DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
2nd CLINICAL TRIALS ADVISORY COMMITTEE MEETING

Summary of Meeting
July 11, 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 2nd meeting on Wednesday, July 11, 2007, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD from 8:30 a.m. – 3:51 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 (via conference call)
Kirby I. Bland
Deborah W. Bruner
Jean B. deKernion
Stephen S. Grubbs
Bruce J. Hillman*
Sandra J. Horning*
Susan A. Leigh
Gabriel M. Leung*
Michael P. Link
Nancy P. Mendenhall*
Heidi Nelson
David R. Parkinson*
Edith A. Perez
Timothy R. Rebbeck (absent)
Carolyn D. Runowicz (absent)
Daniel J. Sargent
Richard L. Schilsky
Joel E. Tepper
Jeffrey M. Trent (absent)
James L. Wade, III
James E. Williams

* pending approval

***Ex Officio* Members**
Anna Barker, NCI (absent)
James H. Doroshow, NCI
Leslye K. Fitterman,* CMS (absent)
Paulette 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, Director, NCI, called to order the 2nd CTAC meeting. After welcoming the Committee and the *ex officio* members, Dr. Niederhuber 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 asked for any corrections to the minutes for the 10 January 2007 meeting; none were given, and the minutes were considered approved.

II. DIRECTOR'S UPDATE—DR. JOHN NIEDERHUBER

Status Report on Fiscal Year (FY) 2007 Appropriations. Dr. Niederhuber reviewed the status report for the final quarter of FY 2007. Type 5 grants are at 2.9 percent below commitment of record per NIH policy, and competing grants averaged $324K per NIH policy. The R01 payline for the end of the year moved to the 15th percentile, with approximately 20 percent of the competing pool reserved for exceptions. The Special Programs of Research Excellence (SPOREs), Cooperative Groups, and Training remained at the FY 2006 levels, whereas the Cancer Centers' budget was increased 2 percent from FY 2006.

Status of Legislation for FY 2008. Members were told that the FY 2008 President's Budget (PB) requests $4.782 B for FY 2008. The Senate Appropriations Subcommittee recommends $4.91 B. The FY 2008 Labor/Health and Human Services (HHS) Appropriations Bill recommends an appropriation of $29.9 B to the NIH and provides $4.91 B to the NCI, which is an increase of $113 M (or 2.3%) over FY 2007. The NCI is planning approximately 3 percent programmatic reductions. If the appropriations were to reach approximately 2%, this would increase the number of new and competing research grants at the NIH to approximately 10,645, which is nearly 550 more than in FY 2007. It also will lift the 2-year freeze on the average cost of new research grants and help train the next generation of researchers. Both House and Senate budgets expect to continue funding the Roadmap Initiative (or the Common Fund) as a direct fund in the NIH Office of the Director (OD) rather than from the Institutes. The House bill allocates $495 M for the Common Fund, which is an increase of $12 M (or 2.5%) over FY 2007, and the Senate bill recommends $531 M, an increase of $48 M (or 10%) over FY 2007.

The NCI will work to address: 1) recruiting and funding the best scientists and the best science, 2) managing expectations, 3) leveraging additional resources, 4) continuing scientific growth, as well as 5) maintaining a balance within the NCI portfolio.

NCI Cooperative Group Funding. Dr. Niederhuber said that the NCI Cooperative Groups had planned for a 10 percent budget reduction for FY 2007 but that the group budget was restored to FY 2006 levels. The final budget totaled $144.944 M, and awards are estimated at $153.945 M. The Cooperative Groups' budget declined $16.5 M between 2002 and 2006. In this time period, 30 or more Phase III trials and 60 Phase II trials were postponed or not initiated. In addition, fewer than 2,600 patients were accrued to Phase II and III studies. Programs have been allowed to cut the T-5s more than the standard 2.9 percent in cases where accrual is slower than anticipated. Programs also have been given the flexibility to make modest changes in their funding plans to adjust for changing circumstances as the year progresses.

Role of the NCI in Building Partnerships. To better address cancer, a disease of staggering complexity, Dr. Niederhuber said that the NCI has developed a number of programs, centers, and networks, including

the Nanobiology Program, the Integrated Cancer Biology Program, the Center for Human Cancer Genetics, and the Network-Centric Biomedicine effort by caBIG. The Institute sees opportunities to work with many partners in a number of areas in the cancer research arena, such as subcellular imaging, protein capture, physics, and technology development. In addition to supporting the extramural community, the NCI is working to build bridges among industry, academia, and the public sector through several activities, including the Advanced Technology Partnership Initiative, the NCI Community Cancer Centers Program (NCCCP), the NIH Clinical Research Center, and NCI's drug discovery and development resource. In these efforts, the NCI views treatment as managing a network, not just a pathway, which is an important concept in the progression toward individualized medicine.

Dr. Niederhuber described the Life Sciences Consortium, which represents a significant number of the private sector entities through a 501[c]3 structure. The Consortium's primary goals are to: 1) develop a common language for contracting; 2) work on intellectual property issues that will support this new age of discovery; and 3) address issues of antitrust.

Questions and Discussion

Dr. Jean B. de Kernion, Professor and Chairman, Department of Urology, and Senior Associate Dean for Clinical Operations, David Geffen School of Medicine, University of California at Los Angeles, requested clarification regarding the link between the CEO Roundtable and the Life Sciences Consortium and also asked about assistance to individual investigators. Dr. Niederhuber referred to Mr. Gabriel M. Leung, Executive Vice President, and President, Oncology, OSI Pharmaceuticals, who explained that in 2001 former President George H. Bush brought major industry leaders together to explore opportunities to drive changes in cancer from the commercial side of the infrastructure; their first project, called the CEO Roundtable Gold Standard, comprises a human resources policy package that provides cancer coverage benefits to companies' employees, such as guaranteed coverage for clinical trial participation and nonsmoking work sites. The second project is the Life Sciences Consortium, which aims to drive better public-private partnerships. Dr. James H. Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), said that the Translational Research Working Group (TRWG) has been working on issues related to the coordination and facilitation of government resources to support individual academic investigators who translate research from the laboratory to the patient.

Dr. Deborah W. Bruner, Independence Professor in Nursing Education, School of Nursing, University of Pennsylvania, suggested that discussions of science at the subcellular level should not ignore the behavioral science that has to occur to influence physicians, clinicians, and patients to uptake findings. Dr. Niederhuber agreed and said that the NCCCP initiative was designed to take advantage of behavioral science input.

Dr. Richard L. Schilsky, Professor of Medicine, Associate Dean for Clinical Research, Biological Sciences Division, University of Chicago Pritzker School of Medicine, expressed the view that the word "restoration" used in reference to the Cooperative Groups' budget presents a rosy picture that does not reflect the situation faced by the Cooperative Groups. Dr. Niederhuber agreed and said the word would be changed.

III. CTWG IMPLEMENTATION UPDATE—DR. SHEILA A. PRINDIVILLE

Dr. Prindiville updated Members on the progress of the restructuring initiatives from the Clinical Trials Working Group (CTWG), including coordination, prioritization/scientific quality, standardization, operational efficiency, and enterprise-wide/integrated management.

Coordination. One of the new initiatives in the coordination section is to establish a comprehensive database; Dr. Prindiville said that Dr. Kenneth H. Buetow, Associate Director, Bioinformatics and Information Technology, would provide an update on this issue later during the meeting. A second new initiative is to realign NCI funding, academic recognition, and other incentives to promote collaborative team science. It is planned to modify award guidelines for NCI-funded clinical trials programs to promote collaboration. Additionally, the feasibility of utilizing NCI's Cancer Trials Support Unit (CTSU) to help accrue patients to phase II studies such as those conducted by SPOREs, Cancer Centers, and other consortiums is being evaluated. One of the initial projects being looked at is a multi-institutional trial to be conducted in a phase I/II clinical trials consortium sponsored by the Investigational Drug Branch of the Cancer Therapy Evaluation Program (CTEP).

Prioritization and Scientific Quality. There are six initiatives underway to: 1) establish an Investigational Drug Steering Committee (IDSC) for early phase trial prioritization; 2) establish initial Disease-specific Scientific Steering Committees (DSSCs) for Phase III trials; 3) increase community oncologist/patient advocate representation on steering committees; 4) establish a funding mechanism and prioritization process for correlative science and quality-of-life (QOL) studies; 5) establish a process to ensure that correlative science studies associated with clinical trials are preformed according to standard protocols and standardized laboratory practices; and 6) develop a plan for integrating Phase II trials into the system.

Dr. Prindiville explained that the IDSC is operational with five task forces, and it is providing strategic input to CTEP's drug development planning process. One of its task forces, the Clinical Trials Design Task Force, met to discuss new endpoints and the use of randomized Phase II trial designs earlier in the drug development process. Regarding the DSSCs, the Gastrointestinal Cancer and the Gynecological Cancer Steering Committees have been established and are actively involved reviewing study concepts. The Head and Neck Committee has been formed and three co-chairs representing the multi-disciplinary nature of the committee have been named. In addition, the Symptom Management and Health Related QOL Committee has been established. The responsibilities of the committee are to: develop and prioritize symptom management intervention clinical trials that are conducted through the Community Clinical Oncology Program (CCOP) mechanism; convene state-of-the-science meetings; provide input to treatment studies with secondary QOL endpoints that are conducted in Cooperative Group network; and to develop criteria for the review of QOL studies that are eligible for the proposed correlative science and QOL set-aside funds. Similar to the other committees, the Symptom Management Committee will represent a broad spectrum of investigators.

The DSSCs have increased the transparency of the concept review progress, with a full spectrum of NCI Clinical Trials funding mechanisms represented on the committees. Community oncologists, patient advocates, and translational scientists are integral parts of the prioritization process. Scientific evaluation is rigorous and is occurring in a timely manner. There are plans to complete the implementation of the Head and Neck and Symptom Management Steering Committees in the coming year. The Gastrointestinal (GI) Steering Committee is planning a State-of-the-Science meeting on pancreatic cancer in the fall of 2007, and the Gynecological (GYN) Steering Committee is working on one for cervical cancer. There are plans to launch additional DSSCs in 2008.

Standardization. Most of the standardization initiatives concern informatics which are being co-managed by caBIG™ and the CCCT. These include standard Case Report Forms (CRFs), harmonization of systems, and a credentialing repository for investigators and sites. Dr. Prindiville noted that Dr. Buetow would describe progress on these initiatives later in the meeting. She discussed one initiative to establish commonly accepted clauses for clinical trials agreements. The CTAC Ad hoc Public-Private Partnerships Subcommittee was formed to address this issue. It includes membership from academia, industry, and government. The CCCT has developed a draft document detailing an approach to

standardize clinical trial agreements for review by this Subcommittee. The CTWG identified potential target clauses, including publishing rights, confidentiality, ownership of data, intellectual property and licensing, and risk and indemnification.

Operational Efficiency. There are three initiatives dealing with operational efficiency. Dr. Prindiville provided an overview of them and noted that each one would be discussed further in presentations later in the day.

1) One activity is to restructure the funding model for Phase III trials. In the current system there is a large differential between NCI per-case reimbursement and the actual cost per accrual to the sites. The CTWG recognized that the ability of the Cooperative Group sites and/or the CCOPs to enroll patients given this large differential in costs will not be sustainable over time. Additionally, there may be some cost inefficiencies in the current system, and sites that accrue only a few patients per year may result in a high per-case cost because of fixed costs. A financial analysis of clinical trial costs is underway as well as an analysis of the quality of data as a function of patient accrual. A new Phase III trial funding model will be developed collaboratively with the Cooperative Groups based on these analyses as well as taking factors such as trial complexity into account. Dr. Prindiville said that there is a perception that high accrual sites are more cost-efficient, and an incentive system to increase the number of high accrual sites may enhance cost-effectiveness. Moreover, the provision of supplements may help cover infrastructure costs associated with higher accruals, and these supplements could be given when the accrual exceeds a certain threshold. Finally, the financial and data quality analyses will assist in setting the appropriate accrual targets. NCI, in collaboration with Cooperative Group Chairs, established a system for providing supplements to reward high accruing sites with the $5M funds available in FY 2007 for this effort. In future years, NCI will work with the Cooperative Groups to restructure the funding model based on the data from the financial analysis and the principles outline above.

2) Another initiative is to identify institutional barriers that prolong the time it takes for a concept to be developed into a protocol open for patient accrual. Dr. Prindiville said that a presentation on analyses of institutional barriers would be given later in the meeting by Dr. Dilts.

3) A recommendation was made to develop approaches to enhance the adoption of a Central Institutional Review Board (CIRB) process. Dr. Prindiville said that Ms. Goldberg would provide results from the NCI CIRB user satisfaction survey that was recently completed. Furthermore, an analysis of the barriers to the acceptance of the CIRB has been initiated, and an analysis has been funded to determine the potential cost savings that would result from the use of the CIRB.

Dr. Prindiville closed by noting that an evaluation process for the entire restructuring is ongoing. The baseline evaluation has begun, and periodic evaluations will occur to assess the impact of the restructuring.

Questions and Discussion

Dr. Bruner requested clarification on the criteria used for selecting the disease sites for Steering Committees. Dr. Prindiville responded that for the disease sites chosen thus far were either an intergroup (such as gastrointestinal) that already existed, or a group that (e.g., head and neck) approached the NCI about forming a steering committee. For future steering committees, the NCI will work with CTEP staff in concert with the Cooperative Group Chairs. Dr. de Kernion said that another resource might be functioning clinical trial groups that specialize in disease-specific sites; a number of these function well in

decision making and vetting and conducting health protocols. Dr. Sandra J. Horning, Professor of Medicine, Stanford Comprehensive Cancer Center, Stanford University Medical Center, asked whether the plan is to look sequentially through all the disease sites or to establish a fixed number of Steering Committees and then evaluate their performance before performing a sequential review. Dr. Prindiville said that the intention is to look at all of the disease sites. Dr. Doroshow added that the report called for an interim analysis to be conducted 3 years after the baseline evaluation, followed by an extensive analysis of all of the various initiatives and their degree of success, which would be reported to the CTAC.

Dr. James L. Abbruzzese, Chairman, Department of Gastroinestinal Medical Oncology, University of Texas M.D. Anderson Cancer Center, added that the American Society of Clinical Oncology (ASCO) recently completed a thorough analysis of the role and lack of use of the CIRB and might be an effective partner is this area.

Dr. Kirby I. Bland, Fay Fletcher Kerner Professor and Chairman, Department of Surgery, School of Medicine, Deputy Director, UAB Comprehensive Cancer Center, University of Alabama at Birmingham, asked about the final plan for the trial funding model, particularly in terms of adjusting the model based on the organ site and the complexity of the trial. Dr. Prindiville replied that ongoing analysis will help inform the model's structure, as will input from the Cooperative Groups and other stakeholders. Dr. Doroshow agreed that the reimbursement should be matched with the complexity of the trials. Dr. Joel E. Tepper, Professor and Chair, Department of Radiation Oncology, University of North Carolina, North Carolina Clinical Cancer Center, observed that efficiency is important but it alone will not solve funding problems. Dr. Bruce J. Hillman, Theodore E. Keats Professor of Radiology, Department of Radiology, and Professor, Department of Health Evaluation Sciences, University of Virginia School of Medicine, said that the American College of Radiology Imaging Network (ACRIN) funds by complexity, based significantly on the imaging utilization.

Dr. Hillman asked whether the plan will be disbursed further to other consortia beyond the therapy group. Dr. Prindiville responded that it was specifically limited in FY 2007 to the therapeutic trials but broader input will be sought from the Cooperative Group chairs regarding expansion in future years.

Dr. Heidi Nelson, Fred C. Anderson Professor, Division of Colon and Rectal Surgery, Department of Surgery, Mayo Clinic Foundation, wondered about the difference between low-volume sites for a high-volume disease versus rare disease. Dr. Prindiville said that this issue of low volume sites does not apply to rare tumors which no single site can have a high volume of patients.

Dr. Michael P. Link, Lydia J. Lee Professor in Pediatric Oncology and Chief, Division of Pediatric Hematology/Oncology, Stanford University School of Medicine, asked about limits to the number of accruals to supplement more complex trials with a reasonable reimbursement rate. Dr. Prindiville indicated that this issue is being considered. Dr. Doroshow said that the NCI is not considering an adjustment based on complexity that would involve decreasing accruals. Dr. Stephen S. Grubbs, Chief of Oncology, Medical Oncology Hematology Consultants, said that his CCOP has seen an increased efficiency in resources through its support of high-volume investigators.

Dr. Grubbs suggested that posting the cancer control trials on the CTSU Web Site would benefit all of the CCOPs.

Dr. Edith A. Perez, Professor of Medicine, Division of Hematology/Oncology, Mayo Medical School, and Director, Breast Cancer Program, Mayo Clinic Foundation, said that a common path to reimbursement for Phase II consortia and Cooperative Groups alike would be helpful.

Dr. Perez said that, in terms of a budget per study, the issue of "what is standard of care" continues to be raised and should be addressed.

Dr. Daniel J. Sargent, Director, Cancer Center Statistics, and Professor, Division of Biostatistics, Mayo Clinical College of Medicine, Mayo Clinic Foundation, asked about the number of reviews that are expected for trials that include QOL elements and whether delays would occur as the result of these additional reviews. Dr. Prindiville clarified that the Symptom Management Subcommittee would not assume primary responsibility for reviewing those studies; the review will occur through the specific DSSCs with liaisons from the Symptom Management Committee also on the DSSCs.

Dr. Sargent wondered whether, as an alternative to working with the CTSU, the SPOREs and the Cancer Centers could link with other Cooperative Groups that have well-established mechanisms for performing data collection and management. Dr. Doroshow referred the question to Dr. Abbruzzese, who indicated that a final decision has not been made about using the CTSU; he said that the goal is to create a harmonized system in an efficient way.

IV. INVESTIGATIONAL DRUG STEERING COMMITTEE: CAREER DEVELOPMENT LETTER OF INTENT—DR. JAMES A. ZWIEBEL

Dr. James A. Zwiebel, Chief, Investigational Drug Branch, CTEP, DCTD, discussed the Career Development Letter of Intent Program (LOI) for Young Investigators. The CTEP Therapeutics Development Program involves Phase I, II, and III trials and encompasses a number of programs and consortia. Some of these include the Adult U01 Phase I program, Pediatric Phase I Consortium, N01 contracts (Phase II), Phase II Consortia, and CNS consortia. Other nonfunded resources, such as Cancer Centers and SPOREs, allow investigators to carry out Phase I and II clinical trials. Additionally, the Cooperative Groups and the CCOPs carry out both Phase II and III studies. The current program involves agreements with approximately 80 industrial partners for more than 140 investigative new drugs (INDs); the exploration of investigational agent combinations that are driven by both medical need and scientific opportunity remains a high priority.

The Therapeutics Development Program provides important career development opportunities for academic investigators and particularly for junior investigators. It allows them to lead clinical trials that would carry out development plans for NCI-sponsored agents, many of which are directed toward new cancer targets. It enables them to perform correlative studies to characterize the effects of new agents on the targets through biopsies and suitable assays, as well as with functional imaging. It is expected that this will lead to the development of new scientific insights into drug mechanisms and determinants of response.

The CTEP receives requests for IND agents in the form of an LOI, which may be solicited by the NCI or submitted through an investigator-initiated process (i.e., unsolicited). The LOI should include basic elements, such as a rationale, trial design, documented accrual, source of support for clinical trial and correlatives, and other relevant information.

The criteria used to evaluate an LOI range from the strength of the scientific rationale and supporting preliminary data to the appropriateness of patient population, adequacy of study design, quality and relevance of laboratory correlatives, and ability to accrue and complete a study in a timely manner. Additionally, there must be consistency with the CTEP development plan, an available agent, concurrence from an industry sponsor, and not be duplicative of existing trials. The review process is conducted through the CTEP protocol review committee on a weekly basis, and involves all CTEP branches: clinical investigations, investigational drug, biometric research, clinical trial monitoring, pharmaceutical management, and regulatory affairs. The process is highly competitive with approximately 400 LOIs

received each year, of which one-third are approved. Young investigators must compete with experienced Principal Investigators (PIs) and thus require mentoring, support, and a competitive edge.

The Career Development LOI Program aims to facilitate career development in translational cancer research through four components. 1) **Outreach to young investigators** involves education regarding CTEP and components of a successful LOI. The NCI has held sessions about the CTEP and the LOI review process at the ASCO annual meeting. To facilitate LOI development, investigators are encouraged to interact with CTEP staff during the development and review process. 2) The **prioritization of solicited LOIs** is important, as the CTEP often receives multiple proposals that are of similar quality in an approvable range. In this situation, the study would be awarded to a young investigator who had submitted the LOI through this program, thus providing a competitive advantage in the review process while supporting the careers of young investigators. 3) To promote **mentorship and institutional support**, the CTEP requires that a senior faculty mentor be identified for the young investigators and that clear institutional commitment exists to provide the resources needed for the study, including research nursing, data management, statistics, and access to patients. Through this process, the LOI prioritization should provide greater incentive for institutions to provide support to their junior faculty. 4) **Submission requirements** include the use of a CTEP-held IND, junior faculty who is within 7 years of completion of training and has demonstrated a major interest in clinical research, an institution with a track record with investigational agents, and the identification of a senior faculty member to serve as a mentor and provide expertise and oversight in the design and the conduct of a particular trial.

Dr. Zwiebel said that the resources and costs to the CTEP are minimal. CTEP staff members are involved with outreach efforts. In addition, modifications made to the CTEP database allow for the tracking of LOIs with junior faculty PIs.

Questions and Discussion

Dr. de Kernion requested clarification regarding the owner of the INDs and the level of support provided to young investigators. Dr. Zwiebel confirmed that the INDs are held by the CTEP and said that young researchers are given priority in terms of access to IND agents to allow them to conduct a trial and to be a PI in a study that will enable them to make presentations at meetings and actually add to the literature.

Dr. David R. Parkinson, Senior Vice President, Oncology Research and Development, Biogen, IDEC, expressed the view that, although this is an important step in supporting young investigators, the NCI should consider additional ways to help them gain credibility, such as through advantages in grant review, funding mechanisms, and consideration in the exception pool, as well as linkages with basic science investigators and cooperation among young investigators. Dr. Zwiebel said that programs like the *R01 program specifically aim to assist young investigators in the review process. Dr. Abbruzzese thought that the biggest hurdle to young investigators is obtaining access to the agent and being allowed to conduct the trial; these concerns are being addressed by the proposed program.

Dr. Laurence H. Baker, Chairman, Southwest Oncology Group, and Professor of Medicine, University of Michigan, wondered whether Cooperative Groups could be included in the Career Development LOI program. Dr. Zwiebel said that the groups are an important component and account for approximately one-half of the Phase II trials enrollment. Junior faculty serving as PI on a group trial would also be eligible under the program.

Dr. James L. Wade, III, Director of Medical Oncology, Department of Clinical Research, Decatur Memorial Hospital Cancer Care Institute, and President, Cancer Care Specialists, asked about the ratio of young investigators in the 400 LOIs that were submitted and how many came from individuals versus the Cooperative Groups or Phase I or II consortia. Dr. Zwiebel said it is not yet known how many of the 400

LOIs were submitted by young investigators, but that information now would be captured under the Career Development LOI program. He estimated that 10 to 15 percent of the proposals are submitted by investigators outside the CTEP-sponsored consortia.

V. MINI-SYMPOSIUM: BIOLOGICAL STUDIES IN ASSOCIATION WITH CLINICAL TRIALS—DRS. JAMES H. DOROSHOW, JANET DANCEY, ALEX A. ADJEI, FRED HIRSCH, AND SHEILA TAUBE

Introduction

Dr. Doroshow explained that the CTWG prioritization initiatives intend to establish a funding mechanism and prioritization process for correlative science and QOL studies performed in the context of NCI-supported trials that can be initiated in a timely manner. In addition, they will establish a process to ensure that essential marker and imaging studies associated with clinical trials are performed according to standard protocols and standardized laboratory practices. The initiatives assume that biomarker and imaging studies will increase in importance and complexity, current funding mechanisms are ill-suited to support critical biomarker studies that provide data for Phase III and larger Phase II trials, and QOL studies are particularly difficult to fund in the Phase III context. Separate prioritization criteria for biomarkers and QOL studies will be developed by extramural expert panels. The NCI Program for the Assessment of Clinical Cancer Tests (PACCT) was charged with the responsibility to develop criteria to use for prioritization of funds and for laboratory standardization. An upcoming Symptom Management and QOL Steering Committee meeting will develop companion criteria for CTAC evaluation. With these criteria and commencing with the FY 2008 budget, CTAC will provide advice on the use of new funds for specific trials. The process for the application and the use of these funds is under active development and will be shared with the CTAC in the fall.

Dr. Doroshow explained that in March 2006, Dr. Niederhuber charged the DCTD with developing a biomarker validation trial in lung cancer that would present a paradigm shift and be coordinated with the U.S. Food and Drug Administration (FDA), Center for Medicare and Medicaid Services (CMS), and the pharmaceutical and diagnostic industries such that results would have immediate relevance for clinical practice. This effort was supported by the Cooperative Group Chairs, Lung Cancer Intergroup, C-Path, CTEP, and numerous lung cancer content experts. The mini-symposium provides details of the biomarker study, including its development and budget, protocol, and the study itself. Dr. Doroshow introduced the speakers: Drs. Janet E. Dancey, Senior Investigator, Investigational Drug Branch, DCTD; Alex A. Adjei, Senior Vice President and Clinical Research Chair, Department of Medicine, Roswell Park Cancer Institute; and Fred R. Hirsch, Professor, Department of Medicine and Pathology, University of Colorado Cancer Center. This would be followed by a presentation of proposed prioritization criteria and draft standardization review criteria by Dr. Sheila Taube, Associate Director, Cancer Diagnosis Programs, DCTD.

Phase III Biomarker Validation Study of Second-Line Therapy in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC)

Dr. Dancey provided background context to the epidermal growth factor receptor (EGFR) biomarker study. Retrospective analyses of specimens from EGFR inhibitor trials have been hampered by limited specimens available for analyses, and prospective studies have been limited by sample size and lack of control arm. Despite erlotinib's common usage in the second-line/third-line setting and, its ongoing evaluation in the first-line setting (i.e., following the response to chemotherapy) as well as in the adjuvant study, the utility and actual use of proposed predictive markers has been limited. The trial represents a convergence of interests, including the Oncology Biomarker Qualification Initiative (OBQI), the FDA Clinical Path Initiative on Cancer Biomarkers, NCI-supported initiatives in translational research, and

Cooperative Groups' clinical trial concepts, to assess potential predictive markers of EGFR inhibitor activity in Phase III settings.

EGFR was ranked as the highest or best opportunity as a prototype molecular target with many acceptable outcomes of collaboration. The partners involved in this trial include the NCI, FDA, CMS, academia, Cooperative Groups, and SPOREs, as well as participants from the diagnostic and pharmaceutical industries and the aggregate community. The goal for the development of this clinical trial was to determine the predictive value of the assays for EGFR biological and clinical activity. The markers that were to be used or prioritized for use would be either FDA approved or approvable and showed the strongest associations with the clinical outcomes with these EGFR inhibitors. Results would include the benefit to patients of identifying predictive markers for a clinical therapeutic gain from erlotinib versus chemotherapy, as well as economic evaluation about the potential past savings that would help identify a cost savings for using these diagnostics, and ultimately possible changes in the FDA labeling for the use of the diagnostics in the therapeutics. It also would serve as a model for future studies addressing the predictive biomarkers and therapeutics and provide a prospective generation of tumor and blood specimens for future studies. Two other goals are the potential for cross-validation studies of different technology platforms and a demonstration of trial methodology, feasibility, and logistics for validation studies of biomarker-treatment trials.

Dr. Dancey described the development of diagnostics protocols, clinical trial design, and clinical protocol. The diagnostic protocol development began in 2006 and was led by C-Path and industry partners, along with other companies with an interest in the development of EGFR diagnostic studies. The clinical design development commenced with a series of teleconference calls in the fall of 2006 and a stakeholders meeting in October; the trial design was finalized in January 2007, and the protocol drafting is underway with completion anticipated this summer. The clinical protocol development committee included the Cooperative Groups Lung Cancer Committee leadership, the DCTD, CTEP, FDA, C-Path, and industry partners. Additional support has come through private-public partnerships with pharmaceutical and diagnostic companies.

Clinical Trial Design

Dr. Adjei explained that retrospective analyses suggested that certain EGFR markers may predict those who may benefit in terms of response rate, tumor shrinkage, or survival benefit, and other situations looked like survival benefit and tumor shrinkage. The North Central Cancer Treatment Group believed that a prospective study could answer the question of whether the markers are predictive for response and survival or simply prognostic. The goals of the study were to validate EGFR Fluorescent In-Situ Hybridization (FISH) as a predictive marker for clinical benefit from erlotinib, and to evaluate immunohistochemistry for expression and mutations as predictive markers for erlotinib, the role of RAS mutation as a negative predictive marker for erlotinib, and the role of specific pharmacogenomic and proteomic markers as predictive markers for activity/toxicity.

N0723 (*A Randomized Phase III Marker Validation Study of Second-Line Therapy in Patients with Advanced NSCLC*) is a stratified randomized Phase III marker-by-treatment interaction design to determine whether candidate EGFR biomarkers predict for benefit from EGFR inhibitors in previously treated non-small cell lung cancer (NSCLC) patients. Because erlotinib was approved for treatment and the chemo-comparator pemetrexed was also approved, the Phase III marker trial focused on second line, NSCLC. The patients are FISH tested and stratified into positives and negatives. The patients receive either erlotinib or pemetrexed to determine the primary endpoint, which is progression-free survival (PFS) or the secondary endpoint, which is overall survival. The study is designed as follows:
1196 NSCLC patients with progressive disease and previously treated with platinum chemotherapy will have tumors prospectively evaluated for FISH status to yield 957 evaluable and randomized patients.

Patients will be stratified by FISH status and randomized to erlotinib versus pemetrexed. Investigators and patients will be blinded to EGFR FISH status until disease progression. The primary endpoint of the study is progression free survival was chosen to due to the high probability of cross-over to the alternate treatment, which would likely result in no apparent difference in overall survival. Tumor samples will also be analyzed for EGFR protein expression by IHC and for mutations. Blood samples will be assessed for proteomics profile and for pharmacogenetic markers.

The trial sample size is based on the following assumptions:

- 80 percent (957) of tissue samples will yield FISH assay results
- 30 percent FISH+, (287 patients) 70% FISH- (670 patients).
- FISH (+) Group: 90 percent power to detect erlotinib is superior to pemetrexed with PFS HR > 1.5 (50% improvement or 3.75 versus 2.5 months in median PFS).
- FISH (-) Group: 90 percent power to detect pemetrexed is superior to erlotinib HR > 1.3 (30% improvement or 2.5 versus 1.9 months median PFS).

If it is shown both that erlotinib is superior to pemetrexed in the FISH (+) group, and pemtrexed is superior to erlotinib in the FISH (-) group, then the clinical predictive utility of EGFR-FISH testing will have been established. Two interim and final analysis are planned. The interim analyses will assess for futility/superiority and evaluate prevalence of marker positivity.

The trial also is designed to assess the biomarker correlation with overall survival as follows: with one more year of followup, the trial has a 78 percent power to detect a HR =1.42 (42% improvement or 11.36 versus 8 months in overall survival) in the FISH(+) subgroup in favor of erlotinib; 94 percent power to detect a HR =1.33 (33% improvement or 8 months versus 6 months in overall survival) in the FISH(-) subgroup in favor of pemetrexed. Accrual will be 25 patients per month, with approximately 4 years of recruitment. Tumor assessments by imaging will be done every 6 weeks until progression/death/off study.

Dr. Adjei noted that using PFS as the primary endpoint has the advantage of more events and a faster completion of the trial. Dr. Adjei stated that PFS is minimally influenced by treatment crossover than OS and is acceptable to the FDA if there is independent confirmation of the PD date. On the other hand, PFS poses challenges, however, including a potential bias in unblinded settings, a benefit in PFS may not translate to a benefit in OS, and a standardization of progression evaluations is needed across treatment arms. The benefits of the trial design are that investigators will be able to distinguish prognostic and predictive effects of the markers and establish whether erlotinib confers meaningful benefit over chemotherapy. It also will allow an unbiased assessment of multiple candidate predictive markers.

The trial is coordinated by the NCCTG operations office, with various partners in charge of tumor and blood specimens. A steering committee of relevant stakeholders has been formed to determine additional studies to be conducted on tissue and blood specimens. Procedures for the central pathology review include registration of patient by site to the NCCTG/CTSU, submission of the tumor to Southwest Oncology Group (SWOG)/University of Colorado for EGFR FISH and results within 5 working days to the NCCTG and site, randomization followed by IHC and mutational analysis, and blood-based studies. Dr. Adjei said that the current discussion is to blind patients and treating physicians to the FISH results initially. Patients and their treating physicians may request FISH results at progression to assist with decisions regarding subsequent therapy. A number of retrospective studies will be integrated, including several focused on proteomics, pharmacogenetics, and other exploratory markers.

Selection of NSCLC Patients to EGFR Inhibitors Studies

Dr. Hirsch described a number of biomarker studies that examined molecular predictive factors for the selection of patients. 1) The SPORE project developed a FISH assay for predicting outcome for EGFR inhibitors and a complicated classification system that defines FISH positivity as high polysomy and gene amplification. 2) Two of the large randomized clinical trials comparing EGFR-TKIs versus placebo in lung cancer patients advanced disease and as second- or third-line therapy included retrospective analyses of biomarkers on tumor specimens. The ISEL trial is done with gefitinib, and the BR21 trial is with erlotinib; for gefitinib and erlotinib. Results from these analyses showed a substantial reduction in HR in FISH+ patients. 4) A recent study with the SWOG led by Dr. Avery Herbst with cetuximab given concurrently with chemotherapy or sequentially, the FISH assay predicted a significant difference in outcome with a doubling of the overall survival. Dr. Hirsch noted that these data were presented at ASCO this year.

The criteria for immunohistochemistry generally have not been clear, and most of the studies are based on a data classification system. Dr. Hirsch said his group has performed DAKO and the hybrid score (H score), which uses intensity multiplied with frequency of cells. The ISEL and BR21 studies have shown substantial reduction in HR. The results showed no difference in the protein-negative patients.

A cohort trial conducted through SWOG and with European collaboration that discovered that the FISH markers, when combined with high-protein expression, correlated with a substantial prolongation of median and 1-year survival, and double-negative patients do as good as placebo-treated patients in the two randomized mentioned trials.

Mutations in EGFR have also been shown to correlate with improved outcome with EGFR inhibitor treatment. Most of the EGFR mutations are located through Exon 19 or 21. Several studies have shown clearly the EGFR mutations are associated with better or dramatic response on EGFR TKIs. In the Western population, it has been difficult to appreciate any association to prolonged survival; in the Eastern Asian population, however, the data are associated with prolonged survival.

Dr. Hirsch next turned to practical issues involving the upcoming study. The SWOG and University of Colorado will be responsible for the pathology and some of the biomarker studies; a kit is being prepared to disseminate to sites, which will return specimens to the tissue repository. The first step is to perform a quality control of the specimen to make certain sufficient tumor tissue is available for the FISH or immunohistochemistry or mutation analysis. The slides then will be sent to different assay laboratories for the analysis. The FISH analysis is based on commercial probes that have not yet received FDA approval. The EGFR immunohistochemistry is based on the DAKO kit that is FDA approved. Regarding the reproducibility of the FISH assay, intra-personnel reproducibility studies have been conducted within Dr. Hirsch's laboratory with success of more than 90 percent. The remaining 10 percent or less discordance results from the fact that lung cancer is a heterogeneous tumor even more than most other solid tumors; it is important to identify and read the exact area. Inter-laboratory reproducibility has been realized for head and neck tumors, with 95 percent reproducibility achieved with another independent laboratory. Data from the ISEL and BR21 trials using the same criteria but in different laboratories should reveal further information about the reproducibility of this assay.

Dr. Hirsch noted that in-house reproducibility for the H score system was more than 90 percent. Moreover, inter-observer variability is less than 10 percent for the DAKO study conducted by different laboratories. A remarkably high reproducibility was observed in the proteomic classifier and in the mass spectrometry tests performed independently at several laboratories, with a reproducibility of 97 percent. A significant difference in outcome between the proteomic classifier positive and negative patients with a substantial reduction in H ratio was found in different cohorts, including gefitinib as second and third line

and erlotinib as first line therapy; the Eastern Cooperative Oncology Group (ECOG) plans to pursue this in the upcoming study.

Regarding feasibility of the FISH assay in prospective multicenter clinical trial, there is an ongoing prospective patient selection trial that has screened 172 patients. For 23 patients (or 13%), no material was received. For the materials received, the quality control failures have been 12 percent to date. For the last 50 patients, because this assay is now also suitable for cytology, there have been only 8 percent failures in this study. When the specimen arrived at the FISH laboratory, there was only 1 patient out of 151 for whom FISH results could not be given and 6 patients for whom immunohistochemistry results could not be provided.

Questions and Discussion

Dr. Schilsky asked about procedures that would be put in place to work out the common language across all of the stakeholders. Dr. Dancey replied that the NCI's clinical trial agreement models have been distributed to the diagnostic companies, agreements are in place with the pharmaceutical companies, and additional details will be worked out. The trial will have a steering committee comprised of representatives from all of the stakeholders, and any proposals for additional studies will be brought to the steering committee for review and approval.

Dr. Parkinson suggested that the study would be useful if the tissue were collected in such a way that the specimens could be available and possibly be a basis to approve a new generation of tests about the EGFR pathway.

Dr. Richard Pazdur, Director, Division of Oncology Drug Products, FDA, asked whether the commercial partners are contributing to the funding of the studies. Dr. Dancey said that industry is providing either reagents or kits.

Dr. Wade asked for further information about the history of EGFR inhibitors in light of the dramatic prolongation of PFS in the second line setting of NSCLC comparing two active agents. Dr. Adjei said that there was some concern of conducting a purely biomarker study with no sense of an inherent therapeutic benefit; the idea was to validate the biomarker and prove the hypothesis that EGFR FISH+ patients would respond better to erlotinib than a chemotherapy agent (i.e., pemetrexed).

Dr. Link asked for a definition of success in this trial and noted that different successful outcomes might have little or no relationship with the proposed statistical design. Dr. Dancey replied that the study aims not just to identify the magnitude of benefit of erlotinib versus pemetrexed but to determine whether the diagnostic test could be used to determine what treatment patients should receive. If the trial is successful, the best treatment could be selected for a patient based on the marker results. Dr. Adjei added that, in terms of toxicity of the different antigens, the agents are fairly equivalent. He said that the primary idea is to determine whether a better outcome would result by using this test.

Dr. Abbruzzese wondered about the overall goal to try to identify whether FISH positivity will predict for activity of erlotinib. He also asked what would be lost by limiting the test to EGFR FISH+ and not including patients who were EGFR FISH-. Dr. Lisa McShane, Ph.D., Mathematical Statistician, NCI Division of Cancer Treatment and Diagnosis, explained that two types of trial designs (interaction and enrichment) were considered and several factors influenced the selection of the interaction design, including that: results from the BR21 trial suggested that erlotinib relative to placebo might have activity in everyone; an enrichment design would not be able to assess whether FISH- patients might have had some benefit; and an enrichment design would answer questions about other markers of interest only in the context of the FISH+ patients, which was seen as limiting. Dr. Sargent spoke as a representative of

the study and noted that limiting the study to FISH+ patients would not accelerate the trial, as all enrollees needed to be screened to identify the FISH+ subjects.

Dr. Parkinson expressed the idea that this study could be a basis for approval of the FISH test. He suggested that designs for future studies could aim to move the therapeutic field forward as well as gain insight into diagnostic markers. One example of this might be to characterize lung cancer patients in every way currently possible, save specimens for future study, and as part of a national program begin to explore therapeutics in patients who have been biologically characterized; this might yield information for patients after PFS. He mentioned that studies at Vanderbilt University have found that even blind hypothesis generating proteomics strongly suggests that there are opportunities beyond the EGFR and its physiology.

A discussion ensued weighing the cost of the study versus the benefits and information gained. Dr. Tepper expressed concern about more than $6 M spent on a trial that will result in a 16-day improvement [in the FISH- group] rather than a significant therapeutic impact. Dr. Peter C. Adamson, Professor, Pediatrics and Pharmacology, and Chief, Clinical Pharmacology and Therapeutics, The Children's Hospital of Philadelphia, University of Pennsylvania, echoed this concern. Dr. Hirsch said that a prospective trial is needed to move forward to individualized therapy to have diagnostic tests approved. Dr. Adjei agreed, noting that although the FISH+ group appears to respond well to EGFR inhibitors, it is unknown how the group would respond to other inhibitors. Dr. Sargent said that it is important to view the trial in its entirety and not focus on just 16 days difference in median PFS in the FISH- group; he said that the trial seeks a 50 percent improvement in FISH+. The sample size and proposed difference to be detected in the FISH negative is determined in part by how many patients in total will need to be screened to identify the required number of FISH+ patients. Dr. McShane reminded members that success in this trial is defined as establishing that the marker is useful for identifying patients who will be taking erlotinib. Dr. Horning said that because the pharmaceutical companies involved likely will gain from a positive study, this might be an opportunity to defray some costs through a partnership. Dr. Pazdur stated that it is important to consider the U.S. taxpayer when entering public-private partnerships, particularly the eventual cost of these drugs and reimbursement issues; it is unfair for the taxpayer to pay substantially for the development of a drug and then also have to pay for it with Medicare dollars at a premium price.

Evaluation and Prioritization of Biological Studies in Association With Clinical Trials

Dr. Taube told members that the PACCT Strategy Group Subcommittee was charged with developing a proposal for the CTAC for the criteria that should guide the decisions about the use of the CCCT's possible supplemental funding for essential *in vitro* laboratory and imaging studies in clinical trials. The Subcommittee worked under the following assumptions: 1) the focus would be on Phase III trials; 2) studies must be essential to the main endpoints of the trial and must have been approved and recommended by an appropriate Scientific Steering Committee; and the Divisions, Centers, and Offices would recommend the approved studies to the CTAC and the Clinical Trials Operations Commitee (CTOC) for prioritization and funding.

Dr. Taube explained the difference between integral and integrated tests: an integral test must be performed for the trial to proceed; an integrated study is intended to identify or validate assays or markers and imaging tests that might be used in future trials. Examples of integral tests include those that establish patient eligibility; patient stratification; or patient assignation to a treatment arm. For integrated studies, plans for evaluation of the tests would have been fully and clearly described in the trial protocol with complete statistical sections, and tests would be performed on all cases even though results would not be used to guide decisions in the current trial. Other studies, described as correlative, are used to develop markers, assays, or imaging approaches that are performed in a retrospective fashion; these

studies are exploratory in nature, do not meet the criteria for integral or integrated studies, and would not be eligible for supplemental funding from the CCCT.

The Subcommittee proposed that integral studies should be the highest priority and that integrated studies should be the second priority. Review criteria were developed to assist with allocating limited funds, including the potential to change practice and strong preliminary data relating to the test, as well as interpretation and standardization to possibly help lead to registration with the FDA. There also should be a discussion of the potential for cost sharing. Dr. Taube said that the justification for the request must address all of the categories listed. Weights should not be assigned to categories, and the priority should be based on the totality of the information and the strength of the data.

For integral assays, the proposal is that the assay itself or the imaging mechanism should meet most of the requirements for FDA clearance or approval at the front end, include sufficient precision data and reproducibility data, provide good justification for any cut points, and have sensitivity and specificity data. Specific information is required, including: a description of the test; specimen type(s) and standard operating procedures for collection, handling, and specimen acceptability definition; a statistical design to establish correlation; information about the laboratory that is performing the assay; and handling of discrepant results.

Integrated assays would have less stringent requirements than integral tests, but they must be well characterized, reproducible, and robust. The information required for these assays include: a clear statistical design to ensure that the correlative hypothesis aligns with the intervention trial and sample size/power are appropriate, description of the test, defined specimen type(s) and standard operating procedures, preliminary data on test performance, and information about the laboratory performing the test.

Dr. Taube said that the information requirements are greater than the current practice. This is appropriate because of the focus on high-impact trials and a desire to improve outcomes and for a more efficient and effective transfer to clinical practice. Furthermore, implementation is expected to take time. These standards mean that appropriate expertise is needed at each stage of the review, the community needs to be informed about the requirements, and support is needed for studies to generate required data.

With CTAC's approval of these proposals, a significantly expanded document will be prepared to explain the requirements. The document will be prepared with broad input, and it will define the level of detail that would be required as well as develop formats for the submission. Dr. Taube said that a plan would be developed for dissemination, and that the staff would work the CCCT and CTEP and others to develop the appropriate review plans.

Questions and Discussion

Dr. Hillman suggested an additional criterion for the evaluation purposes: that the applicants provide a description of how they would archive and make available to other researchers the images and specimens on which the assays were based.

Dr. de Kernion said that the development of these criteria might present a good opportunity to obtain input and upfront investment from CMS. Dr. Taube said that the NCI and CMS have had discussions regarding issues related to reimbursements within the trial context.

Dr. Schilsky expressed concern that these criteria might be used in the review of other clinical trials that are not specifically requesting funding for these assays. Dr. Paulette S. Gray, Director, Division of Extramural Activities, said that the NCI will ensure that this does not occur.

Dr. Taube invited members to submit comments regarding the development of a suite of services that will support the development stages of maturing assays; this request for information was recently published in the *Cancer Letter* and also is available in the *NIH Guide*.

Motions. Two motions were presented, seconded, and approved with amendments.

A motion to concur with the proposed prioritization of requests for supplemental funding of *in vitro* laboratory or imaging studies essential to clinical trials and correlative studies was seconded and approved unanimously with the amendment that applications include a description of how archival of specimens and images and their distribution to other researchers would be accomplished.

A motion to approve assay standardization criteria for clinical trials was seconded and approved unanimously with the amendment that the criteria would be employed only for the evaluation of proposals for funding for those assays.

VI. 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.

Activating and Opening Phase III Clinical Trials: A Process and Timing Study. The amount of time taken to develop a new-to-the-world product in most industries has reduced significantly in a decade, from 42 months in 1995 to 24 months in 2005. During this same time period, however, the time to develop new pharmaceutical agents increased from 56.4 months to 144 months. To understand the difference in these industries, their study has been examining the process to establish Phase III clinical trials at selected comprehensive cancer centers (CCCs: the universities of North Carolina, Vanderbilt, and Ohio State, as well as at the Fox Chase Cancer Center), at selected cooperative oncology groups (the Cancer and Leukemia Group B (CALGB) and the Eastern Cooperative Oncology Group (ECOG)), and at the NCI Cancer Therapy Evaluation Program (CTEP). Through a separate funding mechanism, three pharmaceutical companies also have been studied to understand how they conduct Phase III clinical trials. Drs. Dilts and Sandler noted that lessons can be learned from other industries, such as the automotive industry, where Honda studied how to reset its metal stamping die sets quickly through a streamlined setup process and now can stamp out a car body for a different model every 3 minutes, whereas General Motors requires hours to the same task. Their ongoing study is drawing on experiences from other industries to examine the actual steps and time it takes to activate a clinical trial in order to streamline the setup, review, and other processes used for activation. There are three parts to the study: 1) process mapping, 2) process timing, and 3) accrual data.

Process mapping involves extensive visits to each site to document processes, loops, and decisions, by determining 1) what each site says it does, 2) what policies and procedures say it should do; and 3) chart reviews to determine what actually occurs. A process map is created of the reconciled data. They described the study efforts focused on the CALGB, ECOG, Vanderbilt-Ingram Cancer Center, the Ohio University Comprehensive Cancer Center, and University of North Carolina Lineberger Comprehensive Cancer Center. For example, there are more than 481 process steps to activate a Phase III study at the ECOG. This includes more than 420 working steps, 61 major decision points, 26 processing loops (which could significantly impact actual development as they require additional steps), and 13 stopping points.

Cooperative Group studies are able to omit some steps at CCCs; some of these organizations, however, still run the studies through their individual IRBs.

In **process timing**, calendar time is identified for the total process and for each of the major steps; additionally potential influencers of the time are noted. The median time reported for Phase III studies that were evaluated, starting from the concept date, has been 808 days for ECOG and 784 days for CALGB, plus another 120 to 250 days to open it at a Comprehensive Cancer Center. The fastest time was 435 days and the slowest was 1,600 days. They noted that the role of the IRBs had been a specific concern, but their study has found consistently that the IRBs have not been the cause of slowing the activation of studies. A significant reason for the length of time is the number of loops that a study passes through as various individuals and groups (e.g., the study chair, Cooperative Group, CTEP, and CIRB) each performing quality control reviews. They pointed out that the time involved varies depending on the structure of the organization, including its electronic capabilities. From the concept receipt at the CTEP until a trial is opened, the total overall median number of days for the Cooperative Groups between 2000 and mid 2007 was 594 days; the fastest opening occurred in 203 days and the slowest in 1,900 days. The variance in timing poses a problem for doctors who are ready to send patients to trials.

The third step is to investigate **accrual data**. The study has found that between 20 to 28 percent of all trials opened at Comprehensive Cancer Centers result in zero accruals, and more than 50 percent of all the studies opened at these centers result in fewer than five patients accrued to a trial. A close examination of the preliminary data for CTEP trials studies that were open post 2000 and closed by 2006 revealed that accrual goals that were achieved ranged from less than 20 percent (40.5% of studies), between 20% and 90% (15.2% of studies) and greater than 90 percent (44.3%) . An analysis of the timing showed that development time does not statistically significantly affect success as measured by accruals, but it does predict failure—that is, if the trial takes a long time to open, it has a much higher likelihood of not achieving its accrual goals. Drs. Dilts and Sandler said that the question of why this is happening with so many trials is being examined.

They concluded by describing the study's ongoing efforts. Initial visits to the CTEP have been completed, and additional visits are planned. The Fox Chase Cancer Center and its Affiliates Network is undergoing the mapping process. Initial discussions are underway with several pharmaceutical companies.

Questions and Discussion

Dr. de Kernion asked whether the research had considered that there are certain trials that should be done even though they will not work in a given community, state, or country. Dr. Dilts said this issue affects queuing discipline and the chance of accrual goals being met or dropping by 50 percent. The average queue length at one of the studied cooperative groups for 5 years was 75 concepts under development, with 18 activated; this translates into everybody working on a little bit at a time on a of multiple of high priority trial concepts, without a significant number being completed quickly.

Dr. Adamson wondered about the ownership of specific processes as defined during the mapping process. Dr. Dilts said that ownership and accountability were easy to determine.

Dr. Horning asked about the structure of the system, such as potential duplication and redundancies. Dr. Dilts described a number of non-value added activities, including signatures that do not serve to add to the safety or efficacy of a study, paperwork, and reviews that occur because a predecessor in a given position was included in the review process. Another example was that each review entity (e.g., SRC, IRB, , and finance and contract departments) assigns a different number to the same study; Dr. Dilts said that efficient business models use a single part number for tracking and this might be a way to save a

significant amount of time during the review process. He also noted that some individuals assume inappropriate roles in reviews, such as when non-scientists evaluate the science.

Dr. Link asked whether the issue is caused in part by limited personnel or financial resources. Dr. Dilts said that these were contributing factors, other factors were more important in determining the time to open a study.

Dr. Schilsky said that the simulation exercises with the CALGB showed that the CALGB could do very little on its own to expedite the process significantly, but multiple changes throughout the system that could be enacted by many stakeholders could affect deficiencies in the system.

Dr. Abbruzzese pointed out the importance of involving patients in the process to help understand and answer the "why" question. Dr. Dilts agreed, noting that patient advocates can play an integral role in ensuring that a trial will work in a particular region.

Dr. Nelson asked about the extent to which obtaining stakeholder input into a trial concept, and likely amendments that ensue as a result, can slow down the accrual phase. Dr. Sandler said that more than one-half of the studies examined were amended within their first year. Dr. Pazdur reflected on the FDA experience and said that review work can expand as broadly and consume as much time as allowed. Dr. Dilts recommended improving an inefficient system by analyzing how to make it more efficient, determining steps, setting serious deadlines for each step, and enforcing those deadlines.

VII. NCI CENTRAL IRB EVALUATION—MS. JACQUELYN GOLDBERG

Ms. Jacquelyn Goldberg, Head, Central IRB Initiative, NCI, presented a report on the status of NCI's CIRB, including its evaluation results.

Background and Current Initiative Activities. The goal of establishing a CIRB for Phase III multicenter trials is to determine whether a CIRB could reduce the significant local administrative burdens for multisite trials in cancer and to enhance the protection of research participants by providing consistent expert IRB review at the national level before the protocol is distributed to local investigators. The Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) allows for different CIRB models but emphasizes the need for knowledge of a local research context. Ms. Goldberg described two models: 1) CIRB review only, which is appropriate where no local IRB exists, and involves a large expenditure in time and money to understand the local context through site visits, audits, and teleconferences; and 2) CIRB review with a limited local IRB review, in which the local entity can assist with understanding the local context and reduce the expense of site visits. The NCI chose the second model. Both the central and local IRBs share regulatory responsibilities; the CIRB's primary function is the initial and continuing review of protocols, whereas the local institutions consider the local context and provide oversight of local performance. The NCI offers participation in the CIRB free of charge.

The NCI's CIRB model begins with the CTEP's approval of Cooperative Group Phase II or III protocols, followed by CIRB approval. The NCI then sends a group final approval, and the local investigator is notified of the protocol through a routine group activation announcement or a bimonthly e-mail from the CIRB. A local investigator who decides to open a protocol downloads the completed application, protocol, and consent form from the CIRB Web Site and submits documents to the local IRB; either the investigator or the local IRB downloads the CIRB review documents. The local Chair or subcommittee conducts a "facilitated" review for local concerns and makes an approval decision; the CIRB becomes the IRB of record and handles amendments, continuing reviews, and adverse events. This process benefits local investigators, as there is no advance preparation for IRB review at the local site, no time delays for

the next local IRB meeting, and no need to submit subsequent documents for continuing reviews, amendments, or adverse event (AE) reports to the local IRB.(The only exception is that if an AE occurs locally, the local IRB must be notified). To join, an institution's Federalwide Assurance (FWA) is modified to include the CIRB, an authorization agreement is signed, and the composition of the local IRB subcommittee is determined. Investigators are notified and the CIRB is provided with contact information. Ms. Goldberg said that two CIRBs have been established to cover adult and pediatric trials. There currently are 98 adult studies and 46 pediatric studies ongoing; 64 adult and 42 pediatric trials are open to accrual. More than 300 institutions have joined.. More than 5,000 facilitated reviews have occurred. The median turnaround time has been reduced from 13 weeks in 2004 to 12 weeks in 2005 and 10.6 weeks in 2006.

Evaluation Results. The CIRB user satisfaction survey, conducted between December 2005 and February 2006, is a random sample of 114 IRBs participating in the initiative on the adult side. It was divided between smaller (nine or fewer) and larger protocols and used four online survey instruments to target the IRB Chair, the IRB Coordinator, the local PI, and the Cooperative Group Administrator. The response rate was: IRB Chairs, 50 percent; Coordinators, 70 percent; site PIs, 36 percent; and Cooperative Group Administrators, 100 percent.

The local IRB Chair survey revealed that review materials met the local IRB standard for a complete review (93%) and that CIRB materials were used even when a facilitator review was not conducted (83%). Approximately 40 percent of the local IRB Chairs also indicated that their workload remained the same. Regarding the barriers to use at the institution, some Chairs (17%) believed that their local IRBs were unwilling to waive a full board review; others (9%) indicated that oncology doctors were reluctant to participate. Thirteen percent of those surveyed said that IRB staff turnover was a barrier. Overall, 58 percent of the Chairs said they were very satisfied with the quality of the reviews and 83 percent of them indicated that their overall experience that the CIRB initiative was good or very good. They perceived that the CIRB provided a number of benefits, including: expert reviews; standardization and thoroughness of reviews; a reduction in workload, responsibility, and time; a streamlined review process; and better access for patients. Perceived disadvantages included a loss in local control, impact on local administrative processes, and increased workload for the Chair and subcommittee.

The survey of the local IRB Coordinators showed that most (62%) felt that it took less than 6 months to develop standard operating procedures for incorporating CIRB review into their local procedures and 60 percent indicated that it look less than 3 months to accept the first facilitated review. The Coordinators said that the CIRB operations office staff was approximately 70 percent easy to reach, understood requests, and responded in timely and satisfactory ways. Regarding the Web site, 91 percent of the coordinators visited the Web site to retrieve documents and felt that the documents met their IRB's requirements for a complete review. Approximately 20 percent would still use the CIRB materials even if they were not conducting a formal facilitated review for a specific trial. In estimating the time to protocol approval, 80 percent said it took between 2 and 8 weeks to conduct a review without the CIRB; with the CIRB, however, 42 percent stated that the time decreased by 2 weeks or more, 22 percent noted a decrease of less than 2 weeks, and 22 percent indicated no change in time. Additionally, 35 percent of the Coordinators surveyed said that the CIRB participation did not affect their workload. Most of the Coordinators (81%) said that their overall experience with the CIRB initiative has been good to very good.

The local PIs reported that participation in the CIRB encourages them to open more trials than they would otherwise: 78 percent indicated 3 to 5 more trials, and 20 percent said as many as 10 to 20 more trials. In addition, 75 to 85 percent of the PIs surveyed said that CIRB staff were easy to reach, understood requests, and provided satisfactory and timely responses. Eighty percent felt that participating in the CIRB saved them time and effort, and many (65%) indicated a good to very good overall experience.

The Cooperative Group Administrator survey found that 42 percent of the reviews were timely to very timely and 47 percent indicated somewhat timely. The timeliness of outcome letters from the CIRB were shown as: 37 percent, not timely; 26 percent, somewhat timely; and 11 percent, very timely. Approximately one-half of the Administrators noted that the CIRB requests were easily understood, and the other half indicated that the requests were not easily understood.

Additional Evaluations. Ms. Goldberg mentioned three pending evaluations: 1) a barriers analysis, which is an independent survey of group sites assessing 50 group sites with the highest number of open protocols and the reasons for use or non-use of the CIRB at these sites; 2) an economic analysis, comparing average costs of operating a local IRB versus a CIRB, as well as evaluating differences in the level of effort and costs for participating institutions; and 3) a survey of nine pediatric local IRBs to assess user satisfaction and to learn about local infrastructures for using the CIRB

An evaluation review panel has been established and met twice to assess the evaluation plan and review responses after data were collected. Recommendations from the meetings were to survey sites that do not join an IRB and to pursue accreditation rather than put effort into developing a study to evaluate the quality of CIRB reviews. The meetings included a cross section of people from vested groups, such as representatives from ASCO, advocates, administrators, and ethicists.

Future Plans. The CIRB will complete the remaining evaluations and work through the accreditation process. It also will implement an aggressive outreach plan to an estimated 600 institutions that are eligible for participation in the CIRB. Members were encouraged to visit the CIRB's Web Site (http://www.ncicirb.org) for further information.

Questions and Discussion

Dr. Wade asked about information regarding CIRB audits. Ms. Goldberg replied that the CIRB has not been audited.

Dr. Horning asked whether a goal had been set for the median weeks to approval. Ms. Goldberg said that 6 to 8 weeks would appear to be a reasonable time. Dr. Link asked for clarification on the concerns that take 10 or more weeks to address. Ms. Goldberg said that most surround direct patient care issues and typical IRB concerns.

Dr. Schilsky raised concerns about approvals and revisions during reviews to meet different CTEP and CIRB language requirements, particularly regarding the description of risks for specific toxicities. Dr. Horning said that the NCI could offer a great service by providing specific examples of acceptable language. Ms. Goldberg said that discussions are underway to standardize the language, including descriptions of risks. Dr. Abrams described some of the difficulties in translating between medical and lay reviewers and audiences. Dr. Adamson asked whether a review from the CTEP was necessary. Dr. Abrams said that the CTEP review possibly could be foregone, but that it would heighten several issues, including IND responsibility and the level of expertise on the local IRBs, as the CIRB assumes that IND consents have been obtained and submitted appropriately.

Dr. Sargent asked whether data are available to show that institutional participation in the CIRB allows patients to enter trials more quickly. Ms. Goldberg said that this has not been tracked. Dr. Link noted that the CIRB approval precedes the group activation and that this builds in a 10-week delay for institutions that do not use the CIRB. Dr. Abrams said that the use of the CIRB should result in reduced costs for IRB members. He added that the Cooperative Group Phase III protocols now are being posted

within 1 week of reaching the group site, which previously had not occurred so quickly; Dr. Sargent said that he had noticed the same thing and encouraged the collection of data to quantify this outcome.

VIII. CTWG INFORMATICS INITIATIVES UPDATE—DR. KENNETH H. BUETOW

Dr. Buetow presented an update on NCI's work in clinical trials informatics.

Systems Interoperability and Harmonization. There is a complex landscape of different information systems that involves both technical implementations ranging across the cancer enterprise and a tremendous heterogeneity of standards and other components that underpin the biomedicine industry, including HL7 standards addressing health care delivery, DHHS standards, and FDA requirements. One harmonized standard or model is the Biomedical Research Integrated Domain Group (BRIDG), which was released in June 2007. This serves as a common information model, in which data that crosses from the clinical encounter to FDA submission can be shared and represented. The Clinical Trials Management System (CTMS) Steering Committee recognizes that, although the use of a common, single system might be desirable, it is impractical, and so the aim is to focus on interoperability and define a standard to commonly represent the information and share it between systems. Additionally, information technology (IT) vendors are adopting standards to facilitate electronic regulator submissions, and many research institutes already are using these standards to build or expand their clinical trials infrastructure. The caBIG™ Clinical Trials Components employ BRIDG standards.

Case Report Form (CRF) Standardization. The goal of this work is to achieve industry and FDA concurrence on standard CRFs incorporating Common Data Elements (CDEs). The product of this activity will be a library of standardized CRFs, and other relevant standards activities will be leveraged to support this activity. Standard CRF modules will be created in the Data Collection Instrument (eDCI) formats populated with CDEs that can be used in electronic clinical information systems. The CRF module is a collection of variables (or questions) along with their valid values or responses. Dr. Buetow explained that, in this context, harmonization is a process to obtain agreement on the minimum core set of data needed, whereas standardization sets the specific details in a formal manner. An important element of this effort is the recognition of the importance of the underlying structured data to allow answers to be captured in an electronically accessible form.

The strategy encompasses five steps: 1) compile an inventory, starting with the original collection of modules that were developed for NCI-supported studies and are registered in NCI's Cancer Data Standards Repository; 2) prioritize the initial CRF modules for harmonization based on the inventory and feedback from the steering committee; 3) poll the community for additional relevant forms, agree on the core data, and harmonize the CRF modules; 4) solicit input from relevant stakeholders; and 5) obtain approval from stakeholders and finalize the standards. Dr. Buetow mentioned that work is underway in step 2; specifically, 43 forms/templates have been generated as part of the caBIG™ community that are composed of 507 CDEs, and 18 specialized forms related to prevention studies generated by NCI's Division of Cancer Prevention (DCP) have registered CDEs. In addition, Phase III studies supported by the CTEP and the Cooperative Groups have provided 175 different library of forms with almost 7,000 CDEs as part of those forms, with 12 forms and templates dedicated specifically to Phase II resources. Finally, CTMS Theradex-based reporting has yielded 22 forms and templates, as well as more than 300 CDEs.

Clinical Trials Database and Investigator and Site Credentials Repository. Dr. Buetow described the work performed on the content (i.e., data elements), information systems, and process in support of the clinical trials database activity. The caBIG™ CTMS Steering Committee endorsed the systematic reporting of all trials using the Clinical Data Update System (CDUS) core data elements, particularly for protocol- and patient-specific data. The CDUS is used by the CTEP and DCP, and the content of the

reports is similar to the NCI's Summer Curriculum program. An inventory census was performed to determine the current registration and reporting systems, which included the CTEP CDUS system for the large Cooperative Groups and non-Cooperative Group DCTD-supported treatment trials, DCP's clinical trials database, and the caBIG™ Clinical Data System. The CTMS group suggested, with endorsement from the CTOC, that the CTEP CDUS and DCP clinical trials database continue with no changes to their registration and reporting procedures, but that those groups currently not covered by those reporting arenas (such as other Cancer Centers, SPOREs, R01s, and P01s) report and register their trials through existing infrastructure and submit a single regular report to a common infrastructure through the CDUS reporting mechanisms. Protocol registration involves the PI entering a small set of elements—including the protocol title, description, document, and other common data elements—into the NCI protocol portal.

Questions and Discussion

Dr. Sargent asked about investigators' accessibility to the data and the level of protections in place to ensure the integrity of ongoing trials. Dr. Buetow explained that the IT was designed to include appropriate access control and restriction to information. Dr. Sargent stated that, in many Cooperative Groups, staff at the biostatistical center (not the investigator) submits the data, and thus the investigator actually is prohibited from accessing the data.

Dr. de Kernion encouraged the NCI to put requirements in place to ensure that the electronic cataloguing occurs. Dr. Doroshow said that the CTMS Steering Committee will be actively involved to help establish the best process for this.

IX. TRANSLATIONAL RESEARCH WORKING GROUP (TRWG) REPORT—DR. ERNEST T. HAWK

Dr. Ernest T. Hawk, Director, Office of Centers, Training and Resources (OCTR), described the final report of the TRWG. The TRWG evaluated the status of NCI's investment in translational research and provided input on its future direction in an inclusive, representative, and transparent manner. The NCI's "bench to bedside and back" research infrastructure includes programs, such as SPOREs, Cancer Centers, Cooperative Groups, CCOPs, and many other mechanisms. The TRWG focused on early translational research following from basic studies and extending into Phase I and II trials to make use of advances in the knowledge of cancer biology and living systems, respond to the global environment, and take advantage of opportunities while operating under a flat budget.

Several TRWG activities involved the recruitment of leadership and members; review of 11 foundational documents; analysis of the Clinical Trials Working Group (CTWG) process for ideas, challenges, and lessons learned; and development of a Web-based communication plan. The Working Group also obtained public input through roundtables, analyzed NCI's current investments in translational research, and mapped six developmental pathways to clinical goals. Subcommittees were formed to consider issues related to organization and funding, core services, training/workforce, prioritization, project management, and external integration. The TRWG defined translational research as transforming scientific discoveries arising in the laboratory, clinic, or population into new clinical tools and applications that reduce cancer incidence, morbidity, and mortality. The focus was on early translation and examined risk assessment and intervention pathways as a means to achieve clinical goals to ensure that the most promising concepts entered the developmental pathways and advanced to the clinic or to "productive failure." The NCI's translational research funding in FY 2004 was estimated at $1.3 B, or 30 percent of NCI's budget of $4.4 B.

The TRWG report provided a summary vision to build a collaborative and multidisciplinary enterprise, which was tailored to early translational research, providing an essential link from discovery to patient

and public benefit. The key objectives include: improving coordination and collaboration and instilling a culture of goal-oriented management; improving the identification and entry of the most promising opportunities to tailor existing and new funding programs to promote participation by researchers; and enhancing the efficiency and effectiveness for individual projects and many supporting activities. The report described TRWG initiatives that fell under three common themes: coordinated management, tailored funding programs, and operational effectiveness.

Four TRWG initiatives promoted **coordinated management**. One initiative established a coordinated NCI-wide organizational approach to manage the diverse early translation portfolio, reduce fragmentation and redundancy, and ensure that resources were focused on promising opportunities. Another activity identified part of the NCI's budget that was devoted to translational research. In addition, a set of award codes was developed to accurately capture the nature and scope of the early translational research portfolio. A fourth initiative worked to create a transparent, inclusive prioritization process. The proposed approach to prioritization includes broad public input, 10 ideas chosen for detailed analysis, and several concept packages that are reviewed for public comment and used to inform existing NCI initiatives as well as to develop special awards.

Recommendations to **tailored funding programs** included the modification of guidelines for multiproject, collaborative, early translational research awards and improvements to processes and mechanisms for the review and funding of investigator-initiated early translational research. Additionally, the TRWG recommended that Special Translational Research Acceleration Project (STRAP) awards be established to advance a select number of especially promising early translational research opportunities. Other initiatives were to establish a program for joint NCI/industry funding of collaborative early translational research projects that integrate the complementary strengths of all parties and to more effectively and efficiently provide access to and use of some of the translational research assets that the NCI already has constructed, such as the Rapid Access to Intervention Development (RAID), Rapid Access to Preventive Intervention Development (RAPID), and Development of Clinical Imaging Drugs and Enhancers (DCIDE) programs.

Operational effectiveness included building a project-management system involving staff both at the NCI and at extramural institutions to facilitate coordination, communication, resource identification and access, and management of milestone-based progress for multidisciplinary, early translational research projects. Another initiative aimed to coordinate essential core services to reduce duplication and ensure high-quality services for projects and investigators. A third recommendation for operational effectiveness was to improve standardization, quality control, and accessibility of annotated biospecimen repositories and their associated analytic methods. Three other initiatives focused on negotiating intellectual property agreements and agent access, increasing NCI interaction and collaboration with foundations and advocacy groups, and strengthening training programs and career incentives to maintain an early translational research workforce.

The TRWG identified four principles to guide the timeline and budget: 1) organizational and administrative initiatives should be initiated as soon as possible; 2) a prioritization process must be in place before STRAPs can commence; 3) the budget for administration should be kept to a minimum by leveraging existing structures; and 4) the recommended extramural funding program is expected to require less than 1 percent of the NCI budget. Members were told that, in these recommendations, there is no attempt to manage discovery science, which is different from translational science. There is, however, a firm commitment to the vision, and the Working Group strove to identify "responsible" implementation strategies that could be flexible to adjust to the environment. The TRWG intends to publish its six pathways to clinical goals and develop translational research award codes based on these pathways. The TRWG also plans to implement a communications plan for the TRWG Report and convene an internal working group to discuss implementation strategies. Dr. Hawk concluded by

acknowledging the intense work of co-chairs Drs. Lynn Matrisian, Vanderbilt-Ingram Comprehensive Cancer Center, and William Nelson, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University.

Questions and Discussion

Dr. Niederhuber expressed his appreciation for the efforts of Drs. Hawk and colleagues in developing the TRWG recommendations. The STRAP award is an interesting initiative; he noted that several foundations already have shown interest in the mechanism. Dr. Doroshow echoed Dr. Niederhuber's sentiments and thanked Dr. Hawk for his work.

X. NEW BUSINESS— DR. JOHN NIEDERHUBER

Ad hoc Coordination Subcommittee. Dr. Abbruzzese presented a report from the Subcommittee's meeting on the prior evening. The group discussed three goals: 1) harmonization across the NCI infrastructure; 2) recommendations to the clinical trials infrastructure in response to Dr. Dilts' report; and 3) advice to the NCI regarding the implementation of the TRWG recommendations. The Subcommittee agreed to work on the first and third goals initially and wait for Dr. Dilts' final study in the fall before commencing significant work on the second goal.

Other CTAC Subcommittees. Dr. Prindiville said that the Public-Private Partnership Subcommittee currently is being formed; its first task will be to look at the standardization of clinical trials agreement terms. Additionally, an informatics subcommittee will not be formed at the present time. Rather, members from the CTAC will act as liaisons on the NCI's Clinical Trials Management Work Space Steering Committee.

Future Agenda Items. Members with topics of interest for future meetings were invited to contact Dr. Prindiville with the information.

XI. ADJOURNMENT— DR. JOHN NIEDERHUBER

Dr. Niederhuber thanked all of the Committee members for attending.

There being no further business, the 2nd meeting of the CTAC was adjourned at 3:51 p.m. on Wednesday, July 11, 2007.