSMC) regarding the ethics of accruing patients to underperforming trials. If the CTEP analysis is shared with DSMC, that Committee might be persuaded to add an additional early-stopping rule to shut down trials that are not performing. Dr. Niederhuber added that it is very difficult for NCI leadership to make decisions to stop trials, but the Institute will need to start making tough choices to align metrics, decision points, and stopping points.

Dr. Mendenhall asked whether CTEP has considered looking at other countries when studying operational efficiency. Dr. Niederhuber said that he is under the impression from his international activities that foreign countries have the same problems with clinical trials but have not yet recognized them. Dr. Carolyn Runowicz, Director of the Carole and Ray Neag Comprehensive Cancer Center, commented that pharmaceutical companies are moving their studies to foreign countries because review and enrollment are easier and there are fewer administrative obstacles—trials are completed more quickly but there can be sacrifices in quality. Dr. Abbruzzese added that all European clinical research is funded by the pharmaceutical industry. NCI cannot look outside the United States to correct problems with clinical trials because there is no analogous system.

Dr. Leung commented that all of the company-sponsored trials initiated by OSI Pharmaceuticals were brought to completion. Dr. Dilts added that this success is a result of opening trials in large numbers of facilities. Overall, the trials are successful, but when per-site accrual is examined, one-third of the sites involved in company-sponsored trials achieve zero accruals. This is an overcompensating system that ignores underlying problems with the clinical trials process.

XII. NCI COMMUNITY CANCER CENTERS PROGRAM—DR. MAUREEN JOHNSON AND MS. ANDREA DENICOFF

Overview. Dr. Maureen Johnson, Special Assistant to the Director and Project Officer, NCI Community Cancer Centers Program (NCCCP), discussed the goals of the NCCCP. Approximately 85 percent of cancer patients are treated in their local communities—community hospitals now provide a sophisticated level of care made possible by cutting-edge technology and well-trained medical specialists. However, advances in localized treatment have also resulted in fragmented delivery of cancer care in many places. One of the main goals of the NCCCP is to address this fragmentation.

Dr. Johnson explained the core components of the NCCCP and how it is different from other NCI programs. The core components include disparities, clinical trials, advocacy, survivorship, biospecimens, quality of care, and caBIG™ tools and electronic medical records. Disparities, quality of care, and information technology are being addressed across the cancer continuum and within each core component—a key feature that distinguishes the NCCCP from other NCI programs. The NCCCP creates linkages and integrates many NCI programs, translating the gained knowledge into a community setting. It also creates a strong hospital-based community cancer center network to support NCI goals and share best practices.

The baseline criteria for site participation in the NCCCP included: a distinct hospital-based location with integrated programs; at least 1,000 new cancer cases per year; an effort and commitment to address the underserved, including a policy that anyone diagnosed with cancer is offered treatment; a minimum enrollment of 25 patients with a preference of 50 for clinical trials; and less than $3 million/year in funding from NCI. From these criteria, 10 organizations were selected across the country. Six are community hospitals in urban and semi-rural areas, two are rural hospitals that include Native American populations, and two are national health systems that include multiple sites. Although 10 organizations are funded, there are 16 hospitals participating in the pilot program. NCI's investment in the program is approximately $500,000 per site per year, equaling a total commitment of $15 million over the 3-year pilot period. Sites must use 40 percent of their NCI funding to address heath care disparities, as this is a major component of the program. Other funding comes from a strong public-private partnership, in which the sites pledge to co-invest $47 million—a three-to-one match for every NCI dollar invested.

The NCCCP sites see approximately 27,000 new cancer patients per year, providing a good study group and representing a broad range across the core components of the program. The sites have specific deliverables with metrics for each core component and progress is tracked by quarterly reports, detailed annual assessment surveys, and an independent evaluation contractor. Examples of the deliverables include increased outreach to disparate populations, increased use of multidisciplinary site-specific care committees, and expansion of psychosocial and palliative care initiatives. The evaluation methods include case studies, economic studies, and patient surveys. The purpose of case studies is to understand the implementation of the program, assess change, and determine successful structures and processes. Economic studies include a micro-cost study, a business case study, and a program sustainability study. Patient surveys are conducted to assess the program from the patient's perspective.

One of the cornerstones of the NCCCP is to create a vibrant network to support research and improve quality of care. Part of this collaboration has been to develop NCCCP community tools to help measure progress to meet the deliverables. The pilot sites are utilizing these tools to determine areas for improvement. Dr. Johnson reviewed a few of the tools. The Multidisciplinary Care Assessment Tool defines integrated efforts in case planning, physician engagement, coordination of care, and infrastructure and financial considerations. A Chemotherapy Consent Form was developed as a uniform template for individual institutional modification. The Genetic Counseling Assessment Tool defines the minimal genetic counseling service requirements to guide improvements. The Physician's Conditions of Participation sets recommended requirements for experience and performance. The Biospecimen Assessment Tool is used to assess and report progress on implementation of the *NCI Best Practices for Biospecimen Resources*. It is anticipated that these tools will be used to build the NCCCP network and ultimately improve the quality of patient care.

Dr. Johnson also discussed how the NCCCP network would enhance the cancer research infrastructure. Based on the *NCI Best Practices for Biospecimen Resources*, all 16 pilot sites are adopting optimal processes for formalin fixation—the first necessary step for high-quality biospecimens. Twelve of the 16 sites have gone beyond the information technology deliverable and are adapting to or adopting

caBIG™ clinical trials, tissues, and imaging tools. All of the sites are moving to electronic health records and have already shown increases in accrual to clinical trials. The pilot sites have made many new connections to community organizations, with a focus on reaching the underserved. They have developed plans to work with primary care providers to improve screening, expanded linkages with oncologists to coordinate care, and expanded community linkages for survivorship activities. Much collaboration across the cancer enterprise has also been stimulated. To date, the pilot sites have worked with the American College of Surgeons Commission on Cancer, American Society of Clinical Oncology, American Cancer Society, and NCI-designated Cancer Centers.

Dr. Johnson addressed concerns that the NCCCP program overlaps with the NCI-designated Cancer Centers program; these programs complement each other. NCCCP benefits by gaining access to clinical trials for their patients and NCI-designated Cancer Centers benefit by gaining access to a networked research infrastructure that can provide access to patients for clinical trials, access to clinical data for analysis, and access to quality biospecimens.

In conclusion, Dr. Johnson described how the type of research fostered by NCCCP is different than what is traditionally thought of as translational research. The Institute of Medicine conducted a clinical research roundtable and discussed two translational blocks in the clinical research continuum. T1 research is defined as the transfer of new knowledge of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, prevention, and first human testing; whereas T2 research is defined as the translation of clinical study results into everyday clinical practice and health decision making. T2 research requires a different skill set, as interventions are evaluated in real-world settings. NCCCP is a model of multidisciplinary approaches to evaluate interventions in community settings across the cancer continuum—a T2 research model. Additionally, NCCCP has created a national, networked research platform for research institutions and pharmaceutical companies to utilize for activities such as clinical trial accrual, biospecimen collection, and clinical data analysis. It is important to note that this translational research model is also applicable to other chronic diseases.

Clinical Trials Component. Ms. Andrea Denicoff, Nurse Consultant, NCI Cancer Therapy Evaluation Program, discussed goals and activities within the clinical trials component. The major goals are to increase community connections, with an emphasis on increasing underserved/minority population participation in trials; broaden the types of clinical trials that are offered in the community so patients have the full spectrum of NCI-sponsored trials available to them; and expand the complexity of open trials (i.e., translational-type trials).

Year 1 ended June 30th and some of the major activities included opening a greater variety of trials, increasing the number of physicians participating in clinical trials, and improving protocol activation timelines. In terms of progress made, a survey of clinical trial activity was conducted at each site. Sites were also surveyed regarding use of patient navigators and related job descriptions. The results showed that at many sites patient navigator job descriptions do not include informing patients about clinical trials—highlighting the need to build clinical trials literacy and core culture within these community cancer centers. A Clinical Trials 101 webinar was developed with the disparities subcommittee and the OCE to provide appropriate training for patient navigators. The sites also developed the first draft of a trial screening log and selected three Cooperative Group trials to pilot test the screening log. Challenges faced in the first year were clinical trial insurance coverage, access to early-phase trials, collection of race and ethnicity data, and awareness of and referral to trials by other physicians.

In Year 2, four working groups were established to divide tasks into manageable efforts. Ms. Denicoff discussed the goals and progress of each working group. The Clinical Trials Portfolio Working Group identifies trials for NCCCP sites to engage in as an entire network and shares strategies on trial

selection and accrual. They have selected five NCI-sponsored trials that sites could activate from the Cancer Trials Support Unit, including a cancer control trial, in which to participate. The Clinical Trial Screening Log Working Group is working with NCI's Center for Biomedical Informatics and Information Technology experts to develop a user-friendly, Web-based trial screening log for sites. One of the challenges was to define what is considered a "screened patient" for a trial. It was decided that screened patients are those with whom the trial has actually been discussed. The screening log was launched February 1, 2008, and has shown almost a 25 percent accrual rate for the five selected trials. The goal of the Minority/Underserved Accrual Working Group is to enhance participation of these populations in clinical trials. The Best Practices Working Group was recently initiated and will identify clinical trials best practices that serve to provide enhanced efficiencies and improve operations of site infrastructure.

Year 3 begins in July and NCCCP will continue to expand efforts, increase the types of trials, focus on minority/underserved recruitment, and increase the total number of staff dedicated to clinical trials, including physician participation in trials.

Questions and Discussion

Dr. Grubbs commented that the NCI Community Clinical Oncology Program has greatly benefited from the efforts of NCCCP, especially in regard to tissue procurement. NCCCP has also stimulated CCOP to get involved with caBIG™, increased physician involvement in clinical trials, and improved their quality assurance tools.

Dr. Niederhuber added that the typical competitive fashion in which extramural investigators compete for grants is not a realistic approach when working in the private community setting. NCCCP has greatly fostered collaboration and the resources that the community has contributed to date far exceed NCI's investment.

XIII. NEW BUSINESS—DRS. JAMES ABBRUZZESE AND JOHN NIEDERHUBER

Subcommittee and Working Group Updates. Dr. Abbruzzese briefly discussed the activities of the Ad Hoc Coordination Subcommittee, Guidelines Harmonization Working Group. The Committee is looking for ways to foster communication and collaboration between components of the NCI clinical trials infrastructure, individual investigators, cancer centers, SPOREs, and Cooperative Groups. After starting off with a working definition of collaboration, the Committee examined three successful examples of clinical and translational research collaboration—the I-SPY trial, the development of bortezumib, and the SELECT trial (Selenium and Vitamin E Cancer Prevention Trial). In efforts to improve collaboration, the Committee agreed that a novel funding mechanism is needed to move clinically applicable, exciting research across the spectrum of Phase I to III trials. A more detailed presentation of Committee efforts and findings will be given at the March 2009 CTAC meeting.

Future Agenda Items. Dr. Niederhuber stated that he and Dr. Prindiville will work more proactively with the Committee to set future agenda items. CTAC has taken on a very important role and the issues worked on at these meetings are critical to the future of NCI.