DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
5th CLINICAL TRIALS ADVISORY COMMITTEE MEETING

Summary of Meeting
June 25, 2008

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

CLINICAL TRIALS ADVISORY COMMITTEE
BETHESDA, MARYLAND
Summary of Meeting
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The Clinical Trials Advisory Committee (CTAC) of the National Cancer Institute (NCI) convened for its 5th meeting on Wednesday, June 25, 2008, in Conference Room 10, C-Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. Dr. John Niederhuber, Director, NCI, presided during the meeting.

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

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

Executive Secretary
Sheila A. Prindiville, NCI

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WEDNESDAY, JUNE 25, 2008

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

Dr. Niederhuber called to order the 5th CTAC meeting. He welcomed the Committee and *ex officio* members, and then reviewed the confidentiality and conflict-of-interest practices required of Board members during their deliberations. Members of the public were welcomed and invited to submit comments regarding items discussed during the meeting, in writing, to Dr. Sheila A. Prindiville, Director, NCI Coordinating Center for Clinical Trials (CCCT), within 10 days of the meeting. Any written statements by members of the public will be given careful consideration and attention. Dr. Niederhuber also called Board members' attention to the future CTAC meeting dates, which have been confirmed through 2010.

Motion. A motion was made to approve the minutes of the February 4, 2008 CTAC meeting. The motion was seconded, and the minutes were approved unanimously.

II. DIRECTOR'S UPDATE—DR. JOHN NIEDERHUBER

Dr. John Niederhuber, Director, NCI, began by extending an additional welcome to everyone in attendance and especially to those who stayed over from the Board of Scientific Advisors (BSA) meeting, contributing an additional service to NCI.

NCI FY 2008 Budget. NCI is entering the fourth quarter of the 2008 fiscal year. The NCI budget year will end on September 30, with R01 paylines around the 14th percentile and new investigator paylines at the 19th to 20th percentile. As important as the payline percentiles are the number of applications funded at fiscal year end; this number has remained stable over the past 2-3 years and, again this year, approximately 20 percent of applications will be funded.

Dr. Niederhuber discussed current initiatives for young investigators; efforts are being made to ensure that applicants have a solid mentoring program at NCI. Tracking is also being done on the number of young investigators receiving a first renewal; this is a critical point in academic career development. More exception funding—money not spent as rapidly or to the extent originally budgeted that can be reassigned to other areas—is being applied to young investigator initiatives. It is extremely important to attract and retain the younger workforce into a career in academic medicine and particularly cancer research.

Discussions are ongoing internally at NCI on how to manage the grant review pipeline to increase its efficiency and effectiveness. Currently, only about 7 percent of first-time R01 applications are funded with about 20 percent funded after a first round of revisions. Approximately 45 percent are funded following a second round of revisions. Study sections understandably focus on second-round applications; as no further revisions are accepted if these applications are not funded. It would be desirable to have a "biomarker" for identifying earlier-round fundable applications in order to remove them from the pipeline. It has been suggested that more exception funding be devoted to grants to influence the system. So far this fiscal year, using a rigorous review process, approximately 11 percent of the research project grants (RPG) pool of resources has been allocated for exception funding—a typical amount.

In 2008, NCI will be managing a little over 5,000 grants; funding almost 1,300 competing grants; and likely supporting 220 or more new investigator grants. NCI chose to give a 1 percent increase to their Type 5 grants this year; less than a 3 percent COLA, but an increase, unlike in several previous years. The Special Programs of Research Excellence (SPOREs) and the Cancer Centers programs will finish the year with budgets flat with those of 2007. The Cooperative Groups and training programs budgets increased approximately 5 percent.

President's Budget FY 2009. Dr. Niederhuber expects the 2009 budget to improve. Both the House and the Senate have voted on appropriations, both of which look promising. However, in an election year, it is likely that NCI will operate under a continuing resolution for the beginning of FY 2009. It is also possible that with many Government transitions occurring next year, a continuing resolution at FY 2008 funding levels will be put into place for the entire FY 2009, so NCI must do their financial planning for FY 2009 based on FY 2008. NCI's annual 2-day budget meeting is scheduled for the end of July 2008, and during this time the NCI leadership will be looking at the scientific portfolios of each of the Divisions and Centers for opportunities that need to be addressed to develop the scientific agenda. The leadership will be examining the 2008 budget to see what monies are still available that could be redistributed to fund underfunded projects or those that could not be initiated. Dr. Niederhuber noted that there are urgent facility and infrastructure needs. The meeting will also focus on planning for the 2009 operating budget; once again everyone will be asked to reduce their operating budget by 3 percent to cover inflationary increases in expenses. The leadership will look at priorities in order to make good decisions about redistributing resources. The Cancer Centers programs, SPOREs, Cooperative Groups, and CCOPs will not be subjected to the 3 percent decrease and will remain at 2008 allocations.

Thoughts about the Future. Dr. Niederhuber reiterated that NCI is about translation—creating new knowledge and translating that knowledge into improved diagnosis and treatment of patients with cancer. Along those lines, the series of recommendations and implementation strategies generated by the Clinical Trials Working Group (CTWG) and the Translational Research Working Group (TRWG) continue to be instrumental in guiding NCI leadership. Dr. Niederhuber recognized the efforts of both Dr. Jim Doroshow and Dr. Sheila Prindiville for leading the efforts to implement report recommendations.

Dr. Niederhuber discussed how the leadership of NCI serves as a "platform of connectivity" between academic research universities and the private sector, and also to the public and other agencies of the Federal Government, such as the Food and Drug Administration (FDA), Centers for Medicare and Medicaid Services (CMS), Centers for Disease Control and Prevention (CDC), and Department of Defense.

The NCI is increasing its capacity and capabilities in small-molecule screening and the discovery of potential targets. The planning process of the Chemical Biology Consortium has been recently put into place, which increases NCI's capacity to apply chemistry to small- and large-molecule and biologics development. Increased support is also going to the Rapid Access to Intervention Development (RAID) program to meet the increasing needs of NCI relative to new agent development.

Another prominent area of effort at NCI is genomics. This effort includes identifying regions that predict risk in the germline genome, and to then identify within those regions a specific gene or gene mutation that is responsible for increased disease risk. On top of that is the effort to look at the somatic changes in a genome that occur over one's lifetime. The Cancer Genome Atlas (TCGA) pilot study is looking at three tumors—glioblastoma, ovarian, and lung cancer—and will move on to be a major part of the activity of NCI as these various tumors are further characterized. Genome research is part of NCI's underlying platform of discovery to push forward development of novel small and large molecules that can be used to manage a particular disease. It is the responsibility of NCI to provide resources for the academic world, and also for some private-sector individuals, in the development of agents that the private sector is reluctant to develop. NCI is working aggressively with the private sector to bring new agents forward.

Translational clinical research is a high priority for NCI; the NIH Clinical Center is vital to the "discovery" efforts of NCI. An important effort under way is to increase opportunities for the academic community to do early-phase "Phase 0" trials in the Clinical Center. NCI has a third or more of the activity at the Clinical Center, where the Institute carries a lot of responsibility including leading surgery, pathology, and radiation oncology. Dr. Niederhuber noted that he is working with Dr. Stephen Katz of the

National Institute on Arthritis and Musculoskeletal and Skin Diseases to address some of the concerns around the Clinical Center, such as the costs of pharmaceuticals. Dialogue is also ongoing with Walter Reed National Military Medical Center and Suburban Hospital to develop clinical partnerships. NCI has many concerns regarding the new era of agent development and how the current clinical trials structure will need to be adjusted to meet the demands of this new era. The National Cancer Policy Forum has agreed to explore the clinical trials system and ways to adjust it for the future, beginning with a 2-day meeting on July 1 and 2, 2008.

In other news, NCI was successful in getting NIH and DHHS approval for Small Business Innovation Research (SBIR) bridge awards; this will increase the amount of funding available through the NCI SBIR program and incentivize partnerships with third-party investors. A number of changes have been made in the SPORE program. In response to a recommendation in the TRWG report, the summer SPORE meeting has been replaced with a translational sciences meeting taking place in Washington, DC, November 7-9, 2008. Another positive move for the SPORE program, under the able leadership of Toby Hecht as Acting Head, is its relocation into the Division of Cancer Treatment and Diagnosis; the goal is to strengthen the program in terms of science and its ability to be a major part of the translational research portfolio at NCI. Constructive guideline changes, including a formula for bridge funding to maintain some SPOREs through revisions, are gradually being made to help the SPORE program reach this goal. The Cancer Centers program, a key program led by Linda Weiss, will be strengthened by working more closely with Dr. Niederhuber. NCI training efforts have been moved into a separate trans-NCI center operating out of the Office of the Director with the goal of strengthening this program.

Dr. Niederhuber highlighted a recent exciting event, a Theoretical Physics Meeting that brought together leaders in physics, chemistry, mathematics, and cancer research to explore the relationship between the physical sciences and oncology. As a result, a series of smaller "theoretical cancer biology" workshops is being planned within the next few months looking at topics such as the role of evolution in the development of cancer, mathematical modeling of cell communication, how chemical gradients function *in vivo*, and so forth.

Dr. Niederhuber closed by stating that much work remains to be done to improve the clinical trials system; trials are no longer about development of a single agent but the development of therapeutic solutions and testing of their safety and efficacy. Dr. Niederhuber hopes this advisory committee will help NCI address these new challenges.

Questions and Discussion

Dr. Carolyn Runowicz, Director of the Carole and Ray Naeg Comprehensive Cancer Center, asked what review committee would have the capability of evaluating grants received from the theoretical physics community. Dr. Niederhuber noted that the challenge is to set up a review team that is not reviewing itself. There is also the opportunity to review applications internally by structuring a review group that is knowledgeable, fair, and understandable.

Dr. Richard Pazdur, Director of the FDA's Division of Oncology Drug Products, asked if there are any ongoing efforts to foster collaborative relationships with *in vitro* diagnostic companies. Dr. Niederhuber said that NCI is currently putting a lot of effort in that direction. As new agents are developed, ways to follow those agents (e.g., chemical markers, imaging) need to be developed simultaneously. Dr. Niederhuber is confident they will be able to image at the protein level of a target. Dr. James H. Doroshow, Director of NCI's Division of Cancer Treatment and Diagnosis, commented that the Molecular Diagnostics Evaluation Laboratory program is being developed to do exactly what Dr. Niederhuber mentioned. They hope to partner with small companies or other laboratories to be able to have confirmatory or validation trials along with the clinical attempt to validate the utility of drugs. Dr.

David R. Parkinson, President and CEO of Nodality, Inc., suggested that NCI generate a strategy to support therapeutic development in terms of this form of diagnostics. Dr. Nancy P. Mendenhall, Professor in the Department of Radiation Oncology at the University of Florida Health Science Center, commended this approach to therapeutics development.

III. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations, NCI, reported on the status of appropriations, provided information on hearings and briefings that occurred over the last several months, and highlighted several pieces of legislation.

FY 2009 Appropriations Status. When the President announced his budget in February 2008, it included $29.3 billion for NIH, with $4.8 billion of that sum for NCI. There were a limited number of appropriations hearings in the spring. In comparison with previous years, NIH and NCI did not have much opportunity to be part of the appropriations process; not a single hearing in the House was devoted solely to NIH. However, the House did mark up their bill to include a $1.2 billion increase for NIH; an improvement over the President's budget. In the Senate, the subcommittee markup included a little over $30 billion for NIH; a 3.5 percent increase. Ms. Erickson clarified that, realistically, these bills will not be considered until after the election and into the next Congress, which will begin at the end of January 2009. Although a bill is written, the Senate subcommittee plans to hold a hearing on July 16th to hear from NIH; Dr. Niederhuber will attend this hearing along with Dr. Zerhouni and three other NIH Institute Directors. Ms. Erickson also informed the Committee that a small portion of FY08 appropriations may become available to NIH and NCI as part of the War Supplemental Spending bill; a second version of this bill just passed in the House, which included $150 million for NIH to be spread across the Institutes.

Hearings and Briefings. The Senate HELP committee held a hearing, "Cancer: Challenges and Opportunities in the 21st Century," on May 8th. Senator Kennedy, the committee chair, along with Senator Hutchison, announced their intention to introduce comprehensive cancer legislation. Subsequently, Senator Hutchison laid out the goals of the legislation, which include to remove barriers currently hindering progress in cancer research and treatment, improve access to early detection measures and cancer care, reduce disparities in cancer treatment and increase enrollment in clinical trials, and encourage additional opportunities for cancer research, especially cooperative cancer research. Ms. Erickson noted that this bill will not be introduced until Senator Kennedy returns to the Senate.

On May 21st, the House Energy and Commerce Committee, Subcommittee on Health, held a hearing on two bills related to breast cancer issues—HR1157, the Breast Cancer and the Environment Research bill, and HR758, a bill providing minimum hospital stay for patients having had a mastectomy. Dr. Deborah Winn of NCI's Division of Cancer Control and Population Sciences spoke for NIH and NCI in terms of their position on the Breast Cancer and Environment Research bill. Dr. Winn clarified for the House that NIH does not formally support either the House or the Senate bill because both are disease specific. But they also do not oppose the Senate bill because the most problematic provision of that bill—a Breast Cancer and the Environment Research Panel with the ability to make binding recommendations on which grants would be funded—has been taken out. NIH will continue to work with the Subcommittee to modify this bill.

Legislation. Ms. Erickson briefly discussed some legislation, starting with the Genetic Information Nondiscrimination Act, which was signed into law by the President in May. This bill prohibits health insurance discrimination by mandating that health insurance companies may not adjust premium or contribution amounts based on genetic information obtained from genetic tests. Further, companies may not require an individual or family to undergo genetic testing to acquire information, and may not request, require, or purchase genetic information. There is a penalty for companies who fail to comply with these

provisions. The Act also prohibits employment discrimination on the basis of genetic information. With some foresight, the Congress established a study commission to reevaluate this bill in 6 years and make recommendations to the Congress if modifications are needed.

Questions and Discussion

Dr. Kirby I. Bland, Fay Fletcher Kerner Professor and Chairman of the Department of Surgery and Deputy Director of the UAB Comprehensive Cancer Center at the University of Alabama at Birmingham, questioned whether there will be long-term consequences if a bill with disease-specific provisions is passed. Ms. Erickson responded that after the passage of the NIH Reform Act, NIH adopted a standard position that they would not support any bill that was disease specific. If the Breast Cancer and the Environment Research bill is passed, it will not be a permanent blow to the NIH position; NIH has objected in principle.

IV. CLINICAL TRIALS: NCI-FDA INTERACTIONS—DR. MARGARET MOONEY

Dr. Margaret Mooney, Acting Branch Chief, Clinical Investigations Branch, Cancer Therapy Evaluation Program, NCI, gave the Committee an update on what has been accomplished as part of the CTWG coordination initiatives regarding NCI and FDA interactions; specifically, for large-scale Phase III clinical trials. The goal is to increase cooperation and communication among the NCI, FDA, and industry to develop Phase III trials that better meet industry needs as well as research goals when the trial has been identified as potentially supporting a licensing indication. Dr. Mooney explained that all Cooperative Group Phase III trial ideas that are specifically identified as supporting a licensing indication are forwarded to FDA at the concept stage for a rapid review. A process has also been developed with industry and FDA to integrate and coordinate special protocol assessments (SPAs) with the NCI/CTEP review processes as well. In addition, other Phase III trials with Investigational New Drug (IND) or commercial agents are also forwarded to FDA at the concept stage for informational purposes even if the study has not been specifically identified as supporting a potential licensing indication so that FDA can provide input at the Agency's discretion.

Dr. Mooney explained the specific coordination process used when a biotech/pharmaceutical collaborator expresses interest in using the trial to support a labeling indication. First, there is a CTEP review, or in the case of disease-specific steering committees, a steering committee review. If a concept is identified as having regulatory potential, it is put on hold and sent to FDA for their comments. If there are major comments, they work within a 21-day period to schedule a meeting with the group who is sponsoring or leading the trial, representatives from industry, FDA, CTEP, and other investigators to discuss those comments. Once the protocol development stage is reached, they try to expedite development—aiming for a concept approval to final protocol approval timeline of 60 to 90 days. At the end of the process, they hope to have a final version of the protocol that has been approved by CTEP and the NCI Central IRB that meets FDA's requirements (including Special Protocol Approval or SPA by the FDA if the company collaborator has requested an SPA).

Dr. Mooney went on to outline the timeline of two Phase III trials which were identified very early on to have supplemental licensing indications and which were identified by the company sponsor as protocols they felt should undergo Special Protocol Assessment from FDA. The first was an adjuvant trial led by the National Surgical Adjuvant Breast and Bowel Project (NSABP) in Stage II and III carcinoma of the colon. This trial evaluated bevacizumab added to FOLFOX. It was activated in 2004 and completed accrual of approximately 2,700 patients in October 2006. The second trial was led by the Cancer and Leukemia Group B (CALGB) in advanced pancreatic cancer, looking at the value or potential benefit of bevacizumab in combination with gemcitabine. This was activated in April 2004 and completed accrual in 2006. Unfortunately, the second trial had negative results and an interim futility analysis was

announced in June 2006. To date, about eight Phase III clinical trials have undergone the process of protocol development and approval at NCI with concurrent approval of SPAs by FDA for those trials.

Questions and Discussion

Dr. Heidi Nelson, Fred C. Anderson Professor of the Division of Colon and Rectal Surgery at the Mayo Clinic Foundation, asked Dr. Mooney to comment on what is happening with the Clinical Trials Management Systems (CTMS) effort to coordinate Phase II trial and FDA data. Dr. Niederhuber said this is related to the Cancer Biomedical Informatics Grid (caBIG) and that Dr. Kenneth Buetow, Director of the Center for Biomedical Informatics and Information Technology (CBIIT), would be able to comment on the caBIG effort later in the meeting.

Dr. Parkinson asked whether there is any coordination with the European Medicines Agency (EMEA). Dr. Pazdur responded by informing the Committee that FDA has monthly teleconferences with the EMEA to discuss all applications and will discuss the SPAs they do with NCI. Beginning this summer, they will go to the EMEA on a monthly basis to work with them and attend their industry meetings. Dr. Pazdur also commented that the EMEA has a different system than that of the United States; they have a group providing scientific advice, which is separate from the group making decisions on applications.

Dr. Peter C. Adamson, Professor of Pediatrics and Pharmacology and Chief of Clinical Pharmacology and Therapeutics at The Children's Hospital of Philadelphia, asked if there were any unintended consequences resulting from coordination with FDA, especially for commercial agents that the Cooperative Groups might study. Dr. Mooney said she did not know of any unintended consequences to date for a Phase III trial going forward from the Cooperative Group system. Many of the studies are under IND already. Dr. Pazdur commented that if the study is for licensing, then it is not IND exempt.

Dr. Richard L. Schilsky, Professor of Medicine and Associate Dean for Clinical Research at the Biological Sciences Division of the University of Chicago, asked how the expedited protocol development can be made routine, instead of an exception, and if there are ways to further accelerate the process, such as a single review process for both NCI and FDA. Dr. Doroshow intervened to ask Dr. Schilsky to describe what the process requires, from his perspective, to become routine. Dr. Schilsky said it takes an enormous amount of individual commitment and a lot of logistics in order to get people to stay focused on such a project. Protocol staff who are devoting efforts to this process are detracted from other work activities. The challenge is to determine how to make this routine if there is not an indication triggering it or an individual championing the effort.

Dr. Pazdur added that FDA is looking at ways to streamline the SPA review process by focusing on major issues (i.e., if there is agreement on endpoints, on the statistical plan, or on the interim analyses). Dr. Pazdur also plans on creating a special group of reviewers to work on the project so there is consistency and better interaction with NCI. The review staff can also attend the Cooperative Group meetings and be more interactive in order to know what protocols may be of interest for SPA review. Dr. Sandra J. Horning, Professor of Medicine at Stanford University Medical Center's Comprehensive Cancer Center, wondered if there are any opportunities for earlier interaction or collaboration with FDA. She also asked about financial implications and if there is any additional support from industry for protocols moving towards a new indication. Dr. Pazdur noted that FDA does not get involved in NCI and Cooperative Group financial arrangements, but that opportunities for earlier collaboration are something for NCI and FDA to address; the process doesn't necessarily need to be sequential. Dr. Nelson followed up on Dr. Horning's comments by suggesting that having FDA members on the GI steering committee would allow everyone to come to some common agreement about what constitutes the right endpoints and timing for analyses and data collection for protocol development.

Dr. Niederhuber asked Drs. Mooney and Pazdur whether the problems of efficiency and coordination are manpower problems. Dr. Pazdur answered that if they had more manpower the job could be completed faster. He also added that the other issue is to make a clear realization of what protocols are meant for registration. Dr. Parkinson observed that since 2004, very few trials have been identified for the SPA process, meaning either a lack of trials with indications for novel therapeutics or another issue. Dr. Pazdur said the decision to do an SPA is usually based on industry interest rather than NCI interest. Dr. Parkinson added that industry interest can be related to the time of year due to the 45-day FDA time clock for SPAs. Dr. Schilsky added that a key point to keep in mind is that SPA or not, it is increasingly common at the level of Phase III trials in the Cooperative Group program for there to be an industry partner involved in some way with the study. Those studies will be done under an IND, which involves FDA review, so it is important to harmonize the procedures. Dr. Abbruzzese asked in how many cases industry is bypassing the opportunity to go through CTEP and working directly with FDA and invoking the SPA mechanism. Dr. Pazdur responded by saying the vast majority of trials are done outside of the NCI mechanism for many reasons, especially for primary indications or first indications.

V. RECOGNITION OF RETIRING MEMBERS—DR. JOHN NIEDERHUBER

Dr. Niederhuber recognized two retiring members of the Committee—Susan Leigh, Consultant for the National Coalition for Cancer Survivorship, and Colonel James E. Williams, Co-Chairman of the Pennsylvania Prostate Cancer Coalition. He commended both for being active on the Committee and within the advocacy community; in particular, helping to launch the Patient Advocacy Steering Committee that has tried to link NCI and advocates, especially with the CTWG implementation activities and disease-specific steering committees. Both Ms. Leigh and Col. Williams are cancer survivors and have brought a unique perspective to the Committee. Dr. Niederhuber presented a commemorative plaque to each. A third retiring member, Jean B. deKernion, M.D., was not present.

VI. CTAC AD HOC COORDINATION SUBCOMMITTEE REPORT—DR. JAMES ABBRUZZESE

Dr. James Abbruzzese, Chairman, Department of Gastrointestinal Medical Oncology, University of Texas M.D. Anderson Cancer Center, stated that the Subcommittee, which was formed over a year ago, took on the responsibility of reviewing the clinical trials guidelines to harmonize guidelines with the idea of coordination and collaboration on NCI clinical trials. The purpose of the Subcommittee is to advise the NCI Director on how to foster collaboration among the various components of the NCI-sponsored clinical trials infrastructure in order to develop a fully integrated clinical trials system. The group is currently developing a summary document that will inform NCI staff on areas in which clinical trials guidelines related to the different programs (e.g., SPORES, Cooperative Groups) could be harmonized to promote collaborations. The Subcommittee is also working on developing a simple but comprehensive definition of collaboration. In a series of monthly conference calls over the next 6 months, the Subcommittee will be developing incentives and rewards and eliminating disincentives as part of the harmonization process to promote collaboration.

Another area the Subcommittee is working on is to provide advice to NCI with respect to implementing the Translational Research Working Group report. Preliminary recommendations were made at a February 2008 meeting of the CTAC Planning Working Group led by Dr. Lynn Matrisian. The Planning Working Group made recommendations with respect to three TRWG initiatives. Related to TRWG Initiative A3—the need to develop a set of award codes that accurately capture the nature and scope of the early translational research portfolio—was established as a priority. It was recommended that a pilot coding project be established by the Division of Extramural Activities. TRWG Initiative A4 was to establish a distinctive prioritization process for early translational research. Dr. Abbruzzese stated that Dr. Matrisian would address this in her presentation, but that the recommendation was to assess the feasibility

of identifying and developing concepts for a TRWG-envisioned prioritization process. Initiative C2 was to establish a system to coordinate core services essential for early translational research. Recommendations to achieve this include identifying characteristics that make core services amenable for regionalization and revising guidelines to promote intra- and interinstitutional sharing of cores. Finally, the Working Group recommended that the membership of CTAC be expanded as necessary to ensure that at least 50 percent of the membership have translational research experience.

Motion. A motion was made to accept the Ad Hoc Coordination Subcommittee minutes from the July 10, 2007 and February 3, 2008 meetings. The motion was seconded and unanimously approved.

Motion. A motion was made to accept the Planning Working Group Recommendations from the meeting held on February 4, 2008. The motion was seconded and unanimously approved.

VII. TRANSLATIONAL RESEARCH WORKING GROUP UPDATE—DR. LYNN MATRISIAN

Dr. Lynn M. Matrisian, Special Assistant, Office of the Director, NCI, discussed the progress on implementing 4 of the 15 recommendations that came out of the Translational Research Working Group. The first was to develop a flexible and integrated organizational approach. As a result, the Clinical Trials Advisory Committee is being expanded to include translational research. As new appointments are made to this Committee, they will ensure that laboratory-based translational research is represented. In addition, the NCI Clinical Trials Operations Committee (CTOC) has been expanded to include both clinical and translational research as the Clinical and Translational Research Operations Committee (CTROC). Dr. Matrisian stated that this initiative has been accomplished.

Another initiative was mentioned earlier by Dr. Abbruzzese—to develop award codes for the translational research grants in order to better identify NCI's investment in translational research. Current coding within NCI is on organ site, target population, and other very specific research categories. Dr. Matrisian stated that the recommendation is to use the TRWG pathways as a way to more extensively code research grants. The TRWG pathways provide the foundation for much of the work that is proposed to go forward. The pathways represent early translational research—the point at the end of basic research up to Phase III clinical trials. Using engineering flowcharts, it was determined that early translational research could be coded into one of six pathways, with each of these pathways having five domains. The pilot project with NCI's Division of Extramural Activities (DEA) is currently using these pathways to code grants recognized to be translational. Once this set of grants is coded by DEA, the codes will be compared with the principal investigator's assessment to look at consistency and interpretation of the pathways. The pilot will also be integrated with an NIH effort called the Research Condition and Disease Categorization Project, which is attempting to identify translational research.

Another TRWG initiative in development is coordinating core services to be more efficient and less redundant. The CTAC Coordination Subcommittee has agreed to take on this task and will determine criteria for having regional cores that could be shared by cancer centers, SPOREs, P01s, etc., and how these guidelines could be modified to encourage sharing and reduction of redundancy within NCI-supported core services.

Lastly, Dr. Matrisian discussed the TRWG's vision for a prioritization process. Using this process, the NCI could solicit ideas from the public based on the TRWG pathways (i.e., concepts that could be taken from the top to the bottom of the pathway). A working group could be charged with prioritizing these ideas. For the top 10 ideas, a detailed analysis of scientific validity and feasibility could be completed; the list could then be further prioritized into five concept packages. The five concepts could be distributed again for public comment. Based on this process, NCI investigators could be informed of concepts ripe

for translation; additional resources could be made available to support these concepts. Dr. Matrisian stated that this process is not yet in effect, but there will be a 2-day trans-NCI translational science meeting held in Washington, DC, on November 7-9, 2008, to solicit ideas appropriate for prioritization. This is an invitation-only meeting for individuals based on their NCI-supported translational research. It is hoped that this meeting will generate pre-concepts that can be used to assess the range and quality of potential translational research concepts. These pre-concepts will be brought to the next CTAC meeting in December for evaluation and determination whether to go ahead with a prioritization subcommittee and the development of Special Translational Research Acceleration Projects (STRAPs) as a funding mechanism to accelerate the process of translational research.

Questions and Discussion

Dr. Leigh inquired whether a concept looking at the issues of long-term survivors could fit into any of the abstract categories. Dr. Matrisian responded that a concept regarding the specific long-term effects of a certain drug might fit in the agents category. There is also a lifestyle alteration pathway, which includes nutritional and other modifications. Dr. Matrisian reminded everyone that these pathways are not static and will evolve as more experience working with them is gained. Dr. Niederhuber commented on Dr. Leigh's question by observing that biomarkers fit into translational science and might fall into the survivorship category. Dr. Horning added that the example presented by Dr. Matrisian relating to early detection identified in a high-risk population is a perfect example of a survivorship issue.

Dr. James L. Wade, Director of Medical Oncology at Decatur Memorial Hospital Cancer Care Institute and President of Cancer Care Specialists, asked if the poster abstracts will be available online for review prior to the meeting. Dr. Matrisian said that had not yet been considered, but it would be possible since everything is Web based.

Dr. Daniel J. Sargent, Director of Cancer Center Statistics and Professor in the Division of Biostatistics at the Mayo Clinic College of Medicine, asked how the restricted invitation list for the November meeting is satisfying the prioritization process criteria for broad public input. Dr. Matrisian said the purpose of the initial meeting is to provide information to determine whether broad public input should be pursued. An education process must occur to inform people of the pathways, which will hopefully be accomplished with the November meeting.

Dr. Adamson asked Dr. Matrisian to comment on what role industry will have at the meeting. Dr. Matrisian said she ensured that Small Business Innovation Research programs (SBIRs) and Small Business Technology Transfer programs (STTRs) were represented as a way to include some industry contact at the meeting. Once the process has gone from pre-concept to concept, there will be an opportunity to bring in specific industrial interests.

VIII. SYMPTOM MANAGEMENT STEERING COMMITTEE (SxQOL SC) UPDATE—DRS. DEBORAH BRUNER , LORI MINASIAN, AND MICHAEL FISCH

Dr. Deborah Bruner, Director, Recruitment, Retention and Outreach Core Facility, University of Pennsylvania School of Nursing, Abramson Cancer Center, began by reporting the work in progress of the Symptom Management and Quality of Life Steering Committee. The Committee is in place to prioritize Phase II and III concepts, convene state-of-the-science meetings, and provide expertise to the disease-specific steering committees. A future goal is to develop Phase II and III concepts for new clinical trials based on research gaps identified at the state-of-the-science meetings. To date, the Committee has reviewed seven concepts; two have been approved; four have been declined; and one requires revision and resubmission. The symptoms studied in these concepts included chemotherapy rash, nausea and vomiting, radiation dermatitis, weight loss, and fatigue. Working groups are in development, including a

Scouting and Development Working Group to develop a database of content specialists who can be called upon as needed, and a State of the Science Working Group. A new initiative that evolved from a meeting with Dr. Niederhuber in 2007 is to hire a full-time physician to work within the Division of Cancer Prevention (DCP) and focus entirely on bringing drug development into the symptom management realm.

Dr. Lori Minasian, Chief, Community Oncology Prevention Trials Research Group, DCP, NCI, went on to discuss the State of the Science (SOTS) Initiative. To provide context, she shared that symptom management clinical trials have been funded through the Community Clinical Oncology Program (CCOP); since 2000, 174 symptom management clinical trials have been initiated, nine of which have been specific to evaluate agents or interventions to reduce neuropathy, typically chemotherapy-induced neuropathy. Many drugs cause different types of neuropathy; there is no measurement for assessing chemotherapy-induced neuropathy, nor are there any standard interventions for its prevention or treatment. One goal for the SOTS meeting is to bring experts together to share information and determine the best approaches to assess and measure neuropathy, including effective measurement tools. Another goal is to identify mechanism-based interventions to help reduce treatment-related toxicity, thereby allowing patients to complete their targeted therapy regimens.

Dr. Michael Fisch, Associate Professor, Gastrointestinal Medical Oncology, Medical Director, Clinical Community Oncology Program, M.D. Anderson Cancer Center, discussed the first approved concept of the SxQOL SC. This concept is a Phase III double-blind placebo-controlled study of gabapentin for the treatment of chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly or moderately emetogenic chemotherapy. It was proposed by Dr. Debra Barton on behalf of the North Central Cancer Treatment Group. The target symptom—nausea and vomiting—is classic in that it is readily discernible and can be measured. The drug intervention is also classic with regard to availability of the drug, physicians' familiarity with it, its spectrum of side effects, etc. This is a new indication that was observed anecdotally—patients were prescribed gabapentin for another reason but noticed their nausea and vomiting improved. Dr. Fisch described the proposed study design, primary endpoint, sample size calculation, and committee approval process for this concept. The concept was approved with comments; measurement issues were discussed, including ensuring that nausea was added to the daily diary and making changes to some of the measurement scales. The Committee also felt that since this is a one-cycle study, patients should be chemo-naïve. Several other aspects of the study design were also modified. The general features of the approved concept are that it is a Phase III design, placebo-controlled study. However, the study has a Phase II intent in that there will be a point estimate of efficacy, feasibility, and tolerability. In addition, Dr. Fisch noted that study endpoints and patient-reported outcome measures are validated, the drug intervention is familiar, and there are prior studies on which to base predictions about response rates and estimate magnitude of difference. Dr. Fisch talked briefly about other issues of interest to the SxQOL SC. The Committee is particularly interested in gaining access to novel investigational agents for symptom research; developing, acquiring, and distributing these drugs; and even doing dose-finding and preclinical work with them. Currently, the Committee is broad-based in terms of potential focus, and it might be beneficial to appoint a task force to address proposed ideas from investigators or industry and determine what pathway to take and how to design the trial.

Questions and Discussion

Dr. Adamson asked whether the SxQOL SC has expertise in drug development outside of oncology. Dr. Minasian said they are looking into bringing in that kind of expertise to form a drug development task force under the Symptom Management Steering Committee. Dr. Adamson commented that most people in the drug development world would consider the strategy they've taken—conducting a randomized Phase III without knowing the dose—high risk. Dr. Minasian explained that it's actually a randomized Phase II design because they're really looking at the first signal for efficacy.**

Dr. Pazdur inquired whether the Committee is looking at disease-related symptoms in addition to therapy-induced symptoms. Dr. Minasian agreed it is an area that needs development and noted that the assessment of symptoms specific to the disease is a potential barrier to the advancement of this area. Dr. Pazdur added that the symptom has to be the hallmark of the disease so it can be quantified. Dr. Fisch commented that another issue with symptom management trials is that symptom expression is an endpoint in the treatment trial, and this affects the ability to enroll patients and forces trials to compete with one another. Dr. Pazdur said that in order for these types of trials to be successful, symptoms have to be elevated to the primary endpoint of the trial.

Dr. Schilsky asked if it is necessary to commit 400 patients to what might be a randomized Phase II trial and if the Committee has considered an interim analysis for futility of the trial. Dr. Fisch said that they are aware that the pretrial probability of failure is high and an interim analysis was part of the review suggestion. Dr. Schilsky suggested that an alternative to the 400-patient study might be to do a much smaller study—a placebo and two different dose levels of gabapentin—to note activity and obtain the preliminary data to justify a larger trial. Dr. Perez echoed these comments, adding that if the study is negative after 400 patients it will be necessary to start over or abandon the drug. Dr. Adamson commended the Committee's efforts, but also suggested doing a smaller dose-finding study first and then proceeding to the 400-patient trial.

Dr. Stephen S. Grubbs, Chief of Oncology at Medical Oncology Hematology Consultants, noted that peripheral neuropathy is one of the biggest problems for long-term survivors and would be a great area for correlative science. Dr. Horning stated that they are seeing qualitatively different neuropathy than they've ever seen before and suggested bringing in other groups, such as anesthesiologists and neurosurgeons, to the state-of-the-science meeting. Dr. Minasian welcomed any recommendations of individuals or topic areas to include for this meeting.

Dr. Gabriel M. Leung, Executive Vice President and President of Oncology at OSI Pharmaceuticals, asked if the Committee had considered looking at a treatment schema of dealing with symptoms and toxicities rather than focusing on an individual drug in studies. Dr. Minasian informed the members that there is currently a study with the Eastern Cooperative Oncology Group to look at multiple symptoms or symptom clusters and assess patients for these. Dr. Fisch added that they do not have many single-agent interventions in cancer medicine right now, and more cleverly designed mechanism-based combinations are the future of this field.

**The following clarification was added by Dr. Minasian in proof of the meeting summary: Published data providing the rationale for the dose selected for this study were cited in the study concept reviewed by the Steering Committee.

IX. BARRIERS TO THE UTILIZATION OF THE NCI CENTRAL IRB—MS. MAUREEN MCARTHUR

The Science and Technology Policy Institute (STPI) conducted an NCI Central Institutional Review Board (CIRB) barriers analysis between March 2007 and April 2008. Ms. Maureen McArthur, a consultant for STPI, led the barriers analysis project team and presented the results. The project resulted from the CTWG initiative to enhance adoption of the CIRB process. One of the CTWG goals was to improve the efficiency of the clinical trials system, and there was a perception that increased reliance on the CIRB would improve efficiency. However, many sites in the Cooperative Group system have been reluctant to use the CIRB, so the CTWG recommended analyzing the nature of these barriers, including the nature of reluctance, and any issues related to operating procedures of the CIRB.

STPI conducted interviews at a total of 75 sites; 48 were cancer centers; however, CCOPs, academic medical centers, nonprofit medical centers, and one for-profit medical center were also represented. STPI conducted discussions with a total of 131 individuals; most were IRB administrators or chairs, but others were research coordinators, principal investigators, and individuals who fulfilled some kind of regulatory role within the IRB office or investigator's group. In addition, STPI analyzed Cooperative Group fiscal year 2006 audit data for the 52 most active sites, looking at both major and minor violations relating to IRBs and whether those violations occurred as a result of CIRB actions. Two sites were contacted that are implementing the CIRB process as designed to determine the sites' willingness to share their standard operating procedures (SOPs) and whether their SOPs are generalizable to other sites.

Ms. McArthur next reviewed key findings of the barriers analysis. The primary reason for using the CIRB process was improved efficiency for local IRB members, investigators, and research coordinators. Using the CIRB frees up time for the local IRB and allows the local IRB to focus on higher-risk trials. For investigators and research coordinators, there is significantly less back-and-forth interaction between the investigator's office and the local IRB; however, there is an increased workload for IRB administration, IRB chairs, and others who conduct facilitated reviews. There is wide variability in who makes the decision to join or not join the CIRB; however, local investigators often provide the motivation to join since joining the CIRB can create savings for the investigator's office. STPI assessed whether sites would be interested in expanding the CIRB to Phase II adult trials; the sites were divided on whether they would be willing to rely on the CIRB for review of earlier, higher-risk trials. A feasibility analysis has been recommended to determine whether this additional responsibility should be undertaken by the CIRB.

Ms. McArthur continued with findings, noting that about half of nonmember institutions and nonmember cancer centers cite barriers that will be difficult to resolve; many of these barriers are also issues for CIRB members but they have generally accepted and work around them. Several barriers were identified that could be addressed by the CIRB. The barriers found to be difficult to resolve include the increased workload for IRB administrators and chairs; with a facilitated review they must take on added responsibility. Several sites mentioned legal, liability, and control concerns related to the CIRB; they prefer to conduct their own local full Board review. Others mentioned local context issues (i.e., particular population) and the concern that the CIRB would lack local understanding. Another barrier is the refusal of the U.S. Department of Veterans Affairs (VA) to allow sites that enroll VA patients to use the CIRB.

In terms of addressable barriers, there are local site inefficiencies because member institutions implement the CIRB process in a wide variety of ways. Other issues include the long, labor-intensive process to implement the CIRB at local sites, lack of a single designated CIRB point-of-contact, and objectionable CIRB policies and procedures (i.e., possible regulatory violations with continuing review, delays in receiving reviews and consent form changes resulting from adverse events, lack of Association for the Accreditation of Human Research Protection Programs [AAHRPP] accreditation for the CIRB, and lack of CIRB review of foreign-language consent forms). Operational barriers cited were delays in posting materials, posting of incomplete review materials, and delays in responding to questions. An added frustration for local IRB sites is coordination with the NCI Cancer Trials Support Unit (CTSU); the CTSU requires additional documentation for every amendment, continuing review, etc., if a CIRB-facilitated review is being used.

Ms. McArthur reported that in response to this analysis, the CIRB has already started to take action. First, operating procedures have been modified to ensure that the continuing review meets regulatory guidance. They also continue to work with the current contractor to reduce time to post materials and respond to queries. In addition, the "Division of Responsibilities" document has been modified to include local review of non-English consent forms. Ms. McArthur noted that it might be beneficial for the CIRB to take on review of consent forms in the major languages that are needed at some of the local sites because without CIRB review, the local sites must conduct a review of a translated consent form each time there is

a change to the consent form language. Additional actions recommended include obtaining AAHRPP accreditation, developing a set of best practices and model standard operating procedures for CIRB implementation, designating a single CIRB point of contact for each site, and modifying the CTSU requirements to reduce paperwork for affirming CIRB review. Ms. McArthur concluded by observing that the CIRB can increase efficiency of the clinical trials system if the aforementioned barriers are addressed and resolved to the best of the CIRB's capabilities.

Questions and Discussion

Dr. Nelson asked about the role of the CIRB and what the best practices should be. She also commented that the goal for using the CIRB needs to be clear, because it is currently unclear and having a devastating effect on IRBs. Ms. McArthur acknowledged this issue, but clarified that STPI did not analyze issues of "what" the CIRB should be reviewing but rather the barriers for local sites in implementation of the CIRB process. Dr. Sargent asked if there are data to support the notion that use of the CIRB will reduce the amount of time until a patient can go onto a clinical trial. Ms. McArthur said an economic analysis is planned to analyze such issues. However, CIRB member sites have noted that it is easier to open a trial, since they do not have to wait for a full Board review. Dr. Grubbs added that in contrast, the process of waiting for the CIRB slows down nonmember sites. Dr. Niederhuber commented that the CIRB debate has been ongoing for many years and it may be time to try something new. Dr. Bland echoed concerns about the CIRB and lack of commonality even of forms. He asked Ms. McArthur to reiterate the efficiencies that are gained. Ms. McArthur reiterated that several sites described efficiency in human subject protection gained by the CIRB. When Phase III Cooperative Group trials (which have been reviewed numerous times by different committees prior to full Board review) are removed from the local IRB agenda, it allows the local IRB to devote its time to higher-risk trials. Col. Williams shared Dr. Niederhuber's sentiments, stating that the practicality of the CIRB won't work because the liability and legal ramifications at the local level won't be given up. Dr. Perez added that it's important to be able to do clinical trials in a timely manner; the Office for Human Research Protections and NCI need to empower a national IRB and obviate the need for duplicative local site reviews

Dr. Wade commented in favor of the CIRB; the CIRB has the mandate to ask the Cooperative Groups detailed questions about study designs and statistical analysis, whereas the local IRB is a receptive body that takes and digests but cannot question. He noted that there is great potential for improved efficiency of the CIRB. Dr. Abrams reminded the Committee that the pediatrics CIRB is viewed as successful within that community because more than 50 percent of the active sites participate. Only about 25 percent of the active sites in the adult community participate, and until you hit that 50 percent, the true benefits of the CIRB are hard to assess. Dr. Abrams also stated that in the adult community, 56 percent of the top 50 accruing sites in the Cooperative Group program and 39 of the 60 comprehensive cancer centers have joined the CIRB, which exemplifies progress.

X. REPORT OF THE CORRELATIVE SCIENCE WORKING GROUP: DRS. TEPPER, PRINDIVILLE, SMITH, AND MINASIAN

Introduction to the Biomarker, Imaging, and Quality of Life Supplemental Funding Program. Dr. Sheila Prindiville, Director, Coordinating Center for Clinical Trials, NCI, introduced the Biomarker, Imaging and Quality of Life Supplemental Funding Program. The purpose of this program is to ensure that the most important correlative science and quality of life studies can be initiated in a timely manner when funded in association with clinical trials. Criteria were developed to prioritize the types of studies that should be funded; these prioritization criteria were presented to and approved by the CTAC in July 2007. The two categories of studies eligible for the prioritization process are integral studies (i.e., include a test or a correlative component that must be performed for the trial to proceed) and integrated studies (i.e., intended to identify or validate markers, imaging tests, or QOL instruments that may be used in

future trials). The types of trials eligible for the program in 2008 were restricted to Phase III treatment or Phase III prevention and symptom management studies to be conducted by the Cooperative Groups or CCOP Research Bases. A funding announcement was sent to the Cooperative Groups and CCOP Research Bases in early December, 2007. A total of 23 applications were received; 19 within CTEP treatment trials and 4 within DCP trials. As for the types of applications, 13 were biomarker; 9 were quality of life; and 1 was imaging. Dr. Prindiville noted that following scientific and program review, as well as NCI Executive Committee review, an ad hoc CTAC Correlative Science Working Group, chaired by Dr. Joel Tepper, met last night to review the three concepts put forward by NCI for consideration. Each of the three concepts considered will be presented to the CTAC; following the presentation of each concept, the Committee will vote to accept or reject the Working Group's recommendation.

Biomarker and Imaging Supplements. Dr. Malcolm Smith, Associate Branch Chief, Pediatrics, Clinical Investigations Branch, CTEP, NCI, presented the Children's Oncology Group (COG) proposal in response to this initiative. It is part of the AAML0531 study, which is a current COG Phase III study for children newly diagnosed with Acute Myeloid Leukemia (AML). The primary study evaluates whether the addition of gemtuzumab ozogamicin (GMTZ) improves event-free survival compared with treatment with chemotherapy alone. Dr. Smith noted that GMTZ is an antibody-drug conjugate; the antibody targets CD33 and the drug conjugate is calicheamicin, a potent DNA-damaging agent. This Phase III study will be completed in 2010, enrolling approximately 1,000 children. The proposed supplemental study has one integral and two integrated components. The integral study is assigning patients with FLT3/ITD mutation and high allelic ratio (observed to have prognostic significance) to the high-risk group and to receive an allogeneic stem cell transplant if a matched family donor (MFD) or appropriate alternative donor is available. A comparison will be made to patients receiving a stem cell transplant only if there is a matched, related donor.

Next, Dr. Smith described the two integrated studies proposed as part of the supplement. The first is validating the significance of CEPBA mutations; the hypothesis is that CEBPA mutations confer favorable prognosis, which would enable patients with this mutation in future studies to be assigned to a low-risk group that would not receive a stem cell transplant. The second integrated study is proposed to optimize the use of Second Generation Four-Color Multidimensional Flow (MDF) cytometry to identify patients with minimal residual disease (MRD). Enhancements to this technology increase the ability to detect aberrant cell populations, which in turn should increase the sensitivity and specificity of MDF for detecting MRD, a potential prognostic factor in terms of patient outcomes. Each of the integrated studies, if shown to be reliable, could be incorporated into risk assignment and future studies. The cost for this supplement is $750,000 in Year 1 with a comparable amount for Year 2.

Questions and Discussion

Dr. Schilsky asked where the assay will be done for the FLT3-ITD, whether it is a CLIA (Clinical Laboratory Improvement Amendments)-certified laboratory, what the performance characteristics of the assay are with respect to precision and accuracy, sensitivity, etc., and whether all assays are supported under the proposed budget. Dr. Smith said that all three of the discussed assays would be supported through the proposed budget. He confirmed that the laboratory is CLIA certified and that the assay has been applied to COG specimens for the last 4 to 5 years. Dr. Schilsky emphasized the importance of performance characteristics and recommended that proposals to this Committee provide information on performance characteristics and assurance that the assay meets the developed standard for such studies.

Dr. Horning commented that proposals and presentations should also elucidate in greater detail the impact of the study (i.e., what percent of the population is likely to be affected), as well as provide statistical power calculations. Dr. Smith stated that FLT3/ITD appears in 10-20 percent of the pediatric population; CEBPA appears in about 5 percent; and NPM1 appears in about 10 percent of that population. Dr.

Horning also asked what proportion of patients who are assigned to the transplant actually have a matched family donor and receive the transplant. Dr. Smith said it is on the order of 20 to 30 percent.

Dr. Wade stated that there are several FLT3 inhibitors in development for adults and asked whether there are also some in development for children and if they were approved would they interfere with the completion of the study. Dr. Smith said there is an intense interest both in the adult and pediatric arenas in FLT3 small-molecule inhibitors. There is currently a pediatric ALL study using lestaurtinib as the FLT3 inhibitor, but that would not have an impact on this study. Dr. Smith acknowledged that prognostic factors may need to be modified as more effective therapies emerge.

Dr. Tepper, chair of the CTAC working group reviewing this study, said the working group thought this was a very strong study and unanimously recommended approval. Dr. Parkinson added that the CLIA-certified flow cytometry lab is one of the best in the country.

Motion. A motion was made to accept the Correlative Science Working Group's recommendation to approve the COG-AAML0531 biomarker concept; the motion was seconded and approved with fifteen yeas, zero nays, and five abstentions.

Quality of Life Supplements. Dr. Minasian discussed the two quality of life concepts.

Fatigue Correlative Study

The first is a quality of life correlative study looking at biobehavioral mechanisms for fatigue. This study is associated with NSABP B-45, which is a Phase III treatment trial exploring whether targeted therapy in the post-neoadjuvant-chemotherapy setting will improve outcome. Eligible patients will have had neoadjuvant chemotherapy and surgery with no clinical response, or persistent disease at surgery. Patients are randomized to a placebo or sunitinib for 1 year, with a second year of follow-up. The trial will begin near the end of August 2008 and 2,000 patients will be accrued. Dr. Minasian stated that the background for the correlative study is that fatigue has been reported in up to 30 percent of breast cancer patients for a year or more after completing therapy. Fatigue is also a major toxicity from sunitinib; this can reduce compliance and overall adherence. The correlative study will enroll 600 patients, all of whom will have symptoms prospectively assessed; blood will be drawn prospectively and processed for various immune markers; clinical correlates such as hemoglobin, thyroid, and cardiac function will also be measured. Exploratory studies have shown increased pro-inflammatory cytokines in persistently fatigued breast cancer survivors, as well as elevated lymphocytes. The importance of this study is that it provides a means to evaluate specific medical and biologic markers to assess fatigue associated with sunitinib. It is also a unique opportunity, because it is a placebo-controlled trial, to accurately assess symptoms and functioning specific to sunitinib and correlate them with biologic effects.

Questions and Discussion

Dr. Schilsky asked what the Committee was being asked to approve. Dr. Minasian clarified that it is just the fatigue substudy; the Phase III clinical trial is already approved. The budget for the fatigue substudy is approximately $1.7 million and covers all study components. Dr. Abbruzzese inquired how the 600 patients for the study will be selected. Dr. Minasian clarified that all patients who have agreed to complete the NSABP B-45 patient-reported outcome assessments (the first 1,348 enrolled) will be offered the opportunity to enroll in the substudy, so it will be the first 600 patients who agree to participate.

Dr. Pazdur asked if blinding can be maintained in light of the toxicities of sunitinib. Dr. Minasian said that there will be many women who are persistently fatigued as a result of chemotherapy, so they will not know a priori that a woman is fatigued due to sunitinib. Dr. Pazdur stated that it is difficult to measure fatigue and wondered whether sites that add quality of life as an additional endpoint will be missing

important data that would impair outcome interpretations. Dr. Minasian answered that the particular Cooperative Group working on this study has identified two sites that will collect the quality of life data, which have had excellent success with administering quality of life instruments. They have also written a statistical plan that addresses multiplicity and missing data.

Dr. Tepper said the CTAC Working Group recommended approval of this concept. The group thought it effectively met the review criteria in terms of quality of life and gave it unanimous approval. Dr. Perez added that this study is very responsive to the call for applications and is addressing a commonly described complaint of patients.

Motion. A motion was made to accept the Correlative Science Working Group's recommendation to approve the NSABP B-45 Fatigue QOL Correlative study; the motion was seconded and approved with sixteen yeas, zero nays, and four abstentions.

GOG UC0604

Dr. Minasian presented the second correlative study application recommended for approval: validation of a PROMIS tool for fatigue in conjunction with a treatment trial for endometrial cancer. GOG UC0604 is a Phase III clinical trial of pelvic radiation versus vaginal cuff brachytherapy followed by paclitaxel and carboplatin for patients with high-risk endometrial cancer. PROMIS stands for Patient-Reported Outcomes Measurement Information System, and the goal is to improve the assessment of self-reported symptoms and other health-related quality of life domains across many different diseases. The application for approval is to validate the following seven questions for the PROMIS fatigue short form: How often did you feel tired? How often did you experience extreme exhaustion? How often did you run out of energy? How often did your fatigue limit you at work? How often were you too tired to think clearly? How often were you too tired to take a bath or shower? How often did you have enough energy to exercise strenuously? It is expected that by phrasing questions in terms of "how often" PROMIS will be easier to answer and norm in different populations than previous assessment tools. Approving this initiative will cost $75,000.

Questions and Discussion

Dr. Schilsky asked what criteria have to be met to conclude that the short form is in fact valid. Dr. Minasian said that they are going to determine whether it is a reliable instrument by reviewing how patients are answering the questions and whether there are inconsistencies (i.e., if someone responds they are too tired to take a shower but never extremely exhausted, this would not make sense). They are also going to compare how patients complete the PROMIS in comparison to the FACIT (Functional Assessment of Chronic Illness Therapy) fatigue tool and whether it predicts for any kind of CTC (Common Toxicity Criteria) fatigue. Dr. Minasian added that the ultimate goal is for PROMIS to be a computer-assisted tool; currently, hard copies are given to patients at their clinic visits at 4 weeks when they complete their radiation, and then again at 6 months and at completion of therapy.

Dr. Abbruzzese asked what the patient-added value is of using the PROMIS short form. Dr. Minasian said the real benefit is having a uniform way to assess fatigue across patient populations and different trials. Dr. Tepper commented that the working group recommended approval for this study.

Motion. A motion was made to accept the Correlative Science Working Group's recommendation to approve the GOG UC0604 PROMIS tool concept for fatigue; the motion was seconded and approved with fifteen yeas, zero nays, and two abstentions. Three members were not present.

XI. CLINICAL TRIALS DATABASE UPDATE—DR. KENNETH BUETOW

Dr. Kenneth Buetow, Associate Director, Center for Bioinformatics and Information Technology (CBIIT), NCI, provided an update on implementation of the NCI Clinical Trials Database and its reporting requirements as well as the status of the Library of Standard Case Report Forms.

NCI-Specific Clinical Trials Database. Dr. Buetow first updated the Committee on the Clinical Trials Reporting Program (CTRP), which begins its operational pilot on July 7th, 2008. There are five pilot sites—Dana-Farber Cancer Institute, Mayo Clinic Comprehensive Cancer Center, Northwestern University Robert H. Lurie Comprehensive Cancer Center, St. Jude's Hospital, and Wake Forest Comprehensive Cancer Center—participating in two phases culminating in December 2008. In Phase I, the sites will continue workflow and hand entry, and then move on to resource estimation and full electronic upload to the NCI database during Phase II. The pilot implementation will begin with individual site conference calls, an orientation on how to utilize the database infrastructure, guidelines on accessing Web presentations, explanation of site profiles, application demonstration, and individual site follow-up as needed. The next step of the operational pilot requires registration of individual trials by grantees and sites. As the registrations are submitted, NCI staff from the Clinical Trials Reporting Office will review the entries for accuracy. Information specifically related to protocols will be abstracted and entered into the larger NCI database by NCI program staff. Following registration, pilot groups will be required to submit quarterly accrual reports; NCI will use this information to internally monitor the success of individual trials and provide an overview of NCI-supported clinical trials nationwide. An important point of emphasis for this database is that the structure of the information to be reported will facilitate the generation of Cancer Center Branch Summary 4 (Information on Clinical Research Studies) reports. It will be an electronic resource for anyone coordinating a portfolio of trials.

Full-scale deployment and execution of systematic reporting will commence on January 5, 2009. The reporting will be for both interventional and observational trials and information not already being reported into CTEP or DCP. All new trials after a production date of January 5, 2009 must be entered within 21 days of activation, and all active trials must be reported within 6 months. Starting in July 2009, quarterly reporting of accrual information will be required. Broad-scale communication for this project will begin in September 2008. Updates, downloadable brochures, a podcast based on the pilot training and orientation materials, e-mail list announcements, and/or presentations can all be found at the site, <www.cancer.gov/ncictrp>. Any feedback on the existing public Web site is welcomed and will be beneficial to project implementation.

Questions and Discussion

Dr. Adamson asked Dr. Buetow to clarify which studies would be classified as non-NCI-sponsored trials. Dr. Buetow said that all NCI-supported organizations would be reporting their portfolio of trials, and for industry-sponsored trials what will be required is the same information that one needs to report in the Summary 4 document.

Library of Standard Case Report Forms. Next, Dr. Buetow updated the Committee on the Library of Standard Case Report Forms. He explained that the goal is to create a uniform library of case report forms (CRFs) based on structured Common Data Elements and controlled vocabularies that can be used across the NCI community. caBIG has prioritized and selected data areas for harmonization and has agreed on core questions associated with the CRFs, as well as core data that still need to be collected. The process will move from internal review to a community review and then, ultimately, approval by stakeholders. Dr. Buetow noted that this activity is being coordinated with the FDA-sponsored Clinical Data Acquisition Standards Harmonization (CDASH) initiative. CDASH is focusing on elements common to all clinical studies, so their requirements are a proper subset of the materials for the caBIG database. CRF modules

being generated will include all CDASH "mandatory" questions plus additional oncology content. This collaborative effort entails mutual staffing support, project input, and shared terminology and metadata support.

Dr. Buetow summarized development of the Demography module. The workflow entailed collecting a variety of case report forms from different sources, creating a working group to develop the module, circulating the draft module for wider review, incorporating review comments, and obtaining NCI CTROC approval. The Demography module is now an NCI standard module. Other module development is following a similar workflow. CRFs in various phases of development include Baseline Assessment, Patient Identification, Patient Enrollment, Adverse Events, and Protocol Deviations.

Questions and Discussion

Dr. Adamson asked how the case report forms would initially be made available to the community. Dr. Buetow said that they are available electronically through the cancer data standards repository (caDSR) and will also be created in pdf class forms that map to the specific data elements. They also hope to have clinical trial software vendors import case forms into their individual products. Dr. Parkinson asked if follow-up forms are soon to come, because that is where companies struggle the most in terms of developing new sets of case report forms every time a new disease or drug emerges. Dr. Buetow stated that they recognize the real audience for the case report forms is not the people generating or analyzing the data in internal places, but the receptors of the data. He concluded by saying that as they move forward with this project, particularly into disease-based areas, it will be important to obtain input from the Committee.

XII. ANALYSIS OF COOPERATIVE GROUPS CLINICAL TRIALS COSTS—DR. JUDITH HAUTALA

Dr. Judith Hautala, Science and Technology Policy Institute (STPI), gave an update on the financial and organizational analysis of the Cooperative Groups that STPI is performing for NCI. The project emanates from a CTWG initiative to restructure the funding model for Cooperative Group Phase III trials; the first step in implementation of that initiative is to do a financial analysis of *current* Cooperative Group Phase III clinical trials costs. The goals of the project are to achieve a functional understanding of the Cooperative Group financial structure, identify areas of inadequate funding and examine the resulting consequences, and identify best practices from an organizational and financial approach across the groups and see if there are opportunities for enhanced efficiency. The overall goal is to develop an improved funding model for the Cooperative Group program that aligns funding more closely with actual costs and enhances overall cost-effectiveness.

The project focuses on infrastructure costs; not on analysis of costs for registering and managing patients at a site. However, aggregate site costs for accruing and managing patients are part of the overall analysis as they represent a large part of the functional financial structure. The analysis also compares CTSU costs with Cooperative Group costs for similar activities.

The analysis approach included both a functional mapping of the Cooperative Group grant application budgets and site visits to better understand financial and operational structures. In analyzing the grant applications, requested direct costs were mapped to a Common Budget Outline framework. The mapping was based on the most recent competitive renewals and FY2007 noncompetitive renewals; a detailed analysis of all PHS forms, budget justifications, and position descriptions was performed. Looking first at competitive renewals, a cross-group analysis was performed based on percent allocation across the groups to various budget categories—infrastructure versus site costs, costs for major infrastructure components, and sub-component costs within each major component. The majority of groups spend approximately 50

percent of their budgets on infrastructure and approximately 50 percent on accruing and managing patients. In terms of how various groups allocate infrastructure funding, the majority allocate the largest portion to statistics and data management. Beyond that, there is large variability in percent allocation to various infrastructure components. There is also significant variation in allocation to subcomponents. For example, in the case of operational functions, for half of the groups the largest category is administration costs but it varied widely for the other groups. Part of this variation may be real while part may be due to the way expenses are described in the grant applications. The grant application analysis then compared the competitive versus noncompetitive renewals for each group to assess changes in percent allocation to various budget categories. Awarded funds were always less than requested and no group spent their awarded funds in exactly the same percentage allocation as originally requested.

The site visit portion of the analysis is under way; one of the objectives is to understand the overall cost of operating a Cooperative Group program. This includes assumptions underlying budget requests, activities covered under each budget category, and the rationale for budget allocations and reallocations. Other objectives of the site visits are to assess fixed versus variable costs and understand their interplay, address the issue of "optimal capacity" in various functional areas in terms of the number of protocols ongoing or in development, number of accruals, etc., and look at specific sources and uses of third-party funding. Finally, STPI will look at allocation of costs by functional activity (i.e., Phase II versus Phase III trials, trial development versus trial conduct); examine costs for managing sites with low accruals; and speak with site personnel at the working level to solicit ideas for greater efficiency.

Dr. Hautala concluded with the status of their efforts: Grant application analysis is complete; site visits are under way and are expected to be complete by early October; and that analysis will provide the foundational material for the development of an improved funding model for the groups, which will be brought back to CTAC and NCI.

Questions and Discussion

Dr. Wade asked for clarification as to whether they would be comparing costs for CTSU accrual to Cooperative Group accrual. Dr. Hautala said they are looking at accrual activities of the CTSU compared with accrual activities among the participating Cooperative Groups, and may be able to assess if it is more cost-effective to perform certain activities through one or the other. Dr. Hautala acknowledged that metrics between these two entities may be significantly different.

Dr. Minasian asked if they will look at just the cost of starting the trial or conducting it, and how they consider trials that are started but close early. Dr. Hautala said they are too early in the data collection to know if they will be able to develop an estimate of the cost of running a Phase III or a Phase II trial. Those costs would be difficult to determine, since they will vary significantly by the number of patients, the length of the trial, etc. However, they should be able to identify trial development versus trial conduct costs and the cost-benefit that results from closing trials that do not accrue. Dr. Hillman commented that he hopes to see an extensive look at the model for calculating effectiveness in the fall presentation. Dr. Hautala stated that the ultimate goal is to use the financial analysis as foundational material for the development of an improved funding model that improves cost-effectiveness. Dr. Niederhuber recommended looking at the cost elements in clinical research that a committee of C-Change defined a couple of years ago; Dr. Hautala appreciated this suggestion.

XIII. NEW BUSINESS—DR. SHEILA PRINDIVILLE

Subcommittee and Working Group Updates. Dr. Prindiville reported that the CTAC Public-Private Partnership Ad hoc Subcommittee is continuing work on the clinical trials agreement standards and will present an update at the next meeting.

The proposed Evaluation Subcommittee has yet to form because priorities have been placed on developing the Operational Efficiency Working Group (OEWG). Steps are currently under way to form the OEWG; this working group will be looking at process mapping of institutional steps for clinical trials activation as well as reviewing various detailed analyses under way, some of which were presented today. The OEWG will be looking at the cost analyses presented by Dr. Hautala. The group will also review the CTWG baseline evaluation; this evaluation provides information about how many clinical trials are opening and accruing new patients. In addition, they will review the Central IRB analyses presented by Ms. McArthur. The charge of the Working Group is to try to reduce study activation time by 50 percent and increase the percentage of studies being launched and successful in reaching accrual targets, and then assure that studies are completed in a timely fashion. The OEWG will also be charged with optimizing the efficiency of NCI, sponsor, and investigator interactions.

Dr. Prindiville recognized Dr. Doroshow and Dr. Gabriel Hortobagyi from M.D. Anderson Cancer Center for volunteering to be chairs of this working group. Membership for the committee is currently being considered and the timeline for the start of planning teleconferences is July 2008, with plans for the first face-to-face meeting by the end of the year.

Future Agenda Items. Dr. Prindiville acknowledged that several Committee members have expressed interest in helping to form the agenda; she will communicate via phone or teleconference with these members in planning the December agenda. Suggestions for specific agenda items can be sent to Dr. Prindiville by e-mail.

ADJOURNMENT—DR. JOHN NIEDERHUBER

Dr. Niederhuber expressed his gratitude to all of the Committee members for their participation and input.

There being no further business, the 5th meeting of the CTAC was adjourned at 3:26 p.m. on Wednesday, June 25, 2008.