DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
3rd CLINICAL TRIALS ADVISORY COMMITTEE MEETING

Summary of Meeting
November 14, 2007

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 3rd meeting on Wednesday, November 14, 2007, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD from 8:00 a.m. – 4:15 p.m. Dr. John Niederhuber, Director, NCI, presided during the meeting.

CTAC Members
John Niederhuber, Chair
James L. Abbruzzese
Peter C. Adamson
David S. Alberts
Kirby I. Bland
Deborah W. Bruner
Jean B. deKernion
Stephen S. Grubbs
Bruce J. Hillman* (absent)
Sandra J. Horning*
Susan A. Leigh
Gabriel M. Leung* (absent)
Michael P. Link (absent)
Nancy P. Mendenhall*
Heidi Nelson
David R. Parkinson*
Edith A. Perez
Timothy R. Rebbeck
Carolyn D. Runowicz
Daniel J. Sargent
Richard L. Schilsky (absent)
Joel E. Tepper
Jeffrey M. Trent (absent)
James L. Wade, III
James E. Williams

* pending approval

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

Executive Secretary
Sheila A. Prindiville, NCI

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

Dr. Niederhuber called to order the 3rd CTAC meeting. He welcomed the Committee and the *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 in writing comments, 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 March 2009.

Motion. A motion was made to approve the minutes of the 11 July 2007 CTAC meeting. The motion was seconded, and the Board approved the minutes unanimously.

II. DIRECTOR'S UPDATE—DR. JOHN NIEDERHUBER

Dr. Niederhuber introduced Dr. Lawrence J. Ray, Deputy Director for Management, and Executive Officer of the NCI. Dr. Ray brings 26 years of federal service to the NCI; he also has 10 years of experience in academia.

FY 2007 Budget Summary. Dr. Niederhuber reminded members that the NCI had functioned under a Continuing Resolution (CR) for much of fiscal year (FY) 2007. RPGs were funded at the 15th percentile plus extensive exceptions, which equate to a 20 percent success rate. In addition, *R01s were funded at the 21st percentile. The NCI funded 1,312 competing research project grants (RPGs), meeting the NIH-recommended target. Dr. Niederhuber noted, however, that reaching these targets during a flat budget time means that each non-competing renewal is decreased by 2 to 3 percent. The NCI maintained the existing funding levels of the Special Programs of Research Excellence (SPOREs), and an executive committee for the SPOREs has been established. Two new Cancer Centers (Baylor College of Medicine and Stanford University) also were funded. Dr. Niederhuber expressed appreciation for the efforts of NCI budget staff who wrangled with a new NIH budget management system and still were able to close the FY 2007 books with only a $9,000 balance.

FY 2008 Appropriations. Congressional appropriations currently are proposed for $4.925 B, compared to the President's Budget (PB) of $4.8 B. Based on the PB of $4.8 B, the NCI has seen a 12 percent loss in purchasing power since 2004, during several years of a mostly flat budget. Dr. Niederhuber mentioned that the President vetoed the Congressional Appropriations Bill on November 13; the NCI will continue to operate through mid-December under a CR. He said that the difference between the 2008 PB and the 2008 Congressional Appropriations was $128.101 M, an increase of 2.67 percent; if the Appropriations accounted for inflation at a rate of 3.67 percent, the number would have been $177.513 M.
Dr. Niederhuber described a FY 2008 operating budget based on the Congressional Appropriations number of $4.925 B, and its increase of $128.101 M. NIH taps and assessments are estimated to increase by $20 M, and NCI requirements based on increases in competing RPGs, rents and utilities, small business program, and mandated salaries, as well as the NCI Director's Reserve of $25 M, provide a subtotal available of $15.6 M. The NCI intends to create a pool of $70 M for new initiatives, expansions, and restorations; to offset the estimated $54.4 M negative balance, NCI planning involves a 3 percent decrease in Division, Centers, and Office of the Director (OD) budgets.

NCI Leadership. Dr. Niederhuber said that the NCI is committed as a leader in changing the course of disease for patients, including through its work in prevention, the development of markers of disease, and

interventions. Some of the initiatives created during the past 5 or so years have begun to achieve important results; these include the Integrated Cancer Biology Program; Centers for systems biology, nanobiology, proteomics, and human cancer genetics; the Cancer Genome Project; and network-centric medicine. The NCI is putting resources and effort into subcellular imaging as well, and is interested in bringing groups of individuals together around theoretical physics and applied mathematics.
Dr. Niederhuber mentioned that he and Dr. James H. Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), are working with a life sciences consortium on a common language project, which a CTAC subcommittee also is involved with, as well as to address issues of intellectual property and antitrust; it is hoped that the common language project will be created in spring 2008. Dr. Doroshow also is leading the creation of the Chemical Biology Consortium, which has begun its active phase as part of NCI's drug development program. The NCI is seen as being the platform of connectivity between academia and the private sector, supporting the creation of new targets that are taken forward into actual interventions. The NCI also is working to increase the role of the NIH Clinical Research Center as well as its availability to extramural investigators.

Barriers remain in the battle against cancer. Significant challenges are posed by the resources needed to adequately invest in support of scientific discovery, recruiting and retaining the next generation, and the time and expense required for translation to man. Other barriers include the common language and intellectual property issues, and access for all to the therapies and technology being developed.

Questions and Discussion

Dr. Jean B. deKernion, Professor and Chairman, Department of Urology, and Senior Associate Dean for Clinical Operations, David Geffen School of Medicine, University of California at Los Angeles, expressed his concern about having resources available to make it possible for people, especially new investigators, to enter the field of cancer. Dr. Niederhuber said that when he visits universities, he insists that the schedule include time with graduate students and postdoctoral researchers as a way to encourage them to continue in the field. Dr. Timothy R. Rebbeck, Professor, Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, commented on the difficulties experienced by clinician-investigators because of the clinical and health care system burdens; it is near impossible to get those with an M.D. to do tenure-track research. Dr. Niederhuber acknowledged the many personal sacrifices that clinician-investigators make and called on academic clinical departments to help determine how to better support research and address differentials in pay. Dr. David S. Alberts, Director, Arizona Cancer Center, The University of Arizona College of Medicine, suggested connecting mentor/physician/scientist (K23) awards with the Comprehensive and Clinical Cancer Centers in a meaningful way.

Ms. Susan A. Leigh, Consultant, National Coalition for Cancer Survivorship, said that the advocacy community should continue to remind everyone doing basic sciences and biomedical research that there are real people involved—that is, patients. Dr. Niederhuber said that the NCI's work each day begins and ends with patients, and that this is the reason for NCI's Community Cancer Centers Program (NCCCP), which was launched as a pilot project in June 2007 to help deliver technology and state-of-the-art science into the community.

Mr. James E. Williams, Co-Chairman, Pennsylvania Prostate Cancer Coalition, agreed on the importance of generating the resources needed, and he encouraged stronger marketing and public relations to tell the cancer stories. Dr. Niederhuber said that the NCI looks for opportunities to talk about the progress made, such as sharing the stories with members of Congress and their staff, both on Capitol Hill and in visits to the NIH campus. He said that the NCI is dependent on the outside community to tell the story from the patient; it is a patient's story that really makes the difference.

III. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Legislation of Interest. Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), NCI, described legislative efforts of interest. Several bills were introduced throughout FY 2007, including: The Fair Access to Clinical Trials Act (FACT) (S. 467), which was introduced on January 31, 2007, by Sen. Christopher Dodd (D-CT); the Enhancing Drug Safety and Innovation Act (S. 484 and H.R. 1561), which was introduced on February 1, 2007, by Sen. Michael Enzi (R-WY) and on March 19, 2007 by Rep. Henry Waxman (D-CA); and the Food and Drug Administration (FDA) Amendments Act (S. 1082 and H.R. 2900), which initially was introduced on May 9 by Sen. Edward Kennedy (D-MA) and on June 28 by Rep. John Dingell (D-MI). Language from these bills was modified and reintroduced as the FDA Amendments Act (P.L. 110-85) (H.R. 3580) on September 19, 2007, by Rep. Dingell and enacted on September 27, 2007. It increases transparency in the conduct and reporting of clinical trials, and included two provisions that expanded clinical trial registry to give patients access to basic information about trials and supported the creation of a clinical trial results database that would compel researchers and manufacturers to submit trial results. The new law requires the registration of all Phase II, III, and IV interventional clinical trials for drugs and devices 90 days after enactment, and it includes monetary penalties for noncompliance.

Ms. Erickson provided an update on three additional legislative efforts of interest. 1) Access to Cancer Clinical Trials Act (H.R. 2676), which was introduced by Rep. Deborah Pryce (R-OH) to give protection to individuals who choose to participate in clinical trials; the bill forbids group health plans from denying beneficiary participation in trials, denying coverage of routine costs, or discriminating against patients based on their participation in trials. The Department of Health and Human Services (DHHS) Secretary must study the impact on group health plans. 2) Ovarian Cancer Biomarker Research Act (H.R. 3689), introduced on September 27, 2007, by Rep. Howard Berman (D-CA) authorizes the NCI Director to make grants for the discovery and validation of biomarkers for use in risk stratification for, and early detection and screening of, ovarian cancer. It also establishes an ovarian cancer biomarker clinical trial committee. 6) H.R. 248 was introduced by Rep. Rick Boucher (D-VA) to honor the contributions of clinical trial participants.

FY 2008 Appropriations Status. Ms. Erickson told members that the PB (dated February 5, 2007) allocated $4.78 B to the NCI, the House total (passed on June 19) was $4.87 B, and the Senate total (passed on October 23) was $4.91 B. A Conference Committee report from November 1 allocated $4.92 B. It was passed by the House on November 6 and the Senate on November 7. Ms. Erickson said that, if the President does not sign it into law by November 16, another CR has been proposed that would go through December 14, 2007.

Ms. Erickson referred members to the OGCR's updated Web Site (http://legislative.cancer.gov) for additional information on legislative updates and histories, as well as hearing testimony.

Questions and Discussion

Dr. David R. Parkinson, President and CEO, Nodality, Inc., requested further information about the Clinical Trials Results Database and its management. Dr. Niederhuber said that a number of issues remain to be worked through, including ensuring that patients and their families understand how to interpret trial results that are posted in the database. Dr. Kenneth H. Buetow, Director, Center for Biomedical Informatics and Information Technology, added that the National Library of Medicine (NLM) sees the database as its charge and has begun the process of communicating with other Institutes about its approach to this data management. Dr. Joel E. Tepper, Hector MacLean Distinguished Professor of Cancer Research, Department of Radiation Oncology, University of North Carolina, Lineberger Comprehensive Cancer Center, asked about the data content required by the legislation. Dr. Niederhuber

replied that the NCI will be reviewing the legislation carefully to determine the requirements. Dr. Richard Pazdur, Director, Division of Oncology Drug Products, FDA, said that the FDA shares concerns regarding which results are made available and the interpretation of results. Dr. deKernion asked whether this legislation would apply to all clinical trials, both industry and NIH, and Dr. Niederhuber indicated that it would. Dr. Heidi Nelson, Fred C. Anderson Professor, Division of Colon and Rectal Surgery, Department of Surgery, Mayo Clinic Foundation, raised the issue of information and parameters provided at the commencement of a trial versus what is reported in the results, including the endpoints and sample size. Dr. Sandra J. Horning, Professor of Medicine, Stanford Comprehensive Cancer Center, Stanford University Medical Center, assumed that the legislation pertains only to approved drugs and devices, and Ms. Erickson confirmed this.

Dr. Kirby I. Bland, Fay Fletcher Kerner Professor and Chairman, Department of Surgery, School of Medicine, and Deputy Director, UAB Comprehensive Cancer Center, University of Alabama at Birmingham, asked whether the prohibition on coverage denial of routine trial costs expressed in the Cancer Clinical Trials Act was limited to NCI-supported trials or encompassed industry-sponsored projects as well. He also asked about the scope of coverage and how the term "routine costs" would be treated in terms of applied and evolving technology, which can be expensive to use. Dr. Niederhuber indicated that the legislation currently is not a high priority in the House of Representatives, and Ms. Erickson agreed to provide further details if the bill begins to receive more support.

IV. CLINICAL TRIALS WORKING GROUP (CTWG) IMPLEMENTATION UPDATE—DR. SHEILA A. PRINDIVILLE

Dr. Prindiville provided an update on the Clinical Trials Working Group (CTWG) implementation, particularly the work of its steering committees, the restructuring of the Phase III funding model, and the standardization of clinical trial agreement terms. The CTWG supports the implementation of clinical trial initiatives in conjunction with NCI Divisions, Centers, and Offices.

Disease-Specific Steering Committees. The Gastrointestinal (GI) Steering Committee, which is chaired by Drs. Tepper and Daniel Haller, includes six task forces (colon, esophagogastric, pancreas, rectal-anal, hepatobiliary, and neuroendocrine). It has reviewed six Phase III concepts and approved two; the time of receipt by the PIO office to the Steering Committee usually ranges between 3 and 12 weeks, and the last four concepts were passed through in 3 to 6 weeks. The GI Steering Committee will review Phase III and randomized Phase II concepts.

The Gynecological (GYN) Steering Committee is co-chaired by Drs. William Hoskins and Gillian Thomas. Five Phase III concepts have been reviewed, with four approved or approved pending revisions. The process has ranged from 4 to 13 weeks, with an average time of 8 weeks. The GYN Steering Committee will review Phase III and randomized Phase II concepts. Three task forces (cervical, uterine, and ovarian) have been involved actively in concept evaluation.

The Head and Neck (H&N) Cancer Intergroup transitioned to a Steering Committee in December 2006. The co-chairs include Drs. Arlene Forastiere, David Schuller, and Andrew Trotti. Four task forces have been identified: metastatic/recurrent disease, rare tumors, locally advanced, and tumor biology and imaging. The committee will review Phase II and III studies.

The Symptom Management/Health-Related Quality of Life (SxQOL) Steering Committee is responsible for the review and prioritization of symptom management intervention clinical trial concepts to be conducted through the Community Clinical Oncology Program (CCOP) mechanism, as well as the provision of input to studies with secondary QOL endpoints in cooperative group treatment studies. It also is charged with developing prioritization criteria for QOL studies that are eligible for proposed

correlative science/QOL set-aside funds. Moreover, it will convene state-of-the-science meetings to identify critical questions and unmet needs and to prioritize key strategies. The SxQOL Steering Committee is composed of CCOP principal investigators (PI), Cooperative Group Cancer Control/QOL Committee representatives, R01 investigators, biostatisticians, community oncologists, patient advocates, and NCI staff. The committee is co-chaired by Drs. Deborah W. Bruner, Independence Professor in Nursing Education, School of Nursing, University of Pennsylvania, and Michael Fisch. It has begun to draft the prioritization criteria and is actively working on a strategy to initiate review of symptom management study concepts. In addition, a cervical cancer state-of-the-science meeting was held on September 27-28, 2007, and a similar meeting on pancreas cancer is scheduled for November 30–December 1, 2007.

Process measures that are being followed now and evaluated on a yearly basis for the Steering Committees include timeliness of review and value added by task force discussion. Other outcome measures are: a structured evaluation of the entire clinical system designed by evaluation specialists; and periodic evaluations to assess the impact of restructuring, with the first assessment scheduled for 2009. Measures of the quality and impact of the Disease-Specific Steering Committees on the overall clinical trials system will take years to assess fully.

The CTWG timeline called for the completion of the implementation of Steering Committee structures by the end of 2010. There is a plan to launch the Genitourinary Steering Committee and the Lung and Mesothelioma Steering Committee in FY 2008. A Patient Advocate Steering Committee (PASC) also is planned, in collaboration with NCI's Office of Advocacy Relations; this committee will consist of all advocates who participate in CCCT Steering Committees and, in its first year, would be chaired by the advocate CTAC representatives. Other committees are scheduled for establishment in FY 2009 and 2010.

Restructuring the Phase III Funding Model. The large differential between NCI per-case reimbursement and actual clinical trial costs that exists in the current Phase III trial system is not sustainable over time for the Cooperative Groups or CCOPs. In addition, there may be some cost inefficiencies in the system. Sites that accrue only a few patients per year also may result in a high per-case cost because of fixed costs. The new funding model implementation plan involves conducting a financial analysis of clinical trials costs to identify areas of inadequate funding, overlap, and best practices, as well as to assess cost savings that might result from closing sites that accrue very low numbers of patients. The new model will be developed collaboratively with the Cooperative Groups, and this collaboration will continue in FY 2008 to assess the feasibility of aligning reimbursement with trial and patient complexity.

Standardization of Clinical Trial Agreement Terms. A plan for the development of the terms has been developed in partnership with the Life Sciences Consortium's CEO Roundtable. Extramural oversight is being provided by the CTAC's Public-Private Partnership Subcommittee. The standardization process includes: soliciting the involvement of academic medical centers and industry, which is underway; compiling a list of agreement terms to be standardized; analyzing agreements to identify differences in key terms; and developing a structured approach for achieving consensus among key stakeholders. Another key part is the promotion of the use of the standardized modules for clinical trial agreement terms.

Questions and Discussion

Drs. Peter C. Adamson, Professor, Pediatrics and Pharmacology, and Chief, Clinical Pharmacology and Therapeutics, The Children's Hospital of Philadelphia, University of Pennsylvania, and Edith A. Perez, Professor of Medicine, Division of Hematology/Oncology, Mayo Medical School, and Director, Breast Cancer Program, Mayo Clinic Foundation, asked for clarification on the timelines. Dr. Prindiville said

that most concepts are reviewed by a task force before coming to the steering committee; the goal has been to have the steering committee complete its review of a concept within 1 month of receipt.

Dr. Adamson noted that the Steering Committees decided to focus on randomized Phase II trials and he wondered whether the exclusion of nonrandomized studies would discourage other studies. Dr. Prindiville replied that the Steering Committees are looking at larger studies that may be informative for science and the future development of Phase III studies. Dr. Tepper added that most nonrandomized Phase II trials are designed to become Phase III trials, and that the GI Steering Committee in particular did not want to interfere with the operation of individual Cooperative Groups. Dr. Daniel J. Sargent, Director, Cancer Center Studies, and Professor, Division of Biostatistics, Mayo Clinic College of Medicine, Mayo Clinic Foundation, said that many investigators are designing randomized Phase II trials so that they do not have to be reviewed by a committee. Dr. James L. Abbruzzese, Chairman, Department of Gastrointestinal Medical Oncology, University of Texas, M.D. Anderson Cancer Center, commented that there is a momentum building to move away from the uncontrolled oncology Phase II trial. Dr. Prindiville clarified that nonrandomized models continue to undergo review by the Cancer Therapy Evaluation Program (CTEP). Dr. Alberts encouraged the involvement of Phase III Chairs in discussions of Phase II concepts to ensure a smooth transition between phases.

Dr. Nancy P. Mendenhall, Professor, Department of Radiation Oncology, University of Florida Health Science Center, asked whether concepts are accepted from all investigators. Dr. Prindiville indicated that they are primarily from Cooperative Groups. Dr. Tepper said that a concept from outside the Cooperative Groups had recently been submitted.

Dr. James L. Wade, III, Director of Medical Oncology, Department of Clinical Research, Decatur Memorial Hospital Cancer Care Institute, and President, Cancer Care Specialists, queried about the broadening of the Central Institutional Review Board's (IRB) scope to include Phase II trials and thus reduce upfront costs of trials. Dr. Prindiville referred the question to Dr. Meg Mooney, Acting Branch Chief, Clinical Investigations Branch, CTEP, who said that through the Cancer Trial Support Menu (CTSU), the NCI tries to identify larger (i.e., more than 120), randomized Phase II trials to enter the Central IRB process early.

V. INTERFACE OF THE TRANSLATIONAL RESEARCH WORKING GROUP (TRWG) REPORT AND THE CTWG REPORT—DR. JAMES H. DOROSHOW

Dr. Doroshow reminded members that the common themes of Translational Research Working Group (TRWG) initiatives include coordinated management, prioritization, tailored funding programs, and operational effectiveness. The integration of the TRWG with CTWG involved transforming 15 initiatives into 6 activities under these themes. NCI management is being integrated, including the integration of TRWG implementation with CCCT operations, the establishment of the Translational Research Operations Committee (TROC) that is scheduled to commence work in FY 2008, and the expansion of CTAC's mission and membership (in expertise and number of members) to address translational research.

The translational research award coding, which the NCI will implement for FY 2009 awards, establishes a foundation to identify and manage translational research portfolio decisions. It refines NCI's capabilities to track funding for translational research and is similar to an ongoing activity to define funding levels for clinical trials.

Translational research prioritization involves a comprehensive, annual prioritization of two or three specific translational research opportunities. The process likely will be led by a CTAC Working Group that includes extramural researchers, patient advocates, representatives from industry and foundations, and NCI staff. The Working Group will provide advice to the CTAC and be supported by the CCCT.

Currently, the translational research approach includes NCI-initiated solicitations and investigator-initiated projects, both of which pass through various levels of intramural and extramural review. The proposed additional approach is to select 10 ideas for detailed analysis based on broad public input to a Request for Information (RFI), which are honed to five concept packages and disseminated for public comment. These ideas are expected to yield two to three translational research opportunities and special awards and likely will inform existing NCI initiatives. The process will be developed during FY 2008 and executed through Special Translational Research Acceleration Projects (STRAPs). Emphasis will be placed on development projects that are focused, closely managed, and collaborative. The NCI is considering accelerating the implementation of a STRAP-like mechanism for specific projects in collaboration with foundations. NCI mechanisms currently focus on basic (50%), translational (35%), and clinical (15%) research, and STRAP is intended to complement the existing mechanisms.

The modification and coordination of translational research awards is an important component of tailored funding mechanisms. Changes are planned for guidelines modification for existing multi-project collaborative translational research awards, such as National Cooperative Drug Discovery Groups (NCDDG), SPORE, and Early Detection Research Network (EDRN), as well as the coordination of translational research core services for enhanced efficiency. Other activities include the integration of projects that are funding early stages of translational research (e.g., SPOREs, P01, and STRAP) with preclinical development resources, such as NCI's Rapid Access to Intervention Development (RAID) and Rapid Access to Preventive Intervention Development (RAPID) projects.

To ensure operational effectiveness, a project management system will be established. Its implementation, however, is dependent on the new coding's accuracy in identifying translational research awards, guideline modifications, and the analysis of existing core services and other resources. To allow time for the completion of these activities, implementation of the project management system is being delayed until FY 2009. Regarding external coordination, the NCI's Office of Advocacy Relations and the Director's Consumer Liaison Group (DCLG) initiated a foundation and advocacy group outreach on translational research issues in October 2007. Moreover, TRWG initiatives involving industry collaboration has been proposed to be under the auspices of the CTAC's Public-Private Partnership Subcommittee.

Dr. Doroshow said that the requested FY 2008 budget for TRWG implementation is $1.55 M. He encouraged CTAC members to share their thoughts on: the expansion of the CTAC mission to include oversight of translational research; the expansion of the CTAC parent committee to include translational research membership and expertise; the role of CTAC entities (i.e., the proposed Translational Research Prioritization Working Group, Public-Private Partnership Subcommittee, and Coordination Subcommittee) regarding the TRWG charge; and the need for a Working Group to define the role of the CTAC in guiding the implementation of TRWG initiatives.

Motion. A motion was made to form a Working Group in relation to STRAP and furthering translational research in clinical trials. The motion was seconded and approved unanimously.

Questions and Discussion

Dr. Niederhuber stated that STRAP is intended to be complementary to NCI's existing work, including the SPOREs, and will be focused on the science of biology. A topic under consideration is how STRAP could relate to the Small Business Innovation Research (SBIR) program. He said that an office is being formed within the NCI to manage the SBIR program, and recruitment is underway for biotechnology development experts who can transition an idea and product into a commercialized project; the office will serve at least two other Institutes as well. The second phase of the SBIR program has been modified and now requires investigators to bring venture capital into the process. Dr. Niederhuber also stressed the

importance of integration in all of the NCI's activities. Finally, he announced that negotiations are near completion for Dr. Lynn Matrisian, Vanderbilt-Ingram Comprehensive Cancer Center, to assist the NCI with the integration of TRWG and CTWG work. Dr. Alberts suggested that the NCI consider the Small Business Technology Transfer Research (STTR) program in addition to the SBIR program. He also said that he would like to see STRAP extended to cancer prevention. Dr. Doroshow clarified that STRAP is focused on translational research and not on treatment, diagnosis, or prevention.

Dr. Parkinson said that he recently attended a forum on personalized medicine and that he found the technology emerging to enable biological characterization to be astonishing. He encouraged the NCI to work in concert with the FDA; if the FDA was involved early in the process, tools could be created that have analytic validity and clinical utility. He also commented that industry would be more likely to interface with the SBIR program if it were more user friendly.

Dr. deKernion supported the idea of a CTAC prioritization working group that encompasses all the phases, rather than starting at Phase III.

Dr. Bland expressed support for STRAP and requested further information about the proposed additional approach for translational research. Dr. Doroshow said that the notion was to have the proposed working group devise processes in which scientists and lay people assist in prioritizing scientific concepts through a forum. Dr. Niederhuber said that the intent is to leverage resources with the Foundation for the NIH (FNIH) and potentially the private sector. Dr. Parkinson agreed with the importance of such collaboration and said that the NCI represents access to patients, tissue, and expertise.

VI. INVESTIGATIONAL DRUG STEERING COMMITTEE: CLINICAL TRIAL DESIGN TASK FORCE REPORT—DR. PERCY IVY

Dr. Percy Ivy, Associate Chief, Developmental Chemotherapy, Investigational Drug Branch, CTEP, presented the Investigational Drug Steering Committee's (IDSC) Clinical Trial Design Task Force Report. The goal of the Clinical Trial Design Task Force is to improve Phase II ability to predict Phase III outcome, and the Task Force has considered the importance of specific differences in patient populations and metrics, endpoints, changes in diseases over time, and concurrent controls needed in Phase II. The Task Force's consensus on preliminary plans and conclusions, which are described in the report, include: test different designs, perform a case study using prospective and retrospective designs and compare results, and look at imaging modalities that may accurately document the effects of agents in tumors to correlate radiological response with survival benefit. In addition, the Task Force agreed that RECIST is problematic, but no better way has been defined at this time to patient benefit accurately. There was a lack of consensus on the use of Bayesian designs, which are perceived as resource intensive and complex, and therefore may not be suited for studies in a community setting. Concerns also were expressed about historical versus concurrent controls, as well as other endpoints, such as TTP. During the past 6 months, the Clinical Trial Design Task Force evaluated five projects:

1) **Simulation testing** was used to compare adaptive (i.e., Bayesian) and frequentist models. The next most standard design used in the NCI involves separate Phase II trials for multiple tumor sites; a "new" design involves a single trial open to multiple tumor sites and includes criteria for discontinuing a tumor site if there is evidence of insufficient activity. To compare frequentist and adaptive approaches, a computer simulation study proposes to vary the activity of the new agent and design parameters and compare designs in terms of probability of making a correct decision, accuracy and precision, the probability of receiving an answer early, and the numbers of patients required.

2) A Phase II **historical control database** for retrospective analyses is being developed. It could provide an alternative to conducting randomized Phase II trials. The idea is to evaluate cytostatic agents that may require the use of PFS, adjust the historical control values for PFS to account for prognostic variables, and incorporate PFS and the prognostic variables in two or more diseases into the database. The first disease targeted is melanoma; future databases are being explored in glioblastoma and nonsmall cell lung cancer (NSCLC). The Task Force is collaborating with several consortia and cooperative groups to accomplish this work.

3) **Dual endpoints** for Phase II trials were evaluated for their effective and predictive qualities, especially in terms of response rate and PFS. There was a concern that PFS measured continuously in randomized Phase II trials may be subject to subtle bias from differences in followup intensity. Additionally, for potentially cytostatic agents, it may be desirable to compare both response rates and PFS.

4) Plots were compared in terms of **tumor burden and time**. Researchers looked at: RECIST (percentage of patients that respond by standard criteria); waterfall plots (measures tumor shrinkage at a point in time, but does not account well for the past of disease and time from diagnosis); and spaghetti plots (response over time may be a better measure of prolonged cytostasis or dormancy. The project's objectives are to continuously measure tumor volume reduction to predict progression-free survival and survival in traditional study populations as a whole and in subsets of patients. A series of Phase III studies are proposed in breast, lung, and colon cancer, and the variation in these results across studies will be described using "meta-analysis" methods.

5) **Novel ways of assessing imaging** will be evaluated to further rational drug discovery for molecular targets. Key questions include whether the drug reaches the target, including in the manner that was hypothesized, and whether the drug's effect on the tumor correlates with the effects on the target.

The Task Force identified several research areas for Phase I studies, including: the evaluation of Phase I studies, continuous reassessment methods, shift from MTD to safety and biological efficacy, multiple doses in Phase II studies, and biological endpoints as related to clinical benefit across multiple histologies. Other topics include seamless Phase I-II designs, the relationship between Phases 0 and I, and Phase I combination studies.

Questions and Discussion

Dr. Rebbeck asked about plans to translate the information into practice. Dr. Ivy responded that a detailed meeting summary will be published and that task force subgroups are working on their projects and will commence analysis shortly; the goal is to identify specific clinical trials and apply these designs in a comparative fashion. Dr. Doroshow said that a general solicitation, such as a notification of interest, will need to be made.

Dr. Alberts encouraged interaction with the FDA in this process. He also raised concerns about RECIST. Dr. Ivy said that the RECIST Committee recognizes the limitations of the "evaluation" of stable disease. Dr. Pazdur said that the FDA does not favor any particular measurement criteria, especially the response rate criteria. Dr. Sargent said that he is a member of the RECIST Committee looking at new standards for RECIST, and that the Committee is discussing this issue with the American College of Radiology Imaging Network (ACRIN) and would like to receive community input.

Dr. Pazdur stated that the FDA would be concerned about using historical databases to approve drugs. Dr. Parkinson noted that diseases are being refined, so the natural histories captured in databases will not be the same. Dr. Lawrence V. Rubenstein, Developmental Clinical Trials and Preclinical Studies Section, DCTD, NCI, said that the historical databases project will develop an ongoing, methodologic framework that coordinates prognostic factors with outcome. Dr. Barker mentioned the Interagency Oncology Task Force's work with the FDA on fluorodeoxyglucose-positron emission tomography (FDG-PET) in non-Hodgkin's lymphoma, which was more complex than originally thought.

Dr. Sargent encouraged collaboration with the nonprofit sector, including the American Society of Clinical Oncology (ASCO) and the Society of Clinical Trials, as well as the statistical community. He also noted that this research faces many of the same challenges as translational research, and that funding opportunities will be needed to encourage statisticians to delve into this area. Dr. Sargent raised concerns about findings from waterfall plots, which might need to be validated with other agents.

Dr. Perez commented on the use of bevacizumab in the trial, noting that it doubled the response rate but had no impact in progression-free survival and overall survival, and thus is an outlier compared to everything else; she questioned the predictability of analysis through using this agent.

VII. RECENTLY APPROVED CONCEPTS—DRS. MEG MOONEY AND EDWARD TRIMBLE

Drs. Mooney and Edward Trimble, Head, Gynecologic Cancer Therapeutics and Quality of Cancer Care Therapeutics, Clinical Investigations Branch, CTEP, provided an overview of the clinical trials process in terms of the new review process that is in place with the Disease Specific Steering Committees (DSSCs). They described Phase III trials that recently were approved by the GYN and GI Steering Committees.

RTOG 0436: A Phase III Trial Evaluating the Addition of Cetuximab to Paclitaxel, Cisplatin, and Radiation for Patients With Esophageal Cancer Who Are Treated Without Surgery. Dr. Mooney said that the estimated new cases of esophageal cancer in 2007 totaled 15,560 (12,130 men and 3,430 women); deaths are estimated at 13,940 (10,900 men and 3,040 women). In the past 2 decades, there has been an increased incidence of adenocarcinoma, which now has greater incidence than squamous cell carcinoma. Surgical and nonsurgical treatment options are available for patients with Stage II through Stage IVA esophageal disease. The Radiation Therapy Oncology Group (RTOG) submitted a proposal to evaluate cetuximab with definititve chemoradiation in the nonoperative patient population; one arm would receive Paclitaxel/Cisplatin/radiation therapy (RT), and the second arm would receive these agents along with Cetuximab. All patients would undergo endoscopy and biopsy after treatment of definitive chemo-RT. The sample size was estimated to be 400 patients and would take about 4.5 years to complete accrual.

The GI Steering Committee expressed concerns about the limited availability of data on cetuximab and requested additional data from pilot studies. The committee also requested a review of the substation of cisplatin for carboplatin and desired a detailed toxicity and safety monitoring plan. Committee concerns regarding patient population and statistical design included that adenocarcinoma and squamous cell carcinoma represent different diseases with different biologies and that more confidence in the potential benefit of cetuximab with chemoRT was needed before embarking on a large trial; to address these, the Committee requested that the trial design evaluate the agent in each histology early on and suggested that the design provide substantial test of potential benefit. The Group/Task Force addressed these concerns and suggestions, as well as others related to elegibility criteria, tissue banking, and intergroup participation.

Dr. Mooney reviewed concept and protocol timelines. The concept was submitted in September 2006 to the GI Steering Committee, which completed its first evaluation in October and resubmitted it in late November. The committee's second evaluation and approval were completed in December 2006. The protocol development, FDA concept review, and Central IRB review were completed between January and November 2007.

GOG-CVM-0704: A Randomized Phase III Trial of Cisplatin Plus Paclitaxel With or Without Bevacizumab Versus the Non-Platinum Doublet, Topotecan Plus Paclitaxel, With or Without Bevacizumab in Stage IVB, Recurrent, or Persistent Carcinoma of the Cervix. Dr. Trimble stated that cervical cancer is a world disease and remains among the top three causes of cancer deaths among women. In the United States and throughout the developed world, however, it has been a triumph in terms of cancer prevention and control. There are 450,000 cases and 238,814 deaths estimated worldwide due to this cancer; of these, there are 11,150 incidences and 3,670 deaths in the United States.

The Gynecologic Oncology Group (GOG) has conducted several Phase III trials using the agent platinum in combination with paclitaxel, topotecan, gemcitabine, and venorelbine, as well as a nonplatinum combination of paclitaxel and topotecan. Patients who received platinum with paclitaxel or topotecan had a better response rate than those without the combination, but platinum with topotecan also showed significant improvement in median survival. One trial included a health-related quality of life (HRQOL) component to address issues underlying chemotherapy; no differences were found in HRQOL between arms, despite the increased toxicity with combinations. An interim analysis of another study showed that none of the experimental arms were likely to demonstrate improved survival over the control arm by the end of the study. This led GOG to develop a replacement study, which was for women with advanced, recurrent, or persistent carcinoma of the cervix.

The proposed study was a 2x2 factorial design to look at a control arm of cisplatin and paclitaxel and a nonplatinum combination of topotecan and paclitaxel. It also would evaluate the addition of bevacizumab. Moreover, a FACT-cervix, FACT-neurotoxicity, and a brief pain inventory were included, and the study also looked at smoking correlations. The planned sample size was 450 patients and the primary endpoint was survival. The GYN Steering Committee gave its unanimous approval for the study, adding guidance on the management of and surveillance for toxicities and eliminating the smoking cessation component as the study provided no curative regimens. The committee also suggested adding a translational research component and pursuing international collaboration through the Gynecologic Cancer Intergroup (GCI) to strengthen accrual.

The concept was submitted to and reviewed by the CTF in May 2007. It was reviewed by the GYN Steering Committee in June and approved in July. The GOG is developing the protocol document, which is expected to be completed in late 2007.

Questions and Discussion

Dr. Nelson asked about the process and timeline after the steering committee and the CTEP have approved the concept. Dr. Mooney explained that ideally, the CTEP receives the first version of the protocol within 45 days, revisions are incorporated, and the document is delivered to the Central IRB for review between Day 60 and 90. Following the review of the Central IRB, the protocol receives final approval from the CTEP. She noted that a protocol that is intended to be a registration trial would involve the FDA and lengthen the timeline.

Dr. Tepper raised concerns about the possibility of a specific organization that is a member of a steering committee reviewing and approving its own protocols, and Drs. Runowicz and Alberts echoed this concern. Dr. Abbruzzese asked about the dynamic functioning of the committees and their level of

discussions. Dr. Trimble explained that the GYN Steering Committee was structured on the model of the GI Steering Committee to ensure that all groups were represented; four groups were involved at the outset, and the Southwest Oncology Group (SWOG) and representatives from six SPOREs in GYN cancer also joined. He indicated that both the Task Force and Steering Committee held lengthy discussions on various issues.

Dr. Tepper asked about the limited or nonexistent preliminary data for the experimental arms involving cisplatin, paclitaxel, and bevacizumab. Dr. Trimble noted that a similar leap occurred in ovarian cancer. Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, and Northeast Utilities Chair in Experimental Oncology, University of Connecticut Health Center, spoke from her experience with toxic agents and suggested that the data shown in the presentation for 2 and 3 months did not illustrate clinical significance. She also asked for further information about bevacizumab and whether data were available about it in combination with chemotherapy, or if it achieved a better response in combination with one other drug or two other drugs. Dr. Trimble said that data are not available on the activity of bevacizumab as a single agent or in combination. Dr. Horning asked for information about the statistical design of trials based on little existing data, and whether embedding a Phase II trial within a Phase III was considered that would provide rationale for discontinuance if preexisting milestones were not met. Dr. Alberts suggested that several Phase II trials could be conducted to deal with issues of agents that are not very active but are very toxic. Dr. Trimble said the cervical study had a planned utility analysis to cover for this. Dr. Rubenstein added that ceasing the bevacizumab randomization would not reduce the patient population, and including bevacizumab does not add significant resource costs. Dr. Pazdur said that one could argue that "rare" tumors are not rare outside the United States; he suggested that the activity of sponsors and their relationship with the CTEP could be discussed in future CTAC meetings; he reminded the Board that registration trials and expensive drugs that result are paid for by the U.S. taxpayers.

Dr. Runowicz asked for the rationale in focusing on Stage IV-B patients, who are not available in large numbers in the United States. Dr. Bruner asked about the ongoing process for diseases where the issue is global and accrual rates would be difficult to maintain in the United States alone.

Dr. Doroshow said that the presentation of these protocols was the first time this had occurred in the CTAC meetings and wondered if the Board felt it would be worthwhile to continue such presentations in future meetings. Dr. Barker said that the consensus of interest is overwhelming, and this should be continued.

VIII. BIOMARKER, IMAGING, AND QUALITY OF LIFE SUPPLEMENTAL FUNDING PROGRAM—DRS. SHEILA A. PRINDIVILLE AND DEBORAH BRUNER

Introduction. Dr. Prindiville reminded members that the CTWG Prioritization's Scientific Initiative #4 was to establish a funding mechanism and prioritization process to ensure the initiation of important correlative science and QOL studies in association with clinical trials. This targets the studies that would be conducted in association with Phase III trials when costs for those studies would be too large to be covered by Cooperative Group mechanisms. A task force of the Program for the Assessment of Clinical Cancer Tests (PACCT) developed criteria for prioritization, which were approved by the CTAC in July 2007. The SxQOL Subcommittee is charged with developing criteria for prioritization of essential QOL studies. Three types of studies are considered: integral (i.e., must be performed for a trial to proceed), integrated (i.e., identify or validate assays or markers and imaging tests that might be used in future trials), and other correlative studies (i.e., develop markers and assays or imaging tests that are performed retrospectively). Evaluation criteria for prioritization include: the potential to change practice or have high impact, strong preliminary data relating to the test, interpretation of the test well defined and validated, sufficiently standardized for ease of transfer to the clinical setting, defined process for

specimen or image collection and processing, definitive statistical plan with adequate power and feasible sample sizes, and the potential for cost-sharing. Additional criteria include the justification for the request to address all of the categories listed, weights should not be assigned to categories, and priority should be based on the totality of the information and the strength of the data.

Recommendations for Prioritization of Quality of Life Studies Conducted in Association With NCI-Funded Clinical Trials. Dr. Bruner reminded members that the CTWG initiative called for a funding mechanism and prioritization process to ensure that important correlative science, including *in vitro* laboratory, imaging, and QOL studies, can be initiated in a timely manner in association with clinical trials. Symptoms of disease and side effects of treatment are a central component of health-related QOL. The terms "symptom assessment" and "QOL" are used interchangeably. An important element of QOL studies is the PRO, which involves the measurement of any aspect of a patient's health status that comes directly from the patient.

Four categories of QOL studies have been proposed for prioritization. 1) The assessment of additional factors that impact QOL is important to patient-physician decision making as well as helping patients prepare for and interpret the treatment experience. 2) QOL validation studies would include the evaluation of the added value of PROs as complementary adjuncts to clinical assessed outcomes for measuring toxicity, the validation of QOL measures in Phase II trials that have previously only been tested in small studies or different populations, and the validation of technologic improvements in QOL/PRO data capture. Physician's charting of toxicities often does not correlate with patient self-report of toxicity; additionally, significant differences have been documented in the report of toxicities between patients on PROs compared to clinicians on CTC. The prognostic value of patient self-reported QOL has been shown in lung, esophageal, bladder, breast, and cervical research; Dr. Bruner described various tools involved in this work, such as the European Organization for Research and Treatment of Cancer's (EORTC) Quality of Life Questionnaire (QLQ) scores, as well as baseline FACT-cervix prognostics and lung cancer symptom scale (LCSS). The current standard is to use paper-and-pencil measures, which contributes to the current problem of data quality and missing data. Computer-based approaches show promising signs of improving data reporting and could be validated in larger trials. 3) Studies of objective correlates to PRO measures would provide a concurrent collection of an objective test along with a PRO measure to provide stronger data when following patients on a symptom management or QOL trial. 4) Studies of predictive correlative measures are needed to assess and correlate PROs with biomarkers to increase predictive models of: morbidity; safety; pathophysiologic mechanisms of symptom expression or treatment efficacy; and genetic determinates of symptom expression, QOL endpoints, and treatment efficacy.

Evaluation criteria should include the impact on patient mortality or QOL, the increasing knowledge that will move science in symptom management and QOL forward, preliminary data in support of hypothesis, and a clearly defined process for data collection and completion. Other criteria are a statistical plan with adequate power, reliable and valid measures, feasibility of completion in a reasonable timeframe, and the likelihood to have high impact on cancer research.

Symptom management and QOL clinical research remains challenged by the lack of a program to develop pharmacologic interventions for symptom management trials, as well as the lack of a program for the systematic development of behavioral influences.

Implementation of the Program. Dr. Prindiville said that the program will be funded through administrative supplements to the Cooperative Group and CCOP programs. An announcement will be made in early December 2007, with up to $5 M anticipated in FY 2008. CTWG has recommended the eventual expansion of funding to $10 M, with at least 25 percent of total funds made available for QOL studies. Essential biomarker, imaging, and QOL studies associated with symptom management studies

and Phase III Cooperative Group studies are eligible trials for FY 2008. Review and prioritization in FY 2008 will be handled by Scientific Steering Committees, which will review proposed studies in association with the review of the parent trial concept. The CTEP review process will be used when no Scientific Steering Committee (SSC) exists. In addition, the CTEP and the Division of Cancer Prevention (DCP) will develop a funding plan based on studies recommended by the Scientific Steering Committees, the Clinical Trials Operations Committee (CTOC) will recommend a funding plan across disciplines for consideration by the CTAC, and the CTAC will review the portfolio and make final funding recommendations. A schedule has been developed to accommodate these levels of review, and the CTAC's final recommendations are expected to be announced at its meeting in June 2008.

Questions and Discussion

Dr. Bland asked about the cost of adding symptom improvement to a clinical trial. Dr. Parkinson said that in his experience this approach yields the greatest cost effectiveness; he encouraged the field to develop methodology, technology, and standardization of criteria for judgment of QOL that have been negotiated with regulatory authorities. Dr. Perez commented on the importance of separating QOL tools from symptom improvement strategies. Dr. Bruner stated that the science is evolving and that some instruments need better validation; she noted that the FDA has developed guidance for development. Dr. Lori Minasian, Director, CCOP, stated that there are no funds in the CCOP program for methodologic development of PROs of QOL instruments, and she mentioned several NCI and NIH efforts in this area, including the NIH Patient-Reported Outcomes Measurement Information System (PROMIS) initiative and the Patient-Reported Outcome Assessment in Clinical Trials (PROACT) workshop.

Dr. Barker requested clarification about the use of correlative funds for symptom intervention. Dr. Bruner said that correlative funds can be used for the validation of instruments that already are developed, but not for symptom intervention; the other half of the picture involves behavioral interventions. Dr. Barker said that the FDA needs to be involved with any discussions or changes regarding correlative funds.

Dr. Nelson questioned the idea that QOL can predict the endpoint of survival when it is not heralded in statistical analyses or resources. Dr. Bruner said it might be predictive but is dependent on the instrument and the symptom of interest, such as whether an agent causes neurotoxicity; most likely there will not be a global measurement. Dr. Horning that suggested a broader view of the measurement of QOL across trials should be taken to address issues related to the instrument and the collection and analysis of data. Dr. Sargent noted that the FDA can approve a drug or device for improved survival or improved patient well-being, which provides a great opportunity for work in QOL. He cautioned, however, that improving QOL does not necessarily improve survival.

Dr. Abbruzzese queried about the source of funds to cover QOL components in trials. Dr. Bruner said that the CCOP is an excellent mechanism through which QOL funds could flow but acknowledged that a shift of existing funds would be needed.

Mr. Williams mentioned the difficulty in prostate cancer in persuading men to get annual physicals and said that it was important for the NCI to look at questions in behavior science as well as hard science. Ms. Leigh said that, from a patient perspective, quality of survival is crucial. She also called attention to long-term cancer survivors who develop other cancers or organ system failures for whom QOL is an issue. QOL is one of the reasons that participants do not remain on clinical trials, and this may be an area in which the NCI could work with advocacy groups to find additional resources.

Regarding implementation of the program, Dr. Prindiville clarified that the balancing of the program will encompass diseases as well as modalities. She confirmed that 25 percent is recommended for QOL studies but that at this time the percentage is artificial and could change.

Dr. Runowicz asked whether other NIH institutes would be interested in co-funding QOL and behavioral studies. Dr. Minasian said that other institutes have been approached but have not expressed interest; the Phase III clinical trials generally address a hypothesis specific to cancer. Dr. Runowicz encouraged the NCI to look outside for resources; pharmaceutical companies that market and profit from a drug should provide a comprehensive analysis of it. Dr. Parkinson said that registration trials do contain QOL and related measurements, at great cost, but they generally are not informative.

Dr. Horning wondered about the limitation of funds to Phase III trials. In addition, Dr. Mendenhall asked about the possibility of broadening the program beyond Cooperative Groups and the CCOPs. Dr. Prindiville said that these limitations are solely for this FY because of the newness of the program and the ability to use an existing mechanism to move quickly in the short term. Dr. Wade suggested that funding should be available for exploration in newer approaches.

IX. UPDATE: INSTITUTIONAL BARRIERS TO CLINICAL TRIALS—DRS. DAVID M. DILTS AND ALAN B. SANDLER

Drs. David M. Dilts, Professor, Operations Management, and Director, Center for Management Research in Health Care, Owen Graduate School of Management, and Professor and Director, Engineering Management Program, Vanderbilt University; and Alan B. Sandler, Associate Professor of Medicine, Division of Hematology/Oncology, Vanderbilt-Ingram Cancer Center, presented an interim report of a process and timing study on activating and opening Phase III clinical trials.

Process Steps. Dr. Dilts described the CTEP process to open a cooperative group study. The median time is 800 days to go through Cooperative Groups and to work with CTEP and Central IRB, and an additional 120 days to process through the Comprehensive Cancer Centers; investigator-initiated trials take less time. The time range for these processes, however, varies widely: 435–1,064 days for Cooperative Groups and 21–826 days for Comprehensive Cancer Centers. The CTEP has two processes for review—comprehensive (i.e., traditional) and steering committee—that both take approximately the same number of working steps, decision points, processing loops, and stopping points. A significant number of steps that are required to open a clinical trial are duplicative. Dr. Dilts shared a 45-foot map that illustrated the CTEP steps, including the possible loops and multiple reviews and evaluations as a concept passes through the Comprehensive Cancer Centers, CTEP, and Central IRB. Each time a protocol is changed, it must go back through the system; the median number of revisions for documents in this process is six, and some documents have been revised up to 12 times. In the review process, 11 percent of concepts under review by the cancer centers, 57 percent of protocols under review by the CTEP, and 100 percent of applications under review by the Central IRB are returned to the applicant for significant changes. Each review (and re-review) adds 60 more days to the process; an increase in the number of loops means a much longer process. Dr. Dilts reported that no correlation was found between the amount of time that was spent on the concept versus the protocol. The uncertainty about when a trial will open, caused by so many loops in the process, has multiple ramifications, including disincentives for careers in research and the accrual of patients who are willing and able at a specific point in time to participate in a trial but might not be after lengthy delays. From 2000 to 2007 in CTEP and Comprehensive Cancer Centers, there consistently were concepts that experienced significant delays from concept receipt to activation; the large variance means that trial activation times are hard to predict. In addition, 50 percent of all studies open at a world class Comprehensive Cancer Center accrue fewer than five patients. Preliminary data show that 100 percent of accrual goals were met 44 percent of the time; however, data also show that 40 percent of the time only 20 percent of accrual goals was met. An

analysis of ECOG Phase III accrual performance found that studies that open quickly are more likely to meet accrual goals; this finding was consistent regardless of the organization, including the CTEP and Cooperative Groups, indicating a systemic problem.

Recommendations. Dr. Dilts offered initial, intermediate, and long-term suggestions to address some of these barriers. In the short term, data should be collected and analyzed, and the "entitlement" culture should be eliminated and reviewers should learn to say "no." Additionally, reviewers should stop tweaking concepts and protocols and follow the old adage "two strikes and you're out," and they should use consistent terminology and mean what they say. In the medium term, concepts should be triaged using scientific merit and operational complexity; non-value added, redundant steps should be eliminated from the entire process; other NIH Institutions and pharmaceutical companies should be viewed as benchmarks; and processes that build quality in should be created. The long-term recommendation is to start from the beginning, develop and use standards, and use focused Phase III teams to activate a high-quality Phase III protocol rapidly (in 90 days) and cooperatively.

Questions and Discussion

Dr. Barker commented on the lack of change in any given time to the process. Dr. Dilts said that most people look at an industry's standard processes and assume that these are the processes that must be followed. He also noted that the clinical trials industry includes very good scientists, who are not trained industrial engineers.

Dr. Perez said that her group is working to improve the Phase II system and would be happy to share their guidelines in this effort.

Dr. Adamson asked whether the overall problem is at the investigator or operations level. Dr. Dilts said it is a blend of the two: it is within the organization to enact changes, but investigators should know that an entitlement culture does not exist.

Dr. Abbruzzese noted that there are other pressures (e.g., legal and regulatory) and external forces (e.g., institutional culture, especially affecting how people are promoted) that would require correction simultaneously. Contracting and intellectual property (IP) issues are two significant challenges. Dr. Dilts agreed that changing the system is not going to be easy, but that it becomes easier once the standard is established. For example, using one standard IP form will help simplify a process in which currently there is a new IP form created for each study.

Dr. Parkinson said the culture within each clinical trial organization necessitates a struggle to keep programs funded; quality is non-negotiable, but inefficiencies remain an enormous expense.

In response to a question by Dr. Grubbs, Drs. Dilts and Prindiville clarified that steering committees review the concept but do not approve total protocols.

Dr. Perez said that because changing the entire system will take time, it would be helpful to complete a few activities quickly at the start.

Drs. Perez and Horning agreed that the Central IRB turning away 100 percent of studies is a serious problem. Dr. Alberts agreed and suggested that the scientific review committees be given the tools and power to say "no" to the study. Dr. Horning also requested further details about the committees' structure and mandate and whether the issue lies in deficient studies or better instructions needed for the committee. Dr. Mooney explained that the Central IRB is an independent committee that must adhere to operational guidelines. Dr. Lee Helman, Scientific Director for Clinical Research, Center for Clinical

Research (CCR), said that the problem revolves around a culture of tweaking, and Dr. Dilts said that it was time to abandon this. He also said that the change that is needed should remain separate from the monitoring of that change. A member of the public who works as a patient advocate encouraged the NCI to work in a very transparent and communicative nature. Board members asked to remain updated in future meetings on changes in this area.

Motion. A motion was made and seconded to form a Subcommittee to implement recommendations from the study on Institutional Barriers to Clinical Trials. The motion was amended during discussion, and the amendment was seconded to charge the Subcommittee to discuss the recommendations and over time develop a plan for implementation of the recommendations, with input from the CTAC Coordination Subcommittee, that would be reported back to the CTAC. The amended motion was approved unanimously.

X. CTWG INFORMATICS INITIATIVE UPDATE—DR. KENNETH H. BUETOW

caBIG™ Clinical Trials Task Forces Update. Dr. Buetow provided an update on the CTWG Informatics Initiative. There are four Clinical Trials Task Forces addressing planning and monitoring, conduct, reporting and sharing, and interoperability. The Task Forces were constituted in September 2007, and inaugural 2007 Special Interest Group/Task Force meetings were held in September and will meet monthly. The Steering Committee held its second meeting in August 2007 under the leadership of co-chairs Drs. Sorena Nadaf, Vanderbilt University, and Jan Buckner, Mayo Clinic. Its immediate priority was to focus on the Interoperability Task Force to create an inventory of existing clinical trial systems at the NCI and the NCI-supported extramural community and prioritize systems for harmonization. It also endorsed the first iteration of the Clinical Trials Database, the NCI-wide procurement for the Clinical Data Management System, and Study Conduct SIG's five new Case Report Form (CRF) module activities.

Study Conduct. The NCI enterprise-wide procurement for a clinical trials data capture and management system was publicized as a Request for Proposal (RFP) that was open through November 29, 2007. Its parameters include a robust, commercially supported system for clinical and human-subjects research data that will involve a perpetual use license for unlimited distribution within the NCI system. The RFP is to support cancer trials only and the system must be interoperable with caBIG™.

CRF Working Group activities include standardization of global processes through five components: inventory, prioritization, analysis and harmonization, community input, and standardization. The analysis methodology includes questioning of intent, partition, and detailed analysis; an important caveat is not to create new questions that have not been asked on an existing CRF. Dr. Buetow described work on a demography module analysis and the resulting outcome; the module has been released for public comment through mid-December 2008. Other CRF Module Working Groups that are being established will address patient identification and enrollment, adverse events, baseline assessment, and protocol deviations. The CRF activities are being coordinated with FDA, Clinical Data Interchange Standards Consortium (CDISC), and Clinical Data Acquisition Standards Harmonization (CDASH) project efforts.

Reporting/Sharing. The first iteration of the Clinical Trials Database has been released. It aims to establish a central database as a place to register all trials and amendments and regularly submit accrual and demographic data. It also provides access to data and reporting to authorized users and eliminates redundant reporting. The trial submitter registers with the NCI's Cancer Clinical Trials Unified System (caCTUS) and the trial is registered in the system. The NCI abstracts the protocol from the document to support CDS abbreviated reporting, and the data are submitted via CDS' Web Site. Comprehensive data are available via CDS' analysis and reporting module. caCTUS contains a number of protocol registration data elements, including the protocol title and document, trial type and phase, current status,

lead organization, and PI. Next steps for the Clinical Trials Database include the development of new NCI policy to ensure that all trials are reported, and the formation of NCI policy implementation teams to address legacy data migration and protocol abstraction. In addition, the project will ensure the generation of Summary 4 and PDF and ClinicalTrials.gov submissions, develop a timeline to coordinate activities, and refine as needed the project's vision and scope document.

Interoperability. The deployment of the caBIG™ clinical trials suite involves a two-pronged approach: the adoption of caBIG™ applications and the adaptation of existing caBIG™ compatible applications that can be connected to the caGrid. Sites can adapt their own software to be caBIG™ compatible and then connect to the Grid; only elements that a site desires to expose needs to be made compatible. Moreover, compatibility can be achieved through the adoption of caBIG™ "bundles" that are available through the Clinical Trials Compatibility Framework, Life Sciences Distribution, and Data Sharing and Security Framework. A program, called "Getting Connected with caBIG™" was offered to all NCI-designated Cancer Centers in August 2007; 43 Centers applied successfully in September.

Questions and Discussion

Dr. Parkinson asked about the level of interest expressed by industry and suggested that, to further accelerate the process, efforts should focus on CRFs and FDA-accepted clinical trial input. Dr. Buetow replied that several large pharmaceutical companies have been interested; small biotechnology companies have expressed the most interest in this collection of interoperable open-source software on which to build their capabilities.

Dr. Rebbeck wondered how well the adaptors work for existing applications. Dr. Buetow said that this has not been seen in large scale, but that caBIG™ has been built to commercial standards; a separate problem is whether legacy systems have collected the information that is now considered standard. He added that it is too early to determine the percentage of legacy systems that will be able to adapt.

Dr. Barker asked to what extent the bioinformatics efforts and caBIG™ will be helpful in addressing the institutional barriers to clinical trials that Dr. Dilts discussed. Dr. Buetow said that this is being addressed; he shared as an example the NCI's creation of a bridge model to bring together HL7 data standards, which are used in hospital information management systems to collect all primary observations, with the regulatory submission requirements contained in the CDISC STDM standard. Another example is that the caGRID infrastructure includes the next generation Internet infrastructure to allow users to "plug and play." Dr. Dilts commented that the acceptance of use of the standards, not their development, poses the greatest challenge. Dr. Barker added that a shift from legacy systems also is difficult. Dr. Parkinson said that people need a reason to change; one idea might be to offer a competitive advantage to those who stick to the standards; Dr. Dilts punctuated this point with examples of business decisions by Hewlett Packard and Dell.

XI. CTWG EVALUATION PLAN: RESULTS FROM THE BASELINE FEASIBILITY ANALYSIS—DR. JAMES H. DOROSHOW

Dr. Doroshow said that a systematic evaluation of the NCI clinical trials system was needed because past evaluations were based predominately on opinions of expert panels, and the NCI had never performed a systematic evaluation that integrated qualitative and quantitative information about its clinical trials activities. The CTWG evaluation plan has three components: a structured evaluation system, baseline feasibility analysis, and periodic evaluations. The system establishes a structured framework for continuous monitoring and feedback for mid-course corrections. The analysis involves the design of baseline and future measures, assessment of the feasibility of baseline measures, performance of baseline evaluation where possible, and refinement of measures and identification of future data collection needs.

Two categories of measurement to compare baseline to future performance are those of outcome and performance. System outcome measures address the quality and impact of trials as well as the efficiency of both trial development/initiation and trial conduct. System performance baseline measures for CTWG initiatives include incentives for collaboration among investigators, the extent of multi-site Phase II and multi-Cooperative Group Phase III trials, the extent of collaboration between industry and the NCI, the nature and quality of clinical trial prioritization processes, and the distribution and cost-effectiveness of accrual across sites. Dr. Doroshow noted that the baseline measures will not consider the value of comprehensive clinical trials database, the level of caBIG™-compatible information technology interoperability, the value added by the IDSC and SSC processes, the impact of correlative science funding and standardization, the value and usage of standardized clinical trial tools, or the cost savings achieved by shifting patient accrual to highly accruing, more efficient sites. Multiple data sources will be used to triangulate analysis, including interviews, database analysis, and the review of factual information in documents.

Baseline interviews were held with 81 stakeholders (Phase I, II, and III trialists, CCOP PIs, industry trialists, and NCI staff) in 2007; questions were mostly open-ended, with some designed to elicit perceptions of specific facts or events. CTEP Clinical Data Update System (CDUS) and DCP Enterprise System Knowledgebase (DESK) databases have been analyzed, and the analysis includes all trials and letters of interest (LOIs) and concepts that were active between January 1, 2000, and December 31, 2005; no current database captures all clinical trials performed at the Cancer Centers. The baseline document review covers NCI program guidelines, cancer treatment guidelines, and academic medical center tenure and promotion guidelines. An expert panel, composed of 9 NCI-funded trialists, an industry trialist, and a patient advocate, participated in the development of measures and interview guides and reviewed key findings at the end.

Dr. Doroshow described the work underway regarding the system outcome measures. The analysis of the quality of trials focused on early closure and publications; recommendations were made to include fields for early closure and reason, as well as reporting publications, in clinical trials databases. The impact of trials was discussed in terms of Phase II and III trial linkages and the ability to provide strong evidence to guide the development of agents and diagnostics. Suggestions to improve these were to include Phase II and III linkages provided by NCI staff or PIs in clinical trials databases, and also to include entry in clinical trials databases on the strength of evidence (such as clear dose and toxicity criteria for Phase I trials, and Phase II and III trials that clearly met or failed a primary hypothesis or endpoint). Additionally, recommendations to increase the impact of trials through patient management were to use an annual *Journal of Clinical Oncology* (JCO) Clinical Cancer Advance Series article to assess impact as well as ASCO plenary session presentations. Trial efficiency covers the time to first patient on a study, including Phase II investigational drug trials and Phase III Cooperative Group trials, and the rate of accrual for these trials. Suggestions were to include earlier timepoints in concept development in databases and to facilitate the interpretation of accrual data by including entries for trial complexity and patient eligibility criteria in the databases.

CTWG coordination initiatives were discussed. These include incentives for collaboration in NCI guidelines and academic rewards, and repeat analysis of the collaborative efforts and rewards at regular intervals during CTWG implementation is recommended. To foster collaboration across awards, the NCI should focus on future interviews on collaboration in trial design and on providing infrastructure and include entries for multiple awards in clinical trials databases. Collaboration in accrual and accrual through CTSU also was considered, and repeat analyses at regular intervals were suggested. Another initiative focused on joint NCI-industry participation in trials, and the recommendation was to include an entry for "NCI-industry collaboration" in clinical trials databases.

The CTWG's prioritization initiatives encompass Phase I/II investigational drug trials and Phase III Cooperative Group trials. To address issues of perception and other concerns with these trials, it was recommended that the CTWG focus future interviews on the roles of the IDSCs and SSCs in enhancing transparency, collaboration, and quality of Clinical Development Plans and trials. Dr. Doroshow noted that, for a majority of concepts, the time from concept receipt to CTEP decision for Phase III Cooperative Group trials was between 30 to 59 days.

Regarding initiatives addressing operational efficiency, particularly the efficiency of Phase III trial accrual, baseline findings were that between FY 2000 and FY 2005, 16 percent of institutions accrue more than 100 patients, representing 64 percent of patients accrued. More than 40 percent of the institutions participating in NCI-supported Phase III trials accrued 10 or fewer patients. Baseline findings from NCI patient recruitment efforts reported that most Phase III trialists have not collaborated with or requested patient recruitment assistance from NCI's Office of Communications (OC), and OC interviewees reported few requests by investigators and focused on promoting DCP prevention trials rather than CTEP treatment trials.

Dr. Doroshow concluded with future activities, including the development of a specific plan for future evaluation and protocols for future measures, as well as the refinement of baseline measures. Other proposed next steps are to incorporate additional information in clinical trials databases to strengthen future evaluation efforts, prepare an initiative-specific timeline for future evaluation, and determine whether a CTAC Subcommittee should be formed to oversee the evaluation process.

Motion. A motion was made to form a Subcommittee to examine issues involving the CTWG Evaluation Plan, particularly cancer center sites and their rates of patient accrual. The motion was seconded and approved unanimously.

Questions and Discussion

Dr. Adamson asked whether rare diseases were included in the data on accrual in 150 trials, which could skew the results. Dr. Wade asked if the dataset looked at CTSU as a whole or at all the individual contributors to the CTSU separately. Dr. Doroshow referred to the SWOG and NSABB investigator handbooks, which indicate that an investigator who does not accrue five patients per year or accrue five patients in a period of 2 years in a row loses group membership; this rule has not been enforced. Dr. Doroshow confirmed that the accruals were to Phase III trials.

Dr. Rebbeck asked about whether representation from urban versus rural areas accounted for high versus low accrual rates. The answer is that there is no such correlation. Dr. Bruner noted that increasing the efficiency of accrual will not increase accrual. Dr. Bland suggested an in-depth analysis of the 250 sites. Dr. Doroshow said there is very little cost in accrual to eliminating the lowest decile of accrual sites. Dr. Mendenhall recalled hearing that an investigator who accrues fewer patients is more likely to be noncompliant with protocols and to have poor data submission. Dr. Grubbs indicated that his group culled out those with low accrual rates and the total accrual rate for CCOP rose.

Dr. deKernion asked if there was a process to recommend specific tasks that could be accomplished in the short term. He also supported Dr. Horning's suggestion for the CTAC to receive updates on NCI's work in this area. Dr. Doroshow said that it is important for the CTAC to set up a process to review and comment on measures and evaluation data, and that the interviews conducted consume hours of recording. He noted that information about collaborative efforts is not included in the existing databases. Dr. Tepper expressed agreement with Dr. Doroshow that integration is important, such as between SPORE investigators and the Cooperative Group system; he noted that collaboration even among SPOREs is challenging.