DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
1st CLINICAL TRIALS ADVISORY COMMITTEE MEETING

Summary of Meeting
January 10, 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 1st meeting on Wednesday, January 10, 2007, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD from 8:30 a.m. – 3:27 p.m. Dr. John Niederhuber, Director, NCI, presided during the meeting.

CTAC Members
John Niederhuber, Chair
James L. Abbruzzese*
Peter C. Adamson*
David S. Alberts*
Kirby I. Bland (absent)
Deborah W. Bruner*
Jean B. deKernion (absent)
Stephen S. Grubbs* (absent)
Bruce J. Hillman*
Sandra J. Horning*
Susan A. Leigh (absent)
Gabriel M. Leung*
Michael P. Link
Nancy P. Mendenhall*
Heidi Nelson*
David R. Parkinson* (absent)
Edith A. Perez
Timothy R. Rebbeck
Carolyn D. Runowicz
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
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. John Niederhuber, Director, NCI, called to order the 1st CTAC meeting. He noted that the CTAC is the first new NCI advisory board to be established in the past decade. He welcomed the Committee members, *ex officio* members, and the public. He then introduced Dr. Sheila A. Prindiville, Executive Secretary of the CTAC, and asked CTAC members to introduce themselves briefly.

Dr. Niederhuber told committee members that they must absent themselves during specific discussions whenever their participation in deliberations on a particular product, program, or other specific matter would constitute a conflict of interest or create the appearance of one. It is incumbent upon each member to advise Dr. Prindiville and abstain from any participation in discussion or action regarding that matter. In light of the current policies governing conflict of interest based on financial holdings of special government employees, which include all members of this committee, the NCI depends on members to voluntarily absent themselves during any and all discussions of matters that could conceivably impact the status of those holdings. The committee members' judgment is trusted in these instances. CTAC members will need to review and sign a conflict-of-interest statement at each committee meeting. Dr. Niederhuber also noted that, by law, a quorum of board members is required for each instance in which a vote occurs in an open session; a CTAC meeting is an open board meeting; a minimum of seven appointed members must be present to voice their votes at today's meeting. New members who are not current members of another NCI advisory board are not voting until they have been cleared by the NCI Ethics Office. Members of the public were welcomed and invited to submit in writing to Dr. Prindiville within 10 days of the meeting any comments regarding items discussed during the meeting. Any written statements by members of the public will be given careful consideration and attention.

Dr. Niederhuber encouraged CTAC members to obtain their NIH photograph identification cards to facilitate their ingress to the NIH campus. NCI staff will be available to assist with this at the end of the CTAC meeting.

II. ETHICS OVERVIEW—DR. MAUREEN O. WILSON

Dr. Maureen O. Wilson, Assistant Director, Deputy Ethics Counselor, NCI, provided the CTAC with practical guidance to adhere to the government laws to which the CTAC members must comply. The Recusal List is a document that indicates what each CTAC member is or is not permitted to deal with as part of the committee. It will be updated by members before the beginning of every meeting, and the information it contains is contingent on what each member has already told the NCI. [1]The document states that "By law, you are prohibited from participating in Committee discussions or action on or relating to any specific party matter involving or affecting any of the following entries: [the name of the entity (including financial interests and covered relationships), the nature of the interest/relationship, and the expiration date for each is supplied by the CTAC member]. You are permitted to participate in general matters discussed at either open or closed sessions involving or affecting any of the above entities." As special government employees—that is, employees of the executive branch—CTAC members are bound by both statutory and regulatory restrictions' conflict-of-interest provisions. A statutory restriction is criminal, and the intent is to ensure that all deliberations are free from conflict-of-interest issues.

[1] (N.B. Members are required to update within 30 days prior to each meeting, however, because the subject matter before CTAC can be so specific, each member is expected to disqualify from discussions if matters have arisen during that 30 day interim from last reporting that would require a disqualification.)

Following the mandates of (part 1) 18 U.S.C. Sec. 208, CTAC members may not "personally and substantially participate" in a "particular matter" in which they have a personal or imputed financial interest if the matter will have a "direct and predictable effect" on that interest. A particular matter involves deliberation, action, or decision. There are two kinds of particular matter: (1) specific party matter, in which the parties are identified, and (2) general matter, which will affect the interests of an identifiable class. The NCI considers each activity that a CTAC member participates in as a particular matter.

Imputed interests include the CTAC member's financial holdings; employment; the positions of office or department or directorate of a spouse; a minor child; a general partner in a firm; an organization in which a CTAC member serves as an officer or director, trustee, general partner, or employee; an entity with which a CTAC member is negotiating for employment or for which there is an arrangement for future employment. A CTAC member has a financial interest if that member or one whose interests are imputed to (such as a spouse or child) may financially gain or lose, depending on the outcome of a particular matter and regardless of the magnitude of the expected gain or loss.

Financial interests encompass employment or outside service as an officer, director, or trustee; a personal business or partnership; stock, mutual/sector funds, options, and retirement plans or accounts; debt; and agreements with prospective employers. All CTAC members will be requested to file a confidential financial disclosure document called the OGE 450. The NCI will identify some of the pertinent information from individuals' curriculum vitae (CV) as well as through Internet searches on committee members' current activities.

The term "covered relationship" describes relationships that do not constitute statutory financial interests, but which may cause a reasonable person to question an employee's impartiality, resulting in what might be called an "appearance problem." This involves: an entity (other than a prospective employer) with which a CTAC member has or seeks a business, financial, or other contractual relationship (e.g., funding or award sources); the interests of a member of the CTAC member's household or a close relative; an entity which a CTAC member's parent, spouse, or child is seeking to serve as employee, officer, director, trustee, general partner, agent, attorney, consultant, or contractor; and any entity for which a CTAC member has served within the last year as officer, director, trustee, general partner, agent, attorney, consultant, contractor, speaker, or employee. In this last category, once a "covered relationship" has ended, the NCI will continue to list the entity on the recusal list for 12 months from the termination date.

The CTAC members were advised that the U.S. Constitution says that "no title of nobility shall be granted by the United States and no person holding any office of profit or trust under them shall accept without the consent of congress any emolument, office, title, whatever from a king, prince or foreign state" (Art. 1, Sec. 9, Cl. 8). This clause affects only those CTAC members who also are members of the National Cancer Advisory Board (NCAB) and means that, while they are members of the NCAB, they may not be employed or appointed to a position for a foreign government.

There are prohibitions on what CTAC members can accept as gifts. Foreign gifts and decorations can be accepted if they are one of the following: medals, badges, awards, and orders of merit from chivalric codes; tangible gift items valued at less than US$ 305; educational scholarship or medical treatment; or travel or expenses for travel occurring entirely outside of the United States. However, gifts may not be accepted if they are given to influence a CTAC member as a Council member, or solely because the individual is a Council member. CTAC members need Agency permission before testifying as experts for another in a matter in which they have participated as a special government employee. Finally, CTAC members are not permitted to use the title or position for charity purposes and cannot solicit from an entity having interests that could be affected substantially by Council activities.

With regard to lobbying and politics, appropriated funds cannot be used to lobby Congress or encourage others to do so. Moreover, the Hatch Act restricts the political activities of special government employees while they are engaged in the performance of official government business.

Dr. Wilson invited CTAC members to contact her or her staff with any concerns about the ethical procedures that they need to follow as CTAC members.[2]

III. CLINICAL TRIALS ADVISORY COMMITTEE: STRUCTURE AND CHARGE—DR. JOHN NIEDERHUBER

Dr. Niederhuber presented the CTAC's structure and charge. The CTAC was established in response to the Clinical Trials Working Group's (CTWG) recommendations that an extramural oversight committee be formed to advise the NCI Director on clinical trials. The approval to charter the committee was official in March 2006, with the authority derived from the Public Health Services Act, as amended (42 U.S.C. 285a-2(b)(7), Section 413(b)(7)). It is governed by the Federal Advisory Committee Act (FACA), as amended (5 U.S.C., Appendix 2).

The goals for today's meeting are to provide an overview of the structure and function of the committee as well as the ethics overview required for all special government employees. In addition, the meeting will review the CTWG report and provide an update of the current status of its implementation, and plan future committee activities.

The Structure of the CTAC. The CTAC is chaired by the NCI Director and is comprised of members who are appointed by the NCI Director based on training, experience, background, and qualifications to evaluate NCI clinical trials programs. Ten members hold concurrent membership on other NCI advisory boards, including the NCAB, the Board of Scientific Advisors (BSA), the Boards of Scientific Counselors (BSC), and the Director's Consumer Liaison Group (DCLG). Fourteen members represent the broad clinical trials community. Disciplines represented include medical, surgical, gynecologic, urologic, radiation, and pediatric oncology; pharmaceutics and biotechnology; and nursing. Other disciplines covered are behavioral sciences, epidemiology, biostatistics, basic sciences, and patient advocates. *Ex officio* members include NCI Deputy Directors, the CTWG Chair, the Director of the Division of Extramural Activities (DEA), an NCI intramural clinical scientist, and representatives from the Food and Drug Administration (FDA), the Centers for Medicare and Medicaid Services (CMS), the Department of Defense (DoD), and the Department of Veterans Affairs (VA). The CTAC members who are also Board members will serve for the duration of their term on their respective advisory boards; other CTAC members will hold variable terms that range from 1 to 4 years. There will be approximately three CTAC meetings per year, and the Committee will establish subcommittees and working groups as needed.

The Charge of the CTAC. The CTAC is charged with providing advice to the NCI Director about the entire NCI Clinical Trials Enterprise. Dr. Niederhuber described six functions of the CTAC in carrying out this charge.

(1) The CTAC is to provide **extramural oversight and advice for the implementation of the CTWG recommendations and initiatives**. Its oversight, review and advice transcends the entire NCI, including the intramural program, Cancer Centers program, Specialized Programs of Research Excellence (SPOREs), and Cooperative Groups. The Committee is responsible for oversight of new NCI clinical trials informatics infrastructure, as well as the long-term clinical trials restructuring process that requires ongoing refinement.

[2] NCI Ethics Office 301-496-1148

(2) The CTAC will provide **strategic advice regarding NCI's entire clinical trials portfolio**, including resources associated with clinical trials. The NCI clinical trials' responsibility includes but is not limited to trials in prevention, control and therapy. This function includes the assessment of the funding distribution for clinical trials across the NCI. It also encompasses the review of disease-specific clinical trials portfolios across the Institute.

(3) The CTAC will advise on the **use of new correlative science and quality of life (QOL) funds**. It is noted that there are limited funding mechanisms for correlative science and QOL studies in association with clinical trials. There is a need to establish a funding mechanism and prioritization process to ensure that the most important correlative science and QOL studies can be initiated in a timely manner. The CTWG report recommended that the NCI establish a separate budget line item for these studies with the CTAC providing the final review. Dr. Niederhuber explained that the Trial Assigning Individualized Options for Treatment (TAILORx) study design is an example of NCI's integration of correlative science using genomics and proteomics in clinical trials. The NCI expects further integration in future trial designs.

(4) The CTAC will develop **recommendations for additional refinements to the NCI-supported clinical trials system** based on analyses conducted as part of the implementation of the CTWG plan. Activities under this function include clinical trials operational efficiency evaluations of Cooperative Groups, Cancer Centers, and Cancer Therapy Evaluation Program (CTEP); a financial analysis of Phase III trial costs; and an evaluation of the Central Institutional Review Board (CIRB) function.

(5) The CTAC will advise on the **formal evaluation of the impact of the restructuring plan**.

(6) The CTAC will provide a **forum for the clinical trials community to give advice directly to the NCI Director**. CTAC is dedicated exclusively to clinical trials, and it broadly represents all stakeholders in the clinical trials enterprise.

Questions and Discussion

Dr. Richard L. Schilsky, Professor of Medicine and Associate Dean for Clinical Research, Biological Sciences Division, University of Chicago, requested clarification regarding the authority of the board, as Dr. Niederhuber is the Chair of the CTAC whereas other NCI advisory boards, such as the NCAB and BSA, are chaired by members of the extramural community and those boards provide advice and recommendations to the NCI Director. Dr. Niederhuber responded that all FACA-established boards are advisory. The counsel imparted by the advisory boards is listened to carefully, discussed further by senior management, and implemented as feasible.

Regarding the Chair of this board, it was thought that having Dr. Niederhuber initially serve in the position would send a strong message about the NCI's commitment to clinical trials activities. Dr. James H. Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), agreed and added that the CTAC provides a remarkable opportunity for the clinical trials community, a way to continually update and oversee the activities that have been proposed and their implementation. The CTAC's regular meetings will allow the NCI to make mid-course corrections that will be essential to the long-term health of the clinical trials activities of the NCI. Dr. Niederhuber noted that the Clinical Trials Operating Committee (CTOC), which is an NCI internal committee that Dr. Niederhuber also chairs, provides input at a more specific operational level. Dr. Paulette S. Gray, Director, Division of Extramural Activities, clarified that the CTAC must adhere to FACA regulations; this means that CTAC discussions that occur during open sessions must be approved and accepted by this board before being given to the Chair. Dr. Schilsky offered the comment that, because Dr. Niederhuber is the Chair, an issue that the CTAC approves could be perceived as something that Dr. Niederhuber and the NCI endorses, rather than a

recommendation made to the NCI by an advisory board that is chaired by an individual from the extramural community. Col. (Ret) James E. Williams, Jr., U.S.A., M.S., S.P.H.R., Jim Williams and Associates, echoed this idea, observing that the perspective from the community is probably more important about this new board than other boards; he recommended that the NCI Office of Communication handle the issue with sensitivity. Dr. Niederhuber said that the relationship of the board and the leadership of the board to the Director are important, and the proper care will be given to the issue. Once the CTAC is fully solidified and functional as a board, the structure of the committee could be changed to conform to the structure of the other boards.
Dr. Schilsky asked about the committee's and the general community's input to the meeting agenda. Dr. Prindiville explained that the agenda is set with the Executive Secretary in consultation with the Chair, who incorporates the members' opinions and ideas. A CTAC Agenda Working Group could be established if the committee felt it to be of interest. Dr. Niederhuber added that several of the other advisory boards have such a working group. Part of the CTAC's agenda will be driven by the work that percolates through the CTOC.

Dr. Timothy R. Rebbeck, Professor, Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, requested clarification regarding the overlap or relationship between this board and the existing boards. Dr. Niederhuber replied that there will need to be a liaison among the boards, and the NCI will ensure that the proper communication occurs.

IV. DIRECTOR'S UPDATE—DR. JOHN NIEDERHUBER

Overview of the NCI Budget. Dr. Niederhuber provided an update of the NCI budget, starting with where the NCI was at the end of fiscal year (FY) 2006. The NCI experienced a mid-year increase of almost $4 M in taps for utility costs. The end-of-year R01 payline reached the 12th percentile, and the *R01 payline was at the 18th percentile. Approximately 15 percent of the competing pool was reserved for exceptions, and Type 5s (i.e., noncompeting grants) generally were 2.35 percent below the commitment of record. Additionally, SPORES were about 6.1 percent below, the Cancer Centers were 3.9 percent above, and training was 1 percent above the FY 2005 levels.

Dr. Niederhuber next explained how the FY 2007 operating budget has been developed, despite that the annual appropriation has not occurred. The NCI's FY 2006 obligations were $4.79 B. The FY 2007 President's Budget was $4.753, a difference of -$36 M, or a -0.8 percent change between the two years. Dr. Niederhuber described additional budgetary line items. He noted that it is not known if either the potential NIH Director's transfer of up to 1 percent or a potential Department of Health and Human Services (DHHS) Secretary's transfer will occur. In FY 2006, the DHHS Secretary required a $3 M contribution from the NCI for support to CMS. The NCI's contribution to the NIH Roadmap increased by $14.5 M, and it is estimated that NIH taps and assessments will increase by $20 M from FY 2006 levels. Moreover, NCI-wide requirements include an estimated $7 M for mandated salary increases and $10 M for increases in rent, leases, and utilities. The NCI also contributes to trans-NIH initiatives, including the Genes and Environment ($7.8 M) and the Pathways to Independence Career Program ($1.8 M). A total of $25 M has been allocated for the NCI Director's Reserve to meet emergencies. Based on these anticipated needs, the projected budget was close to -$123 M. The Executive Committee (EC) and NCI Directors worked closely with Dr. Niederhuber to deal with this potential deficit; together they identified $175 M from projects being closed and reductions to ongoing NCI programs. The net available for new initiatives and expansions totals $52 M. However, if Congress applies a 1 percent across-the-board reduction, that amount becomes $4.8 M.

Dr. Niederhuber showed a chart that illustrated the NCI's Congressional Appropriations from FY 1998 to FY 2007. He pointed out that the flat anticipated budget of $4.8 B actually is a reduction each year because of inflation. Regarding competing RPGs, the number of awards have remained at a stationary

level, but the number of applications has nearly doubled since 1998. The success rate and payline decrease as the number of applications increases, and this becomes an important factor in determining the budget. Both the NIH and the NCI face the same challenge of maintaining the research enterprise vitality in light of reduced purchasing power and increased demand; each dollar spent is reduced in value by 3 to 4 percent based on purchasing power.

Dr. Niederhuber summarized NCI budget facts for the CTAC. (1) There were 1,280 competing RPGs awarded in FY 2006, down from 1,492 in FY 2004. (2) Across the NIH overall, there were 5,172 RPGs in FY 2006, up from 5,070 in FY 2004. In FY 2005, there were at least 53 NCI grantees who received funds from the Roadmap. (3) The average amount funded per competing grant in FY 2006 was $324,000, down from $346,000 in FY 2003. (4) Seven percent of the competing pool was allocated to RFAs in FY 2006, down from 9 percent in FY 2004. (5) There were 5,679 individual investigators supported in FY 2006, up from 5,636 in FY 2004. (6) The NCI contributed $42.8 M to the Roadmap in FY 2006, up from $16.2 M in FY 2004. (7) In FY 2006, the NCI has $60 M in flexible dollars, compared to $108 M in FY 2005.

Bringing Science to Patients. Dr. Niederhuber characterized the NCI's work as encompassing three "spaces"—biologic, chemical, and translational—and described what the NCI does in each one. He said that the NCI's mission is to help make the whole process optimal for all the parties involved, including the academic community, the private sector, and patients. In the biologic space, the NCI examines signal pathways that become abnormal; the tissue microenvironment, angiogenesis, and cancer-activated fibroblasts; and cancer stem cells and the stem cell "niche." Tumors are looked at as "organs" that are composed of many interdependent cell types that contribute to tumor development and metastasis. In the chemical space, the aim is to learn from the biologic space and discover molecules that can interfere with the pathways that are identified within the biologic space process. The NCI focuses specifically on developing the Molecular Targets Development Program, connectivity mapping, a complete chemical library space, and a chemistry resource to re-engineer molecules. The translational space concerns animal models, first-in-human studies (e.g., targets and biomarkers that inform drug development), and molecular imaging. This continuum is a process that must be supported by the NCI informatics platform as well. Dr. Niederhuber reflected on the needs of various stakeholders in the continuum of bringing science to patients. Patients, for example, want the NCI to find ways to make earlier diagnosis possible, in addition to new treatments for diseases. The private sector seeks assistance in identifying biomarkers to expedite the process of drug development, as well as streamlined and efficient contractual and research processes. The academic community, which works mostly in the biologic space, often seeks help in moving its work into the chemical and translational spaces. The technology platforms in which the NCI works—such as nanobiology, nanotechnology, and imaging—integrate the three spaces.

Clinical Research. The NCI's Clinical Trials Cooperative Group Program is distinctive among NIH-supported clinical trials programs. It includes a clinical trials infrastructure that is continuously available to test new therapeutic strategies. The Program also consists of researchers at institutions affiliated with the Program who jointly develop and conduct trials in multi-institutional settings across state boundaries. Moreover, a flexible research agenda allows changes in strategy in response to surfacing scientific opportunities and new discoveries.

In 2006, the Program included 11 groups, 10 of which focused on adult trials and 1 that focused on pediatric issues. A number of the Program groups address multimodality trials, including: the Cancer and Acute Leukemia Group B (CALGB), the Eastern Cooperative Oncology Group (ECOG), the North Central Cancer Treatment Group (NCCTG), the Southwest Oncology Group (SWOG), and the NCI of Canada—Clinical Trials Group (NCIC-CTG). Specialty groups in the Program include: the American College of Surgeons Oncology Group (ACOSOG), the National Surgical Adjuvant Breast & Bowel Project (NSABP), the Gynecologic Oncology Group (GOG), the Radiation Therapy Oncology Group

(RTOG), the Children's Oncology Group (COG), and the American College of Radiology Imaging Network (ACRIN). Dr. Niederhuber presented a map of the United States that located U.S. clinical trials treatment sites.

The Program supports trials that focus on development of treatment approaches, such as integrating new agents into standard regimens or comparing two or more novel approaches to an accepted standard. Other trials examine multimodality treatments; emphasize the inclusion of correlative sciences, banking tissues, and quality-of-life issues; or study uncommon diseases or less common presentations of common diseases. During the past 7 years, NCI's CTEP-sponsored Program trials have contributed to seven FDA-approved indications for new agents. Moreover, since 2005, NCI/CTEP-sponsored Program trials have played a significant role in three new treatment approaches in oncology.

Dr. Niederhuber presented a financial overview of the Program, including its past funding history and budgetary scenarios for FY 2007. He showed a table illustrating the Cooperative Group Funding from 1998 through 2006, noting that increases occurred as the overall NCI budget increased, and that decreases are occurring as the NCI budget is reduced. Dr. Niederhuber pointed out that, even prior to FY 2007, the funding for Cooperative Groups has been decreased significantly.

The effects of the reduced capitation and infrastructure cuts have resulted in a decrease of patient accrual by approximately 2,600 (exclusive of Community Clinical Oncology Program [CCOP] reductions) as well as the elimination or postponement of trials. There also has been a decrease in the collection of specimens for tumor banks, particularly for CALGB lung cancers and all of GOG's gynecological cancers. Furthermore, the funding reductions will eliminate selected disease committees from the Program, such as sarcoma and head/neck committees in SWOG, as well as eliminate multiple Phase 2 trials in rare tumors.

The overall effect on the Cooperative Group system is that a decrease in staff will encourage the Program members to focus on their core activities and delay collaborative efforts. Several areas of innovation likely will be slowed, including the single electronic data capture system and the single eligibility and randomization system for all Group trials at the Cancer Trials Support Unit (CTSU).

Questions and Discussion

Dr. Bruce J. Hillman, Theodore E. Keats Professor of Radiology, University of Virginia School of Medicine, asked for further information about the Director's Reserve. Dr. Niederhuber replied that in the past years a little more than $100 M was set aside to allow the Director to respond to scientific opportunities that arose as well as to meet special needs. In FY 2006, a much reduced reserve was used to meet emergency taps, increased utility costs, a renegotiated indirect cost for an institution, and a DHHS tap to meet CMS telephone expenses; the Director's Reserve was not used to fund scientific opportunities. Dr. Niederhuber mentioned that the NCI Division and Center Directors have worked together to develop a list of those programs that could be funded from redeployed monies.

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 whether the CTWG's recommended budget was included in the NCI's budgetary analysis. Dr. Niederhuber said that the CTWG's recommended budget is included in the list to consider for funding, but that the NCI is waiting for the authorized FY 2007 budget before prioritizations are made. In response to a further question from Dr. Wade regarding the scope of topics, including the NCI budget and the funding for SPORES versus the Clinical Trials Cooperative Groups, that the CTAC should address, Dr. Niederhuber recognized the CTAC as an opportunity for knowledgeable and respected experts to weigh in, and he encouraged the committee members to do so.

Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, pointed out that the CTWG report said that adequate resources needed to be available to create a more effective functioning system, but that the FY 2007 budget scenario plans for a 10 percent reduction in the Cooperative Group budget; this quandary leaves the CTAC uncertain as to how to respond.
Dr. Niederhuber agreed that the budget creates an awkward position for all of the advisory boards and the NCI, but felt that it was important to provide the CTAC will all of the available information.

V. CLINICAL TRIALS WORKING GROUP REPORT—DR. JAMES H. DOROSHOW

Dr. Doroshow reviewed the CTWG's report on *Restructuring the National Cancer Clinical Trials Enterprise: Report to the NCAB.* The aim in the restructuring was to enhance the best of all the components of the NCI-supported clinical trials system to develop a cooperative enterprise built on a strong scientific infrastructure and a broadly engaged coalition of critical stakeholders.

The report identified three requirements for success.

(1) The tools of cancer biology need to be incorporated routinely into cancer clinical trials. These advances require comprehensive information sharing and close collaboration among basic, translational, and clinical investigators; new resources for real-time integration of molecular analysis tools into clinical trials that will change medical practice; coordinated networks of investigators to allow for the timely completion of trials for patients with specific, molecularly defined profiles who are drawn from larger cohorts; and scientific prioritization to focus investment on specific new targeted agents and the best-designed, scientifically driven clinical trials.

(2) A cooperative, interdisciplinary, efficient, and functionally integrated approach is needed for clinical trials conduct. This includes the integration of the functionally diverse elements of the current enterprise, while improving effectiveness and retaining innovation, as well as the active and ongoing involvement of community oncologists and patient advocates to develop clinical trials appropriate for patients and their treating physicians. Moreover, closer collaboration between NCI staff and the extramural clinical trials community will facilitate the design, prioritization, and execution of trials. The early and vigorous participation of industry and government regulatory agencies will help speed therapeutic development.

(3) An implementation strategy is needed that recognizes the high-value components of the current clinical trials system, and simultaneously challenges them to work together in fundamentally new ways. A successful approach will recognize the essential value of Cancer Centers, SPORES, Cooperative Groups, grant-supported clinical trial investigators, CCOPs, community oncologists, and patient advocates in the current clinical trials process, and simultaneously acknowledge that real progress means challenging each component of the current system to work together in fundamentally new ways. An enhanced commitment by the extramural community to the increased effort and responsibility is required to assist the NCI more broadly in governance of the entire cancer clinical trials enterprise. Finally, a formal system must be developed to evaluate and measure the impact of the restructuring initiatives.

Five common themes of the restructuring plan will improve the work of the clinical trials:
(1) coordination, which aims to coordinate clinical trials research through data sharing and providing incentives for collaboration; (2) prioritization/scientific quality involves all stakeholders in the design and prioritization of clinical trials that address the most important questions, using the tools of modern cancer biology; (3) standardization works to standardize information and technology (IT) infrastructure and clinical research tools; (4) operational efficiency uses resources most efficiently through improved cost-

effectiveness and accrual rates, as well as more rapid trial initiation; and (5) integrated management, which aims to restructure extramural and intramural oversight of NCI clinical trials.

Dr. Doroshow next presented details about initiatives being undertaken under four of the five common themes: coordination, prioritization/scientific quality, standardization, and operational efficiency. He noted that Dr. Kenneth H. Buetow, Associate Director, Biomedical Informatics and Information Technology, and Chief, Laboratory of Population Genetics, would discuss IT activities later in the day. The restructuring plan encompasses 22 initiatives organized by the common themes described above. It will take 4 to 5 years to complete, with a majority of initiatives implemented by the end of Year 3 and will be established as routine practice by the end of Year 7.

There are three key coordination activities. (1) One initiative is to establish a comprehensive clinical trials database, which will serve as a critical prioritization and coordination tool. This is to be initiated in Year 1 and implemented in Year 3. It will contain data on all NCI-supported trials, across all funding mechanisms. Data elements will include descriptive information on trial status, clinical trial results, and links to published or presented data. It will use defined access controls and be developed in concert with the cancer Biomedical Informatics Grid (caBIG™). The NCI will review the safety and outcome data. (2) The NCI reward system and academic incentives will be realigned. This will be implemented in Year 2. Collaborations among SPOREs, P01s, early trials groups, and NCI-supported multi-site clinical trials networks will be rewarded, as well as Cooperative Groups and multi-site networks for their participation in trials conducted throughout the NCI-supported clinical trials system. An additional reward will be for NCI-supported programs that move innovative clinical trials forward. Competitive awards will be available for mid-level, non-prinicipal investigator (PI) researchers who play a critical role in collaborative clinical trials. (3) A third initiative, which will be implemented in Year 1, is to enhance coordination with federal agencies. This will increase cooperation between the NCI, FDA, and industry in oncology clinical trials, as well as expand awareness of the NCI-FDA expedited approval process to speed trial initiation. Furthermore, the initiative will work with the CMS to identify clinical studies that address both NCI and CMS objectives.

The prioritization/scientific quality initiatives have the goals of establishing a prioritization system that is transparent and facilitating correlative studies. To make NCI's work in early phase therapeutics more transparent, an Investigational Drug Steering Committee has been created to enhance the design and prioritization of early phase drug development trials. Moreover, a network of Scientific Steering Committees has been developed for the design and prioritization of Phase III trials. This network leverages the current Intergroup, Cooperative Group, SPOREs, and Cancer Center structures, and will hold state-of-the-science meetings. Community oncologist and patient advocate involvement will be increased in clinical trial design and prioritization. In addition, the integration of all Phase II trials into the overall prioritization process will be investigated. To facilitate the inclusion of correlative science in studies, research topics given special consideration will include clinical trial-specific, molecular profile, imaging, and QOL. Priority also will be given for studies integral to the design of the trial, such as an entry criterion. There will be a budget set-aside, as well as timely prioritization and a funding process. Finally, a standards-setting process for biomarker measurements in association with clinical trials will be developed.

Standardization initiatives will focus on creating standard clinical research tools. An IT infrastructure that is fully interoperable with caBIG™ will be established for cancer clinical trials. In consultation with industry and the FDA, a standard Case Report Form (CRF) that incorporates common data elements will be developed. Moreover, a credentialing system for investigators and sites recognized by the NCI and industry will be built, and commonly accepted clauses will be developed for clinical trial contracts with industry.

Operational efficiency initiatives will work to improve cost-effectiveness and accrual rates by restructuring the Phase III funding model, increasing patient awareness and understanding of clinical trials, and increasing minority patient access to clinical trials. Other activities to improve operations include speed trial initiation at sites. This involves reducing institutional barriers to timely trial initiation and promoting the adoption of the NCI CIRB-facilitated review process.

Enterprise-wide initiatives include the creation of the Clinical Trials Committee to advise the NCI Director on the conduct of clinical trials across the Institute. Dr. Doroshow acknowledged the efforts of Dr. Paulette S. Gray, Director, DEA, in facilitating this activity. Another NCI-wide initiative is the development of a coordinated NCI organizational structure to manage the entire clinical trials enterprise supported by the Institute.

Dr. Doroshow presented a chart that illustrated the initiatives as interactive and interdependent. He noted that this is a process of coordination and integration that aims to help the NCI prioritize better and conduct studies more efficiently. The IT infrastructure plays an important role in developing consistency across the NCI and the cancer community.

The 5-year estimated CTWG implementation budget is $7.1 M for Year 1; $20.6 M for Year 2; $28.0 M for Year 3; $28.5 M for Year 4; and $28.7 M for Year 5.

Evaluation and outcome measures have been considered from the onset. To facilitate this, a structured evaluation system will be designed by experienced evaluation specialists, to include a blend of qualitative and quantitative measures and establish evaluations that involve clinical trial experts and structured empirical data. Moreover, a baseline evaluation will be performed as well as periodic evaluations.

In conclusion, 50 years ago, the NCI had the foresight to initiate support for networks of investigators and institutions engaged in clinical trials that could speed the development of new cancer therapies. During the next half-century, with an enhanced commitment of time and scientific expertise from extramural investigators, physicians, and advocates, as well as the new investment called for by this restructuring, it is expected that the NCI—in collaboration with the entire clinical trials community—will lead the process of translating extraordinary advances in cancer biology into the clinical trials that materially improve the outcome of cancer patients everywhere.

Questions and Discussion

Dr. Niederhuber invited Dr. Ernest T. Hawk, Director, Office of Centers, Training and Resources (OCTR), to describe the status of the Translational Research Working Group (TRWG), which is another area that the NCI has identified where its work can make a difference for patients. Dr. Hawk said that all of the Division, Centers, and Office Directors have worked together to identify a pool of funds that could be re-commissioned to implement activities. The process has been participatory and balanced, but also painful. To accomplish this, the NCI has had to cut into some existing programs. In light of the budget situation, the NCI identified important activities to fund, such as the reengineering of the clinical trials enterprise and the TRWG. The TRWG was initiated about 1 year ago with deliberate overlap in terms of the membership, the processes, and the activities with the CTWG because of the importance of the handoff between translational and clinical scientists. The group went through a process of defining what translational research is in that committee, so that it could be defined based on basic science and clinical activities. The TRWG analyzed the processes and created approximately six maps of the steps, the people, and the decisions involved in translational science. The group also conducted a portfolio analysis looking at the entire NCI's translational activities to understand where the work was being conducted and who was involved, as well as the funding and current processes being used. The TRWG has proposed a number of initiatives and will provide a final recommendation to the NCAB in February 2007. The NCI

is working diligently to ensure that the TRWG's recommendations fit with the CTWG implementation plans, as the two areas build on each other in terms of success. Dr. Hawk noted that many CTAC members have participated either on the TRWG itself or in its large roundtables.

Dr. Joel E. Tepper, Professor and Chair, Department of Radiation Oncology, University of North Carolina, North Carolina Clinical Cancer Center, asked for further details regarding the NCI's collaboration with the FDA. Dr. Richard Pazdur, Director, Division of Oncology Drug Products, FDA, answered that the Agencies have been working together for the past 3 years on an ongoing Interagency Task Force that deals with multiple issues of clinical trials, including data management, CRFs, and points projects. This is in addition to several longstanding programs about which the FDA and the NCI meet monthly. The FDA has been involved in the early review of clinical trial protocols, along with the NCI, the industry sponsor, and other stakeholders, such as the Cooperative Groups, to ensure that questions are answered early in the process and a suitable registration program ensues. Dr. Niederhuber remarked on the collaboration occurring in the biomarkers arena through the Foundation of the NIH (FNIH), which involves a consortium of the FDA, CMS, NCI and other NIH Institutes, and industry; the initial two activities are fluorodeoxyglucose-positron emission tomography (FDG-PET) projects focused on the treatment of B cell lymphoma and non-small cell lung cancer (NSCLC).

Dr. Nancy P. Mendenhall, Professor, Department of Radiation Oncology, University of Florida Health Science Center, asked whether the CMS could be engaged in co-funding relevant clinical trials. Dr. Niederhuber responded that, although the CMS is excited about participating with the planning, the actual co-funding of trials likely is not within the CMS budget. Dr. Schilsky said that the CMS has been co-supporting several projects, including colon cancer clinical trials that are utilizing expensive new agents, in which the CMS is committed to support all the patient care costs associated with those studies, as well as the National Oncologic PET registry.

Dr. Deborah W. Bruner, Independence Professor in Nursing Education, School of Nursing, University of Pennsylvania, commented that increasing patient and public awareness of clinical trials is one of the biggest areas that is underserved and underfunded. She wondered what work has been done to enhance minority accrual in clinical trials. Dr. Edith A. Perez, Professor of Medicine, Division of Hematology/ Oncology, Mayo Medical School, and Director, Breast Cancer Program, Mayo Clinic Foundation, noted that the decrease in NCI's budget means that patient accrual, including minority accrual, also will likely decrease. Dr. Doroshow stated that, with the development of the Disease Specific Steering Committees, the NCI communications and information offices will have a better understanding of the studies that exist or are likely to be approved and can assist with patient education about the nature of these trials at an earlier stage in their evolution.

Dr. Pazdur asked about the internationalization of enrollment in clinical trials, particularly for pediatric trials, noting the number of commercial firms that are employing this strategy to increase enrollments and conduct studies in a more expeditious manner. Dr. Doroshow replied that, in the event that U.S. patient volume is insufficient to complete studies in a timely manner, collaboration has been sought with European trial organizations. Mr. Gabriel M. Leung, Executive Vice President, President, Oncology, OSI Pharmaceuticals, said that consensus on trial designs can be difficult to garner when collaborating across borders, especially in terms of intellectual ownership of the design. Dr. Pazdur said that most of the issues appear to be structural rather than scientific and expressed the belief that they could be overcome. Dr. Michael P. Link, Lydia J. Lee Professor in Pediatric Oncology, Chief, Division of Pediatric Hematology/Oncology, Stanford University School of Medicine, agreed that regulatory requirements can pose problems, particularly when trying to obtain certificates that all parties agree to and that comply with patient protection.

Dr. Daniel J. Sargent, Director, Cancer Center Statistics, and Professor, Division of Biostatistics, Mayo Clinic College of Medicine, Mayo Clinic Foundation, observed that the CTAC will need to consider all of these issues—i.e., increased public-private partnerships, the relationship with the FDA, the budget reduction—carefully, across the clinical trials spectrum. Dr. Niederhuber agreed that the dialogue will need to continue, and said that he was pleased that the CTAC was comprised of key stakeholders in the clinical trials arena.

VI. CTWG IMPLEMENTATION PLAN UPDATE— DR. SHEILA A. PRINDIVILLE

Dr. Prindiville provided an update on the CTWG Implementation Plan for 22 interactive and inter-independent initiatives that fall under five common themes: (1) enterprise-wide/integrated management; (2) coordination; (3) prioritization/scientific quality; (4) standardization; and (5) operational efficiency. Members were informed that a 2-page summary of these initiatives was available in their notebooks.

(1) Enterprise-Wide/Integrated Management. The CTWG suggested that: (1) an external clinical trials oversight committee be established to advise the NCI Director; and (2) a coordinated organizational structure be developed within the NCI to manage the clinical trials enterprise. Consequently, a Coordinating Center for Clinical Trials (CCCT) was established in NCI's Office of the Director (OD) in 2006 (http://ccct.nci.nih.gov). The CCCT supports the implementation of the CTWG initiatives in conjunction with NCI's structure, as well as CTOC and CTAC. The CCCT currently is staffed with five full-time employees: a Director, three program directors, and an administrative assistant.

The CTOC is an internal NCI committee established in December 2005 to provide strategic oversight for NCI clinical trials programs and infrastructures. It draws its membership from all NCI Divisions, Offices, and Centers involved in NCI-supported clinical trials (including DCTD, the Division of Cancer Prevention (DCP), OCTR, the Division of Cancer Control and Population Sciences (DCCPS), Center for Cancer Research (CCR), Division of Cancer Epidemiology and Genetics (DCEG), NCI Center for Bioinformatics (NCICB), DEA, and CCCT), and is chaired by Dr. John Niederhuber. It has five primary responsibilities: (1) reviews and prioritizes clinical trial programs proposed by Divisions, Centers, and Offices to coordinate efforts Institute-wide; (2) evaluates organizational infrastructures to reduce duplication; (3) partners with caBIG™ on development and support of clinical trial informatics infrastructure; (4) evaluates all requests for applications (RFAs) and program announcements (PAs) involving clinical trials prior to NCI Executive Committee review; (5) provides guidance on policies, procedures, tools, and so on for prioritization and coordination of clinical trials. During the past year, CTOC has reviewed all RFAs and PAs involving clinical trials. It also has provided input to NCICB on the CTWG informatics implementation plan. It is evaluating the feasibility of modifying clinical trials data reporting requirements for grant funded trials (e.g., R01 and Program Project grants). CTOC has approved minority accrual supplements and is responsible for programmatic and disease-specific portfolio reviews.

Dr. Prindiville showed a chart illustrating how the CTAC provides the primary conduit from the external clinical trials community and advises the NCI Director, whereas the CTOC provides the coordination of clinical trials activities across the institute and receives inputs from NCI's Divisions, Centers, and Offices. The CCCT is the management structure that provides the coordination of these activities as well as supports CTOC and CTAC.

(2) Coordination. Initiatives related to coordination aim to: (1) establish a comprehensive database containing regularly updated information on all NCI-funded clinical trials, which is discussed later by Dr. Buetow; and (2) realign NCI funding, academic recognition, and other incentives to promote collaborative team science and clinical trial cooperation, which involves the modification of award criteria, funding practice modification, and new forms of recognition for clinical trials investigators.

Dr. Prindiville explained that the Cooperative Group review guidelines are in the process of modification to reflect collaboration with SPOREs and Cancer Centers positively. Furthermore, there is a plan to modify SPORE and Cancer Center review guidelines to consider collaboration with Cooperative Groups positively. The funding practice modification evaluates the feasibility of accruing patients to SPORE and Cancer Center clinical trials through NCI's CTSU. Finally, new forms of recognition for cancer clinical investigators include the Cancer Clinical Investigator Team Leadership Award, which recognizes mid-level clinical investigators for exceptional participation in NCI-funded collaborative clinical trials.

(3) Prioritization/Scientific Quality. A number of prioritization and scientific quality initiatives have been undertaken to: (1) establish an Investigational Drug Steering Committee; (2) establish a network of Scientific Steering Committees; (3) enhance patient advocate and community oncologist involvement in clinical trial design and prioritization through representation on Scientific Steering Committees; (4) establish a funding mechanism and prioritization process to ensure that the most important correlative science and QOL studies can be initiated in a timely manner in association with clinical trials; and (5) establish a process for ensuring that correlative science studies conducted in association with clinical trials are performed according to standard protocols and standardized laboratory practices.

Regarding the correlative science and QOL studies, a task force has been established to define prioritization criteria for correlative science studies, as well as a Symptom Management and Health-Related QOL Steering Committee to define QOL prioritization criteria. Moreover, a workshop is being planned to define standards for the development of predictive biomarkers in cancer clinical trials.

(4) Standardization. Initiatives are focusing on informatics infrastructure interoperable with caBIG™; the development of standard CRFs incorporating common data elements; a repository for investigators and site credentials that is recognized and accepted by the NCI, industry sponsors, clinical investigators, and clinical trial sites; and the establishment of commonly accepted clauses for clinical trial contracts. Target clauses include: intellectual property and licensing, publishing rights, confidentiality, ownership of data, and risk and indemnification. A preliminary meeting has been held with representatives from the pharmaceutical industry to discuss standard clauses for clinical trials contracts. A working group will be convened to assess the feasibility and define the approach to this issue.

(5) Operational Efficiency. Initiatives to improve operational efficiency include the restructuring of the funding model for Phase III efficacy trials to create more incentives for more rapid rates of patient accrual. A financial analysis of phase III trial costs has been initiated to identify areas of inadequate funding, where increased financial compensation could significantly improve clinical trial conduct, as well as to identify areas of overlap, duplication or redundancy which, if eliminated, could result in cost-savings. The analysis also will identify best practices for budget allocations and financial management that could potentially be standardized across Cooperative Groups and assess the cost savings that might result from closing sites that accrue very low numbers of patients.

A second initiative was to identify the institutional barriers that prolong the time from concept approval to accrual of the first patient, and develop solutions for overcoming these barriers. Dr. David Dilts conducted an analysis of the steps needed to take a clinical trial concept from the concept phase all the way to protocol initiation, at a Cooperative Group as well as at a cancer center. Dr. Prindiville referred CTAC members to their notebooks for two manuscripts written by Dr. Dilts and recently published in the *Journal of Clinical Oncology* that detail these analyses. More than 350 steps were needed to get a protocol open, with more than 43 major decision points. The median calendar time to activate a Phase III study was more than 2 years. The areas requiring the longest time were protocol development, forms development, and regulatory affairs. Dr. Dilts currently is conducting a similar analysis at another Cooperative Group, looking internally in the NCI at CTEP and other Cancer Centers to gain an overview

of the entire NCI clinical trials enterprise. The NCI hopes that this will form the basis for recommendations to streamline processes and speed up the activation of clinical trials.

A third initiative expands current outreach programs to increase the recruitment of minority populations to cancer clinical trials. The CCCT met with the NCI Clinical Trials Minority Recruitment Working Group, which has representation from all areas of the NCI that are involved in health disparity issues that have an impact on clinical trials. As a result of these meetings, a trans-NCI partnership has been established to propose mechanisms and solicit concepts from minority outreach programs to enhance minority accrual. Funds for this initiative are included in the CCCT budget and totaled $500,000 for FY 2006. Programs that have received supplemental funding include the Cancer Disparities Research Partnership to expand its available trials beyond radiation oncology to include surgical and medical oncology trials; moreover, the Minority Based Community Clinical Oncology Program (MBCCOP) and Patient Navigator Research Program also will receive supplemental funding to evaluate the impact of patient navigators and minority accrual in cancer prevention and control trials capitalizing on the experience of both of those programs. The program is scheduled to expand significantly in FY 2007; it is not certain, however, that the $2 M budget will be available as the NCI is awaiting to receive its authorized budget for FY 2007.

Another initiative developed approaches to enhance the adoption of the Central IRB (CIRB) facilitated review process. An analysis of the barriers to the acceptance of the NCI CIRB has been initiated. Additionally, an analysis of the potential cost savings that would result from the use of the CIRB has been funded.

Dr. Prindiville concluded the presentation with a brief discussion of evaluation and outcome measures. There is a structured evaluation system in place that was designed by experienced evaluation specialists and includes a blend of quantitative and qualitative measures. An external clinical trials expert panel has reviewed the proposed measures. A baseline evaluation will be performed in FY 2007, and periodic evaluations will assess the impact of restructuring.

Questions and Discussion

Dr. Schilsky offered several comments about the results of Dr. Dilts' study, including the many decision points in the process of activating Phase III trials. Moreover, the study found, but has not yet published, there was almost nothing that any one contributor could do to the process that would rapidly accelerate the activation process; however, the modeling suggested that small changes made by all of the individual participants in the process would do so. He encouraged the CTAC to look at the system globally because of the significant interaction among its components, particularly in light of more potential registration trials that involve public-private partnerships and multiple Agencies.

Dr. Sargent requested further information on the plans for the financial analysis of the Phase III costs. Dr. Prindiville replied that some of the analysis has been initiated, looking at NCI's actual costs for Phase III trials. Dr. Judy Hautula, Science and Technology Policy Institute, elaborated that the analysis will focus on how the money given to the Cooperative Groups is spent; the initiative currently is amassing large amounts of data, and it is expected that the analysis will be completed in 6 to 9 months. Dr. Prindiville added that a report will be presented to the CTAC once the analysis has been completed.

Mr. Leung asked about the NCI's approach to Phase III studies, which he said many pharmaceutical companies will fund fully on their own; he later added that the NCI should be careful not to fund a study that primarily answers a question that industry would ask and fund studies to answer. Dr. Niederhuber replied that this has been an ongoing topic of discussion in the NCI. There are some things that fall into the Phase III category that would not be done if the NCI did not put resources into it. Dr. Link said that,

at the 2007 Joint Boards meeting, there was a feeling that pharmaceutical companies who benefit from the NCI's work should fund at least some portion of the studies. Dr. Niederhuber said that this is an issue that the NCI struggles with, particularly with the time commitment and the time that would be lost on negotiating with each individual trial or investigational new drug (IND). He recalled a separate discussion with Dr. Wade regarding a real or perceived bias that occurs when the NCI partners with the private sector.

Dr. Perez made several comments. First, Phase III clinical trials benefit patients if data are available. Second, the NCI has a role in Phase III trials, as pharmaceutical companies will not fund biospecimens collections, QOL studies, or the following of patients for 15 or 20 years to look at long-term toxicities, among other activities.

Dr. James L. Abbruzzese, Chairman, Department of Gastrointestinal Medical Oncology, University of Texas M.D. Anderson Cancer Center, cautioned that more detailed discussions on the potential relationship between the NCI and the pharmaceutical companies are needed before relying on the pharmaceutical industry for an increasing amount of funding for clinical studies. Dr. David S. Alberts, Director, Arizona Cancer Center, The University of Arizona College of Medicine, agreed, noting that clinical trials in Europe that are being co-funded by government and the pharmaceutical industry are asking pedestrian questions rather than creating new science or conducting correlative studies. He posited that large pharmaceuticals need to recognize that the clinical trials engine needs contributions to correlative studies to move properly in the United States.

Mr. Williams wondered about the NCI's lack of control over indirect costs and how academia could be further engaged to deal differently with this issue. Dr. Niederhuber noted that the NCI advisory boards include academic administrators, and that indirect costs cover only a portion of the academic institutions' costs of conducting research and maintaining research facilities. Dr. Schilsky stated that the indirect cost rate that an institution receives is a negotiated rate usually at the level of the university; Dr. Niederhuber added that the indirect rates for NIH Institutes and Centers are negotiated at the NIH level.

Dr. Pazdur said that the FDA is an end user of this information, and excessive collaboration with pharmaceutical firms can be problematic. He noted that drug companies do a good job at developing drugs, but they do not look at targets or diseases as the NCI or other federal agencies do. A further concern is the possible conflict of interest that arises when two federal agencies, such as the NCI and FDA, that are involved in negotiations with a pharmaceutical company present different opinions regarding a specific drug.

Dr. Sandra J. Horning, Professor of Medicine, Stanford Comprehensive Cancer Center, Stanford University Medical Center, asked whether the report discussed academic reward practices or the promotion of team science or collaborative academic work. Dr. Prindiville indicated that this is in the plan for a later time. Dr. Niederhuber added that this issue reaches just clinical research, and that a new model with a number of institutional changes may be needed to effectively satisfy the needs of the people of the country who are investing in it.

Dr. Lawrence Green, Education Network to Advance Enhanced Clinical Trials, requested more information about the NCI's intentions regarding enhancing minority accrual in FY 2007. Dr. Prindiville explained that the budget will depend on 2007 funding, which has not been received yet, and that there are no current plans to cut the programs that were funded in FY 2006.

VII. INVESTIGATIONAL DRUG STEERING COMMITTEE—DRS. JAMES H. DOROSHOW AND PETER C. ADAMSON

Drs. Doroshow and Peter C. Adamson, Professor, Pediatrics and Pharmacology, and Chief, Clinical Pharmacology and Therapeutics, The Children's Hospital of Philadelphia, University of Pennsylvania, described the work of the Investigational Drug Steering Committee. The CTWG recommends that all stakeholders should be involved in the design and prioritization of clinical trials that address the most important questions, using the tools of modern cancer biology. The committee aims to: (1) provide external strategic input into the prioritization of Phase I and II trials for new agents; (2) increase the transparency of the prioritization process; (3) optimize the design of clinical trials to improve the effectiveness of early phase therapeutics; and (4) provide an opportunity to maximize the productivity of NCI-supported early therapeutics through the development of a new forum for interaction among grantees.

The Investigational Drug Steering Committee has the responsibility to look at new strategies or directions for the clinical trials methodology that will incorporate correlative science for early therapeutics. In this way, the committee will help identify gaps in the NCI's drug pipeline. Based on its scope, the group needs to be functionally interrelated with the Disease Specific Steering Committee. It presents a formal way for the NCI to transition from early phase therapeutics to later Stage II and Stage III development, as well as advise in the prioritization of resources.

The committee includes PIs of all NCI-funded Phase I U01 grants and Phase II N01 contracts, representatives from Cooperative Groups, and scientific experts in biostatistics and imaging and radiation oncology, clinical and pre-clinical pharmacologists, other industry representatives, and patient advocates, as well as NCI staff. The committee is chaired by two PIs—Drs. Mark Ratain and David Gandara, and is overseen by a coordination team. The committee has established working groups and both issue-oriented and agent-oriented task forces. The task forces are co-chaired by a member of the Investigational Drug Steering Committee and a representative from CTEP.

Dr. Adamson highlighted the Committee's progress in policies and procedures, particularly regarding the process and timeline for input on drug development plans, which should occur prior to the release of a Letter of Intent (LOI) solicitation and be assigned to a task force as appropriate. A process for the strategic analysis of LOIs involving a review of solicited and unsolicited proposals has been discussed, as have potential mechanisms for reviewing investigators' appeals of LOI decisions. Each task force is charged with advising on and reviewing LOI solicitations, a well as suggesting modifications to the overall clinical development plan.

The two Investigational Drug Steering Committee working groups include: (1) Conflict of Interest and Confidentiality, which uses an approach analogous to the FDA, co-chaired by Drs. Mace Rothenberg and Sherry Ansher; and (2) Scientific Meeting Planning, which assists CTEP in planning the Early Drug Development Meeting, and is co-chaired by Drs. Don Kufe and Dimitri Colevas.

There are three issue-oriented task forces. (1) The Clinical Trial Design Task Force is co-chaired by Drs. Alex Adjei and Michaele Christian. It covers several Phase I topics, including mechanism-based toxicities, such as the issue of first-in-class versus subsequent drugs; combination studies; and optimal biologic dose versus maximum tolerated doses (MTD). Discussions about Phase II have encompassed the improvement of predictive power as well as efficiency. Other topics include randomized trials and other designs, the use of more than one primary endpoint, and designs that incorporate clinical benefit endpoints for new agents. (2) The Pharmacology Task Force, which is co-chaired by Drs. Ned Newman and Jerry Collins, has begun discussions about optimal pharmacologic requirements needed prior to starting a first in human study, such as pharmacokinetic (PK) assay and animal PK requirements,

information on metabolism, pharmacodynamic (PD) assays, and the need for liaison with the Biomarkers Task Force. It is also undertaking issues concerning a central banking repository, which is needed for future pharmacogenomic studies as Phase I and II studies collect extensive toxicity and response data. The CTEP staff is evaluating the cost to initiate and maintain a repository. (3) The Biomarker Task Force is co-chaired by Drs. Michael Grever and Janet Dancey. It will review CTEP guidelines for LOIs and correlative studies, develop a catalog of biomarkers resources, and define a minimal set of criteria for biomarker proposals. A liaison will be established between the Biomarker and Angiogenesis Task Forces.

There are two agent-oriented task forces. (1) The Signal Transduction Task Force, which is co-chaired by Drs. Razelle Kurzrock and John Wright, has assisted CTEP in developing a solicitation for a new agent, ImClone's IMC-A12, a fully human monoclonal antibody to the IGF-1 receptor. (2) The Angiogenesis Task Force is co-chaired by Drs. George Wilding and Percy Ivy. It is reviewing CTEP's portfolio through a gap analysis approach. It is also considering the correlative science that accompanies angiogenesis studies, such as imaging, pharmacodynamic markers, circulating endothelial cells, and circulating/tissue markers. Finally, the task force is working to develop guidelines and approaches to symptom management and side effects.

Questions and Discussion

Dr. Abbruzzese asked whether the CTEP viewed the work that has occurred as being a positive. Dr. Christian replied that it is too early to tell.

Dr. Bruner raised a crosscutting issue in terms of standardized reporting and the toxicities that each one of these individual disease sites or types of committees will examine, particularly in terms of symptom management and side effects; the standardized Common Terminology Criteria for Adverse Events (CTCAE) reporting might miss many patients' concerns, and there has been no standardization of patient reported outcomes (PROs). Dr. Adamson said that this has been raised by the Angiogenesis Task Force. Regarding CTEP's plans on the issue, Dr. Christian noted that many ongoing efforts are working to incorporate PROs more effectively in clinical trials. One example of this is an effort to translate CTC into lay terminology that thus facilitates greater use of CTC.

VIII. DISEASE SPECIFIC STEERING COMMITTEE—DRS. JEFFREY ABRAMS AND JOEL E. TEPPER

Dr. Jeffrey Abrams, Chief, Clinical Investigations Branch, CTEP, DCTD, described the work of the Disease Specific Steering Committee. He was joined by Dr. Joel E. Tepper, Professor and Chair, Department of Radiation Oncology, University of North Carolina School of Medicine, UNC/Lineberger Comprehensive Cancer Center, who provided an update on the progress of the Gastrointestinal Steering Committee. The overall themes of the CTWG's restructuring plan center around an integrated management, enterprise-wide series of recommendations; prioritization and scientific quality issues; coordination and standardization; and operational efficiency. The CTWG recommends that all stakeholders should be involved in the design and prioritization of clinical trials that address the most important questions, using the tools of modern cancer biology.

The Disease Specific Steering Committees are mandated to prioritize Phase III concepts for therapeutic clinical trials, convene state-of-the-science meetings to identify critical questions to prioritize key strategies and future concepts for NCI-supported clinical trials, develop Phase III concepts for new clinical trials using Task Forces, and periodically review accrual and unforeseen implementation issues.

Dr. Adams described the evolving relationship between the groups, task forces, and steering committees.

The Cooperative Group disease committees develop, conduct, and analyze preliminary Phase I and II data that are the basis for generating Phase III concepts. These disease committees address many important logistical issues with industry partners and with other Cooperative Group collaborations. They often submit the Phase III concept to the appropriate task force of the Disease Specific Steering Committee. The role of the task forces is to refine these concepts to help optimize collaborations; in their additional role of examining gaps in opportunities, the task forces discuss Phase II trial results, pilot studies, and the need for additional research. They would decide which concepts to move forward to the steering committee and suggest new concepts to the groups. The steering committee is tasked with prioritizing among multiple concepts and diseases, helping gauge the accrual capacity of the system, monitoring the task force performance, and providing a formal evaluation and approval of Phase III trial concepts.

Currently, there are four subcommittees: gastrointestinal cancer (Co-Chairs: Drs. Joel Tepper and Dan Haller); gynecologic cancer (Co-Chairs: Drs. William Hoskins and Gillian Thomas); head and neck cancer (Co-Chairs: Drs. Arlene Forastiere, P.G. Shankar Giri, and David Schuller), and symptom management and health-related QOL (Co-Chairs pending). Membership for all of the steering committees includes a broad representation from the community of stakeholders, such as Cooperative Groups, the SPOREs, translational scientists, community oncologists, and patient advocates, as well as NCI staff. The subcommittees' activities are overseen by respective co-chairs and NCI's Therapeutic Disease Head, with management support from the CCCT.

The Gastrointestinal Steering Committee holds monthly teleconferences and has conducted two in-person meetings since January 2006. Six disease task forces (colon, esophagogastric, pancreas, rectal-anal, hepatobiliary, and neuroendocrine) are now in place. To date, the committee has reviewed four Phase III concepts and approved one of them pending revisions. Moreover, new task force chairs have been identified and membership is nearly complete. The Pancreas Task Force is planning a state-of-the-science meeting.

The Gynecologic Steering Committee holds regular committee meetings and includes a liaison to the Investigational Drug Steering Committee. Task forces will be formed to focus on ovarian, cervical, and uterine cancers. The committee will review both Phase III and large, randomized Phase II concepts. Three concepts and protocols have been reviewed; one was approved pending revisions. Furthermore, an endometrial cancer state-of-the-science meeting was held on November 28-29, 2006, in Manchester, England. There are possible immunotherapy solid organ transplantations (SOTs) scheduled for late 2007.

The Head and Neck Steering Committee will hold its first in-person meeting in December 2006. The co-chairs include surgical, medical, and radiation oncologists.

The Symptom Management and Health Related QOL Steering Committee will review symptom management intervention studies conducted by the CCOP, as well as develop and review studies with QOL secondary endpoints in the Cooperative Group treatment studies. The NCI planning committee includes representatives from the DCP, CTEP, and DCCPS; the CCCT is planning actively for the launch of this committee. The first in-person meeting is expected to occur at the American Society of Clinical Oncology's (ASCO) annual 2007 meeting. Representatives from this committee will be appointed to the Disease Specific Steering Committee.

The formation of Disease Specific Steering Committees has ensured that community oncologists and patient advocates are now an integral part of the prioritization process through their participation in these steering committees. The full spectrum of NCI clinical trials funding mechanisms is represented, and translational scientists are actively participating. A more rigorous scientific review process also has resulted in substantial changes to trial design, as well as the evaluation of the priority of concepts.

Future goals for the steering committees include a baseline evaluation of the current prioritization process, a plan to evaluate the initial scientific steering committees, and the development of additional disease-specific steering committees beyond the initial set.

Progress of the Gastrointestinal Steering Committee. Dr. Tepper explained that the membership of the Gastrointestinal Steering Committee evolved from a preexisting Gastrointestinal Intergroup that had functioned effectively for many years but had no specific authority or charge. Its membership has expanded to include nine Cooperative Groups: ACOSOG, ACRIN, CALGB, ECOG, NCCTG, NCIC, NSABP, RTOG, and SWOG.

Much of the initial work has been organizational, such as obtaining additional membership from other stakeholders (e.g., laboratory science, advocates, community oncologists, and SPORES); revising all task forces with regard to leadership and increased membership; and establishing two new task forces on hepatobiliary and neuroendocrine. The committee also has been setting up operational procedures, defining responsibilities for members, and integrating newer Cooperative Groups into the mechanism. It currently is allocating the tasks for the co-chairs. Protocol reviews are underway; there has been a high rate of failure for the initial protocols reviewed. This is in part because the role of the task forces has changed, and education has begun to help the task forces obtain a better understanding of their responsibilities.

The Gastrointestinal Subcommittee has begun to expand its efforts beyond the formal charge of looking at Phase III trials. This includes the review of Phase II trials, the coordination of Phase II trial development between multiple Cooperative Groups, the integration of laboratory efforts from outside the Cooperative Group of origin, and the development of a complete listing of all NCI-sponsored Phase II studies. The importance of carrying out these initiatives without destroying the structure of the individual Cooperative Groups was noted.

Questions and Discussion

Dr. Niederhuber asked whether Drs. Tepper and Abbruzzese felt that the NCI was better off for having undertaken this work. Both agreed, noting that the evolution of the Steering Committee reflects how serious everyone takes the charge to conduct the highest quality Phase III trials, despite the resource-constrained environment. Dr. Niederhuber asked how focus and site-oriented groups (e.g., SPOREs) would be used to move into the earlier phase trials, such as Phase I translation or Phase I to Phase II. Dr. Tepper replied that the Steering Committees might facilitate the movement of ideas from the SPORE program into the Cooperative Group mechanism; there have not yet been any specific trials that have come out of the SPORE mechanism in the gastrointestinal area, but it is hoped that this will occur and that SPORE and other investigators will obtain a better idea of what is happening. Dr. Abbruzzese added that a challenge remains regarding how to incorporate SPORE science into the trials either as correlative studies that are added to a Phase III question or that go into a Phase III trial to ask whether an advance is being made. One of the challenges is that some SPOREs sit at the Phase I/Phase II interface and their trials will not be ready for Phase III for several years; it will take time to determine how the SPOREs can be integrated into the Phase III science in which the Steering Committees currently are operating. Dr. Niederhuber said that it is important that the work be translated across the spectrum rather than to have research conducted in "silos" or in isolation. Dr. Alberts provided an example of the SWOG that illustrated the involvement of the SPOREs into the later Phase studies and incorporated correlative endpoints by thinking in a community way about how to design these studies effectively.

Dr. Alberts requested clarification about the care paid to the selection of chairs of the Steering Committees to ensure that there was an adequate broad selection, rather than all clinical researchers or translational experts.

Dr. Mendenhall shared several comments. (1) She applauded the concept of the Steering Committees; noted that U.S. clinical trials industry is not the top in the world; and stressed that the committee rosters should include the people who are familiar with the clinic and understand the feasibility of obtaining an informed consent from the patient and performing clinical trials. (2) She suggested that the NCI "think outside the box" in terms of the endpoints to use, as well as the inclusion of cost and QOL issues.

Dr. Perez commented that, based on the way that the system currently is structured, the NCI-funded activities continue to compete with themselves; she suggested that better harmonization of the kinds of work conducted by the SPOREs, Cooperative Groups, and R01 researchers should be considered.

Dr. Helman asked for an update on ECOG's concept Phase III study after it was disapproved by the Steering Committee. Dr. Tepper replied that the ECOG understood that it needed to restart or revise the concept substantially. Dr. Helman asked if the ECOG experience should be considered as a model for the Cooperative Groups' engagement in the process. Dr. Doroshow answered that the goal is to complete trials as rapidly as possible, and this particular instance was the NCI's first attempt to prevent a duplication of trials. Dr. Adamson expressed alarm at the 80 percent disapproval rate by the Steering Committee; he offered two explanations: (1) a fundamental failure at the group level; and (2) a major disconnect in the vision between the Steering Committee and the Group Committees. Dr. Tepper recognized the concern but said that the rate has changed somewhat as the Steering Committees have evolved. Dr. Sargent added that the rejections are much more public now than previously; he said that he would like to know what the rate is to know if the percent is high. Dr. Abrams explained that the CTEP review system, which has been used for many years, approves one-third of the concepts outright, disapproves one-third, and the remaining one-third are returned for revisions and become approved.

Dr. Horning commented that this mechanism could work independently without influence and promote an effective and valuable partnership; she cited the study that was approved as an example.

Dr. Heidi Nelson, Fred C. Anderson Professor, Division of Colon and Rectal Surgery, Department of Surgery, Mayo Clinic Foundation, pointed out that a primary issue under discussion is how to get harmonization of science from the discovery level of R01s to Phase I and II trials, and ultimately into Phase III trials and clinical practice.

Dr. Bruner recommended that a symptom management and QOL person be included on each Steering Committee. Dr. Prindiville said that the plan is to include a representative from the symptom management committee on each of the Disease Specific Committees. Dr. Abrams added that the committees also will include a liaison back to the Steering Committee for Symptom Control and QOL.

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

Dr. Buetow described the CTWG's work in biomedical informatics and its integration into NCI's larger reengineering activity. His presentation covered the rationale and specific recommendations of the CTWG Informatics Initiatives, the approach to implementation through caBIG™ and a governance structure, and implementation progress and plans.

The CTWG recognizes that a shared foundation of comprehensive up-to-date information is critical for cancer clinical trials, and that this foundation rests on the implementation of IT. Consequently, the CTWG established four related informatics-focused initiatives. (1) A **clinical trials database** would contain regularly updated information on all NCI-funded clinical trials. This would be comprehensive and accessible by the community and provide a single source for NCI's clinical trial data and transparency on the status of clinical trials. It would enhance the ability to mine, compare, and analyze

data across trials and possibly be expanded to include data from other sponsors from the public and private sectors. Moreover, NCI's experience and expertise in the design, development, and maintenance of clinical trials databases would be leveraged. (2) **Standard CRFs** incorporate common data elements in consultation with industry and the FDA. This will reduce the time, cost, and effort used in initiating and executing clinical trials. It also will facilitate the capture of standardized data, as well as enhance the ability to compare and analyze data across trials downstream. The capture of clinically insignificant data will be minimized. The regulatory review process will be facilitated, and NCI's expertise in standardization will be leveraged. (3) **System interoperatibility and harmonization** promotes the establishment of a National Clinical Trial Information Technology Infrastructure that is fully interoperable with caBIG™. This includes the alignment of NCI intramural and extramural applications and databases to facilitate the sharing and exchange of research data; the facilitation of secure and transparent NCI community access to clinical trials data; and the development of a web portal to support clinical research activities, including tools and services (e.g., a study initiation tool) to support protocol initiation activities. (4) An **Investigator and Site Credentialing Repository** that is recognized and accepted by the NCI, industry sponsors, clinical investigators, and clinical trial sites will simplify and expedite the cumbersome trial initiation process. It will enable the rapid communication of changes in the status of individual investigators and sites to sponsors and serve as a means of keeping the investigator community abreast of new trends in clinical trials, including legal, safety, and regulatory changes.

Dr. Buetow next described CTWG's focus on standardization in terms of the informatics and caBIG™ initiatives. caBIG™ is an information network that enables all constituencies in the cancer community—researchers, clinicians, and patients—to share data and knowledge to accelerate the discovery of new diagnostics and therapeutics, and improve patient outcomes. It aims to connect scientists and practitioners through a shareable, interoperable infrastructure; develop standard rules and a common language to more easily share information; and build or adapt tools for collecting, analyzing, integrating, and disseminating information associated with cancer research and care. Dr. Buetow showed this to the CTAC through a cartoon, explaining that caBIG™ takes disparate communities that are spread out geographically and intellectually and puts in place a common infrastructure that allows the various communities and information to join together to create a much stronger whole. caBIG™ is a pilot project that was launched in February 2004 and today includes more than 50 Cancer Centers and 30 collaborating organizations. It has delivered more than 27 software products to the broader cancer community, and preexisting software is being "retrofitted" for caBIG™ compatibility.

caBIG™ activities work across the different cancer domains in clinical trials management, including basic and translational sciences in the integrative cancer research arena. It collaborates with the tissue banks and pathology community to assemble and build tools that support the broader communities, as well as participate in a large and aggressive effort to have a common infrastructure to share and support *in vivo* image analysis. The initiative helps build a standard vocabulary, data elements, and collection instruments, as well as a common architecture. One example of this is the Clinical Trials Management System (CTMS) Workspace, which counters the challenges posed by clinical trial management processes that mostly are highly heterogeneous, disconnected, error-prone, and paper-based. The current cancer clinical research community informatics landscape ranges from large-scale integrated systems to mixes of individual components that may or may not work together to a number of organizational groups that do not have an informatics system. In addition, clinical data integration faces challenges from hospital information management systems, which are not connected to the clinical trials industry, and from the regulatory world. To develop an electronic infrastructure that allows all of these pieces to come together, the NCI began the process of conceptualizing the IT landscape across the entire clinical system. Many components needed to conduct trials were taken into consideration, such as electronic data capture, participant registry, adverse event reporting, life-cycle management, and the infrastructure needed to support external reporting. A number of organizations have been involved with this effort; recently, for example, caBIG™ has worked with the FDA through the Interagency Oncology Task Force to build a

common infrastructure that the NCI, FDA, and commercial and other groups can use for data collection and storage, regulatory reporting, and other needs. Dr. Buetow showed an illustration of the modular, interoperable architecture being used to accomplish this. He noted that more than 50 percent of this infrastructure already has been given to the Cancer Centers. Everything that is being developed in caBIG™ will be fully available by the end of February 2007 to the cancer community at large.

In its recommendations, the CTWG thought that caBIG™ and, in particular, the CTMS Workspace should be leveraged rather than an entirely new infrastructure be created. The initiative could coordinate with the CCCT; establish a formal governance mechanism; and focus on increasing clinical research community participation in both the collaborative definition of requirements and in governance. Best industry practices could be employed to solve complex problems. Dr. Buetow described the governance structure, including the relationships between the CTAC, CTOC, and the NCICB Clinical Trials Informatics Management Team. The CTMS Steering Committee is comprised of 16 clinical trial researchers, 13 informatics specialists, 2 patient advocates, and 12 federal observers.

This project can succeed where others have failed because it has adopted industry best practices centered around a unified process framework. This includes: (1) multidisciplinary project teams comprised of clinical research, informatics, and leadership experts; (2) continuous, structured management of project risks that identify obstacles to the success of the project early and develop formal mitigation/contingency plans for those risks; (3) iterative, incremental development that delivers increasingly functional prototype systems as preemptively as possible; and (4) a focus on underlying architecture that assumes constantly changing requirements for functionality.

Dr. Buetow explained the progress and plans for implementation of activities, starting with the steps identified for the Clinical Trials Database and the system interoperability and harmonization, and including the standardization of the CRF, the development of the Investigator and Site Credential Repository, and the creation of the Study Initiation Tool.

The initiation of the Clinical Trials Database involves documenting the community's requirements for access to NCI clinical trial data—that is, for high-level use cases; developing high-level requirements for searches, analyses, reporting, data sharing, data storage, query performance, and data access, among other needs; evaluating existing intramural and extramural clinical trial databases; and determining the types of trials to be covered. Moreover, policies and procedures need to be established for access controls, security, intellectual property protection, and other issues; design and architecture candidates need to be developed; prototypes should be developed and tested; and the production of the clinical trials database should be commenced.

To ensure the system interoperability and harmonization, cancer research community requirements for data sharing and exchange need to be defined; a comprehensive NCI Clinical Trials Systems Inventory encompassing intramural and extramural systems should be compiled; and information exchange requirements for these systems should be drafted. Policies and procedures are needed for information sharing and the creation of interfaces. Moreover, a strategy should be developed to target interoperability across the NCI-funded cancer clinical trials environment.

The activities needed to standardize the CRF include: the defining of the community's data capture needs; an inventory of NCI CRFs; an estimated degree of standardization; a high-level analysis of NCI CRFs; and the identification and prioritization of NCI CRFs for harmonization. In addition, the development of the Cancer Data Standards repository (caDSR) will need to be assessed for support of standardized CRFs, as well as the Common Data Element curation process. The standardization process will need to be aligned with ongoing FDA and industry efforts to develop standardized electronic Data Collection Instruments (eDCI). Finally, a core library of standardized CRFs will need to be established.

The implementation plan for the Investigator and Site Credential Repository includes the following steps: (1) define cancer research community requirements for investigator and site credential repositories; (2) analyze existing NCI data sources that could serve as a foundation for the credentialing repository, such as CTSU's Regulatory Support System (RSS) or the Federal Investigator Registry of Biomedical Informatics Research Data (FIReBIRD); (3) establish policies and procedures for access controls, security, and intellectual property protection; (4) develop prototypes and conduct testing; and (5) implement the repository and conduct the migration of existing data to the new repository.

The process to implement the Study Initiation Tool will commence after the harmonization and integration components have begun. It will include the development of detailed requirements; the identification and analysis of NCI's intramural and extramural study initiation tools; and the establishment of policies and procedures for access controls, security, and intellectual property protection. Additional activities include the development of the design and architecture candidates, the development and testing of prototype iterations, and the implementation of the Study Initiation Tool.

Dr. Buetow concluded by noting the importance of input received from experts in the industry, including NCI's intramural and extramural communities. He noted that, although the Informatics Initiatives are focused on the four specific activities that he described, the project scope is much larger and includes anything that caBIG™ is doing in the clinical trials arena. The charge is to build a structure that will enable caBIG™ to deliver the maximum value to the NCI and all of the cancer clinical research community.

Questions and Discussion

Dr. Adamson asked when the clinical trials database would be functional. Dr. Buetow answered that it would be available for use in early 2008.

Dr. Rebbeck wondered whether there will be a mandate or a minimum set of requirements for institutions, cooperative groups, or others to use caBIG™ standards. Dr. Buetow responded that there will be a mandate that all groups must report clinical trials information into NCI-designated databases in standard structured forms that will be derived. With respect to the broader deployment of a common infrastructure, the caBIG™ infrastructure has been developed to serve as a bridge or a path from other institutions' systems into the database structure.

Dr. Leung asked whether a formal link or interface with industry currently existed in terms of the rollout of caBIG™; he also asked for clarification about the mechanism to persuade industry to fall in line with the database structure. Dr. Buetow replied that a number of industry participants have worked with caBIG™ in its pilot phase. In addition, the FDA and other industry stakeholders have helped with the building of the regulatory reporting infrastructure through the Interagency Oncology Task Force's involvement in caBIG™. Dr. Schilsky followed up on the theme of harmonization with a question about how caBIG™ can help organizations that are looking at electronic data capture systems—such as the Cooperative Groups, the CTSU, and the FDA—harness their interests and resources and avoid redundancy to develop an efficient, universal electronic data capture system. Dr. Buetow replied that stakeholders should be involved at the time when decisions are made to generate the appropriate technical and operational specifications. It also is important to look at what needs to be built or accomplished in the context of the broader agenda of what exists.

In response to a question from Dr. Mendenhall regarding narrative data versus imaging and archiving of RT objects, Dr. Buetow explained that the CTMS work space itself is not defined formally to contain the

specific definitions of imaging components. caBIG™, however, has made a large investment in building up a parallel infrastructure that supports the collection in structured ways of image-related information.

Dr. Hillman asked whether there were plans to add additional workspaces and how the workspaces will be integrated to abet the clinical trials environment. Dr. Buetow said that no new workspaces have been formally planned for caBIG™, but that it would be helpful if NCI's advisory groups recommended specific additional workspaces. The integration of the workspaces is a complex issue; the informatics group has used services-oriented architecture and a standards-based infrastructure to register information from particular domains. This ensures, for instance, that *in vivo* imaging is not constructed in isolation from CTMS events.

A participant asked about activities that organizations with large, legacy databases, such as the Cancer Centers, should do to feed into caBIG™. Dr. Buetow explained that NCI Cancer Centers and Cooperative Groups already have legacy responsibilities to report key information to the NCI; the NCI's informatics initiative works to synchronize and coordinate that information such that it can either use the groups' current electronic systems and be brought into caBIG™ or the NCI can give those groups the capability to generate or regenerate the information so that it will come into the NCI's system.

Dr. Adamson asked if the cost of the migration from existing databases into this system had been estimated. Dr. Buetow indicated that a formal cost projection had not been completed.

Dr. Tepper asked about the ease of data retrieval from the system and the protection of information. Dr. Buetow responded that the Clinical Trials Database has been structured to be shared with the community. HIPAA restrictions require that some information not be available or accessible. The caBIG™ infrastructure is organized such that the protection of information is incumbent on the people who originally hold the information and then choose to share it out.

Dr. Niederhuber suggested that the CTAC should remain abreast of the work of the Informatics Initiative and caBIG™ progress.

X. NEW BUSINESS— DRS. JOHN NIEDERHUBER AND SHEILA A. PRINDIVILLE

Dr. Prindiville described upcoming activities and solicited feedback from the CTAC regarding whether the Committee would like to consider forming some working groups to facilitate conducting business and take a finer look at some of the issues described today, particularly working groups that focus on collaboration, interaction with pharmacology and biotechnology, and informatics. A Collaboration Working Group, for instance, could focus on harmonizing review guidelines among Cancer Centers, SPOREs, and Cooperative Groups to enhance collaboration, as well as make recommendations on how to foster collaboration among these groups to enhance trial accrual. Recommendations also could be made for shared use of core facilities that exist across NCI clinical trials infrastructure. A Pharmacology/ Biotechnology Working Group could develop a strategy for implementing common contract clauses for clinical trials. An Informatics Working Group could provide indepth review of progress toward the implementation of CTWG informatics initiatives to the CTAC. Additionally, it could interface with the NCICB and the CTMS Workspace Steering Committee.

Questions and Discussion

Dr. Schilsky pointed out that the national clinical trials system actually is a collection of various activities that interface but do not function in a systematic way. He suggested that the CTAC could adopt a long-term goal of helping to develop a series of recommendations and structural changes to allow an NCI-supported system that functions more efficiently.

Dr. Rebbeck said that it would be helpful to hold a discussion on whether standards for bioinformatics and databases are needed. Dr. Prindiville responded that this would be a good task for either the CTAC or a CTAC Informatics Working Group. Dr. Buetow clarified that standards are a critical part of the CTWG's Informatics Initiative; in particular, caBIG™ has been the definition of standards in terms of both data and electronic interfaces. He noted that ultimately, however, the community selects the standards and their implementation rate, not the NCI.

Dr. Wade requested clarification from Dr. Schilsky regarding his reference to one clinical trials system. Dr. Schilsky explained that what is needed is a system that truly functions in a systematic way with better information exchanges and processes to share strategic development plans among levels; he was not referring to a common uniform standard or a network of different Cooperative Groups.

Dr. Sargent advocated that the CTAC should put together two working groups, addressing collaboration and pharmacology/biotechnology interactions, to begin its work; an informatics working group should be pursued but would be informed greatly by ongoing cost analyses. Dr. Niederhuber thought that the CTAC could take on all three areas and called for volunteers to chair each of them. Dr. Gray noted that the Collaboration Working Group will not harmonize review guidelines, as the guidelines for review are established by the NIH and the Institutes; the working group could focus on harmonizing program guidelines governing specific programmatic activities or the review of particular mechanisms. Dr. Prindiville said that before the next meeting, the NCI can define and refine this charge with the co-chairs and describe at the next CTAC meeting what each of these working groups will do.

Dr. Schilsky seconded Dr. Niederhuber's approach to interacting with the pharmaceutical industry; he said that he views the pharmaceutical companies and the Cooperative Groups as complementary rather than competitive, and a thoughtful discussion by a working group could help effect a good partnering.

Dr. Niederhuber favored electronic communications to expedite the creation of the working groups. He also pointed out that the Committee members' books include the schedules of upcoming NCAB and BSA meetings; the CTAC needs a similar schedule, and the NCI will contact the Committee members to identify the date for the next CTAC meeting.

Dr. Prindiville said that CTAC members are welcome to submit agenda items to her via e-mail.

XI. ADJOURNMENT— DR. JOHN NIEDERHUBER

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

There being no further business, the 1st meeting of the CTAC was adjourned at 3:27 p.m. on Wednesday, January 10, 2007.

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Date John Niederhuber, M.D., Chair

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Date Sheila A. Prindiville, M.D., M.P.H., Executive Secretary