DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
4th CLINICAL TRIALS ADVISORY COMMITTEE MEETING

Summary of Meeting
February 4, 2008

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

CLINICAL TRIALS ADVISORY COMMITTEE
BETHESDA, MARYLAND
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The Clinical Trials Advisory Committee (CTAC) of the National Cancer Institute (NCI) convened for its 4th meeting on Wednesday, February 4, 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 (absent)
David S. Alberts
Kirby I. Bland
Deborah W. Bruner (absent)
Jean B. deKernion
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 (absent)
Timothy R. Rebbeck
Carolyn D. Runowicz
Daniel J. Sargent (absent)
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 (absent)
Paulette S. Gray, NCI
Lee Helman, NCI
Richard Pazdur, FDA
John F. Potter, DOD
Alan Rabson, NCI (via conference call)

Executive Secretary
Sheila A. Prindiville, NCI

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MONDAY, FEBRUARY 4, 2008

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

Dr. Niederhuber called to order the 4th CTAC meeting. He welcomed the Committee and the *ex officio* members, and then reviewed the confidentiality and conflict-of-interest practices required of the Board members during their deliberations. Members of the public were welcomed and invited to submit comments in writing, regarding items discussed during the meeting, to Dr. Sheila A. Prindiville, Director, NCI Coordinating Center for Clinical Trials (CCCT), within 10 days of the meeting. Any written statements by members of the public will be given careful consideration and attention. Dr. Niederhuber also called Board members' attention to the future CTAC meeting dates, which have been confirmed through 2009.

Motion. A motion was made to approve the minutes of the 14 November 2007 CTAC meeting. The motion was seconded, and the Board approved the minutes unanimously.

II. ANNUAL ETHICS UPDATE—DR. MAUREEN WILSON

Dr. Maureen Wilson, Deputy Ethics Counselor, Office of the Director (OD), provided an update on ethics issues for Federal Advisory Committee members. Per 18 USC Section 203 and 205, Conflict of Interest Statute, committee members may not participate personally and substantially in a particular matter in which the member has a personal or imputed financial interest if the matter will have a direct and predictable effect on that interest. Personal and substantial participation includes decision making, recommendations, evaluations, and negotiations. Particular matters involve actions that are focused on the interests of specific entities or a class of entities. Members were told that personal or imputed financial interests encompass the member, immediate family member, general partner, or organization in which the member is or is negotiating to be an employee or officer, director, or partner.

Standards of conduct for Committee members (Impartiality, 5 CFR Section 2635.502) include matters that are not statutory conflicts of interest but would raise a question, regarding the special government employee's impartiality in the matter. During the past 12 months, Dr. Wilson said that there are special concerns about this regarding activities that have been conducted particularly with regards to an entity with which a member or a member's household has or seeks employment or a business relationship, or an entity in which the member is actively involved with or has served as an employee or in a business relationship.

Dr. Wilson described Committee members' responsibilities, regarding representation (18 USC Section 205). The member may not represent a third party before the Federal Government in a matter involving specific parties in which the United States is a party or has a substantial interest if the member personally and substantially participated in the matter as a special government employee. Additionally, during the member's tenure as a special government employee, the member may not receive compensation for representational services rendered by the member or another before the Federal Government in a matter involving specific parties in which the United States is a party or has a substantial interest. The exceptions to these rules are if the representation is done in proper discharge of the member's official duties for the member, family, or estate for which the member is a trustee or the matter is a personnel action.
Dr. Wilson provided several scenarios, as examples, and invited CTAC members to contact her with specific questions or concerns, regarding ethics.

III. DIRECTOR'S UPDATE—DR. JOHN NIEDERHUBER

Dr. Niederhuber began by stating that the NCI's work to reduce the human and economic burden of cancer is important. In 2007, more than 1.4 million people were diagnosed with the disease, and more than 500,000 Americans died of cancer. In 2006, $206.3 B was spent on health care costs for cancer. Data show a decline in cancer mortality for both male and female populations. Dr. Niederhuber pointed out that the incidence rate for female breast cancer dropped 3.4 percent per year between 2001 and 2004, and he credited similar numbers seen for colon cancer to the impact of screening.

NCI FY 2008 Budget. The NCI budget remains a challenge, with appropriations that essentially are flat and likely to remain so in the coming years. In other words, the NCI has sustained a 12 percent loss in purchasing power since 2004. The fiscal year (FY) 2007 operating budget was $4.97 B and the FY 2008 appropriation is $4.8 B, a slight increase of $7.5 M (+0.16%). Dr. Niederhuber said that the NCI has continued to work through its budgetary process, including a partial restoration of the cuts that had been made to the Cancer Centers, Special Programs of Research Excellence (SPOREs), and Cooperative Groups; the remaining deficit stands at approximately 2 percent.

In developing its operating budget, the NCI established several policies, including that there would be 1 percent inflationary adjustments on non-competing grants, an approximately 2 percent decrease from commitments of record for categorical (non-modular) grants, and no reductions to modular non-competing research project grants (RPGs). In addition, the NCI would award fewer competing RPGs than in FY 2007 (1,283, down from 1,312), while meeting the NIH-provided target for competing new investigator R01 grants, and the average cost of competing RPGs would be 3 percent above the FY 2007 level. Other policies that were adopted are as follows: Type-2 (competing continuing) grants would receive 3 percent above current levels unless the principal investigator (PI) requested less than 3 percent or the peer review recommended a budget less than a 3 percent increase, grants recommended for seven modules or fewer would be reduced by 13 percent, and Type-1 (new competing) grants would be cut by 17 percent from the level requested and approved by peer review. Based on these policies, it is estimated that R01 paylines will be at the 12th percentile; new investigator paylines at the 19th percentile, and very large R01s (i.e., those that request more than $700,000 in direct costs) at the 14th percentile for the first and second rounds. Other RPG projections included R21 grants at the 14th percentile, R03 at a 210 priority score, R33 at a 155 priority score, and P01 grants selected on an individual basis.

President's Budget FY 2009. Dr. Niederhuber said that the President's Budget (PB) for FY 2008 would be released during the afternoon. He stated that it is likely that the NCI will operate under a continuing resolution for FY 2009. Little change, if any, is expected until after the inauguration of the next President of the United States, and it is probable that the NIH, as a whole, will toil under a flat budget for the upcoming 4 to 6 years.

Thoughts About the Future. Dr. Niederhuber stated that NCI's strategic objectives remain the preemption of cancer at every opportunity and the achievement of the best outcomes for all. To accomplish these goals, the NCI is working to understand the causes and mechanisms of cancer, accelerate progress in cancer prevention, improve early detection and diagnosis, and develop effective and efficient treatments. Its activities also aim to understand the factors that influence cancer outcomes, improve the quality of cancer care, improve the quality of life for cancer patients, and overcome cancer health disparities. Dr. Niederhuber described several ongoing and planned activities to help realize these objectives.

It is important to identify and understand the genetic defects that are present and lead to cancer, as the NCI continues its strong support of the Human Genome Project and the HapMap to understand germline defects. The wealth of information that results from these efforts will have a significant impact on the

ability to diagnose cancers and hopefully translate them into preventive measures, as well as facilitate studies in pharmacogenomics and the development of therapeutics - both gene therapy and novel small and large molecules and biologics. Innovation will be needed to translate the genetic information into research activities that target gene expression, defects in or absence of proteins, and the effect on cell signaling pathways or communication pathways between cells as well as tissue function and the presence or absence of disease.

Dr. Niederhuber highlighted several upcoming events. The NCI workshop on "Integrating and Leveraging the Physical Sciences to Open New Frontiers in Oncology," which will be held in late February, will explore opportunities to incentivize collaborations with leaders in physics, chemistry, mathematics, and cancer research, so theoretical physics can be used in the battle against cancer. The NCI and the American Association for Cancer Research (AACR) are co-sponsoring a cancer prevention think tank event, which will bring together basic, translational, and behavioral research scientists and clinicians to develop a comprehensive cancer prevention strategy that includes technology, emphasizes translational science, and enhances behavioral science. An annual meeting on translational research is being planned for the fall of 2008 and is co-chaired by Drs. Sheila Prindiville and Lynn Matrisian of the NCI Coordinating Center for Clinical Trials (CCCT). It was stated that the annual meeting on translational research will replace the summer SPORE meeting. Dr. Matrisian is also helping the NCI integrate the Translational Research Working Group (TRWG) recommendations into the CCCT, through the establishment of a Translational Research Operation Committee (TROC) under CTAC. The Small Business Innovation Research (SBIR) Bridge Award in Drug Development intends to cover the gap between Phase I and II SBIRs and private investment. Dr. Niederhuber noted that the bridge mechanism, which requires matching or greater funds from venture capital, has been used quite effectively by the National Science Foundation (NSF).

NCI initiatives at the Clinical Research Center include the strengthening of the medical oncology division, recruitment of a new chief of laboratory pathology, pathology space renovations, and the development of an Oncology Imaging Center. Additional activities include the exploration of a satellite center at Suburban Hospital, the strengthening of fellowship training, and participation in a rare diseases clinic. The Clinical Research Center had a very successful start up of the first trial in which the PI was an extramural investigator; it is a Phase I/II trial focused on hereditary medullary thyroid carcinoma. With pediatric and adolescent patients from throughout the United States and some foreign locales, who are enrolled in the study and admitted to the Center, the Clinical Research Center is now truly heralded as a national resource.

Barriers to overcoming cancer include resources to support scientific discovery, the recruitment and retention of future scientists and investigators, the time and expense required for translation to man, an old clinical trials system and regulatory process, and the provision of access to health care for everyone. In closing, Dr. Niederhuber referred members to copies of the FY 2009 Bypass Budget, included in the meeting materials.

Questions and Discussion

Dr. David R. Parkinson, President and CEO, Nodality, Inc., asked for further details about the SBIR Bridge Award. Dr. Niederhuber said that the mechanism is expected to be used starting in late 2008 or early 2009, and that it involves a very rigorous process that includes due diligence that should facilitate review processes. To assist the NCI with this contract vehicle, an NCAB subcommittee will likely be established. Dr. Nancy P. Mendenhall, Professor, Department of Radiation Oncology, University of Florida Health Science Center, wondered whether the projects other than drug development, such as technology development, would be considered. Dr. Niederhuber affirmed this and added that there has been a shift toward solicited projects. Dr. Jean B. deKernion, Professor and Chairman, Department of Urology, and Senior Associate Dean for Clinical Operations, David Geffen School of Medicine,

University of California at Los Angeles, favored the concept and asked about the placement of the SBIR Bridge Awards along the clinical trials continuum as well as the funding level. Dr. Niederhuber replied that awards can be made to different phases and the funding will depend on the individual project; he said that costs increase significantly when studies focus on agents in humans and that this mechanism should greatly enhance the ability of many worthy small projects to move forward.

Dr. Joel E. Tepper, Hector MacLean Distinguished Professor of Cancer Research, Department of Radiation Oncology, University of North Carolina, Lineberger Comprehensive Cancer Center, asked about the integration of other mechanisms in addition to the SPOREs into the NCI portfolio.
Dr. Niederhuber said that the SPORE program has elected among itself a group of four individuals to serve as an executive group of PIs, and they have held meetings with Drs. Niederhuber and James H. Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD); it is hoped that the SPORE program will play an important role in the NCI's clinical and translational research. Dr. Doroshow added that the NCI leadership has committed to involve the entire NCI Executive Committee (EC) in the overall management and integration of the SPORE program within the NCI. Dr. Kirby I. Bland, Fay Fletcher Kerner Professor and Chairman, Department of Surgery, School of Medicine, and Deputy Director, UAB Comprehensive Cancer Center, University of Alabama at Birmingham, agreed about the great advantage of a strong interface between the SPOREs and the NCI leadership.

IV. COORDINATING CENTER FOR CLINICAL TRIALS (CCCT) UPDATE—DR. SHEILA A. PRINDIVILLE

Dr. Prindiville stated that implementation of most of the Clinical Trials Working Group (CTWG) initiatives has begun. Coordination initiatives include establishing a comprehensive database, containing regularly updated information on all NCI-funded clinical trials and to realign NCI funding, academic recognition, and other incentives to promote collaborative team science and clinical trial cooperation.

To promote collaborative team science, a project to modify the Clinical Trials Program guidelines has been initiated under the CTAC Ad hoc Coordination Subcommittee. In addition, the NCI is evaluating the feasibility of accruing patients to SPORE and Cancer Center clinical trials through NCI's Cancer Trials Support Unit (CTSU). The Cancer Therapy Evaluation Program (CTEP) is sponsoring a multi-institutional Phase II trial as well. The Cancer Clinical Investigator Team Leadership Award provides a new form of recognition for investigators, who offer excellent contributions that advance effective new treatments toward practice through collaborative team science; Dr. Prindiville noted that approximately $1 M is needed for 20 to 30 awards that provide 10 to 20 percent salary support. Modifications to institutional incentives to reward clinical investigation were recommended by the CTWG with the intent to change the career development, promotion, and other reward criteria of academic institutions. It was noted that any institutional modifications require the coordination of organizations outside the NCI and NIH and that the other proposed activities have higher priority, given their likelihood of a higher success rate.

Questions and Discussion

Dr. David S. Alberts, Director, Arizona Cancer Center, The University of Arizona College of Medicine, suggested that academic deans could be encouraged to become more involved; for instance, the NCI could require that grants to investigators in a university be matched by the university. Dr. Bruce J. Hillman, Theodore E. Keats Professor of Radiology, Department of Radiology, and Professor, Department of Health Evaluation Sciences, University of Virginia School of Medicine, stated that a greater amount of collaboration would be good, but that recognition should be given to all partners. Dr. James L. Abbruzzese, Chairman, Department of Gastrointestinal Medical Oncology, University of Texas M.D. Anderson Cancer Center, agreed but cautioned that the CTAC and NCI will need to determine priorities carefully, as many of these ideas require a change in the culture of academia that need to occur outside the NCI. Dr. Joel E. Tepper, Hector MacLean Distinguished Professor of Cancer Research, Department of Radiation Oncology, University of North Carolina, Lineberger Comprehensive Cancer Center, commented that academic recognition could be influenced through the language of grants and peer review awards. Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, Northeast Utilities Chair in Experimental Oncology, University of Connecticut Health Center, noted that clinical mechanisms, such as Cooperative Groups, currently are underfunded and suggested that current cooperative mechanisms be rewarded and provided adequate time for implementation rather than starting a new activity. She also stated that smaller institutions would not be able to provide matching funds to the extent that large institutions might. Dr. Richard L. Schilsky, Professor of Medicine and Associate Dean for Clinical Research, Biological Sciences Division, University of Chicago Pritzker School of Medicine, wondered at the inception of this initiative at a time when the NCI has been actively phasing out the use of U10 grants. Dr. Schilsky stated that any new initiative should be fashioned so that academia recognizes it in terms of grant support. Dr. Jean DeKernion, Fran and Ray Stark Professor of Urology, Professor and Chairman of the Deparment of Urology, David Geffen School of Medicine at UCLA, echoed the importance of speaking a language that captures the deans' attention, particularly for the impact on investigators' career prospects. Dr. Timothy R. Rebbeck, Professor, Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, wondered if data have been collected on the influence of collaborative work on promotions.

Dr. Doroshow responded that the NCI's baseline evaluation revealed that out of 52 institutions, none listed collaborative clinical investigation, as a criterion.

Dr. Sandra J. Horning, Professor of Medicine, Stanford Comprehensive Cancer Center, Stanford University Medical Center, said that grant support is important; no other organization is funding clinical trials in the way that the NCI does. Dr. Heidi Nelson, Fred C. Anderson Professor, Division of Colon and Rectal Surgery, Department of Surgery, Mayo Clinic Foundation, added that other institutions follow the lead of the NIH. Dr. Niederhuber stated that the challenges posed by the clinical and academic cultures will not be solved solely through financial increases; a change is needed in the recognition of those, who conduct translational research, from the initial concept to the first patient. Dr. Stephen S. Grubbs, Chief of Oncology, Medical Oncology Hematology Consultants, PA, noted that there is a large number of clinical investigators in the community, who would welcome recognition. Dr. Parkinson added that it is very difficult to change behavior; one way to reward recognition would be to change evaluation criteria that could help set up a system to drive behaviors. Dr. Niederhuber noted that changes would be easier if the budget kept up with inflation. Dr. deKernion stated that he has observed some shifts and felt that the emphasis on translational research is paying off.

V. RECENT GASTROINTESTINAL (GI) CANCER STEERING COMMITTEE ACTIVITIES—DRS. MEG MOONEY AND JOEL TEPPER

ACOSOG-Z6051: A Phase III Prospective Randomized Trial Comparing Laparoscopic-Assisted Rectal Resection (LARR) to Open Resection for Rectal Cancer

Dr. Meg Mooney, Acting Branch Chief, Clinical Investigations Branch, CTEP, described a Phase III trial concept that the Gastrointestinal (GI) Steering Committee recently approved: Comparing Laparoscopic-Assisted Rectal Resection (LARR) to Open Resection for Rectal Cancer (ACOSOG-Z6051). Previous Phase III trials on laparoscopic surgery for colon cancer included a US Cooperative Group intergroup trial led by the North Central Cancer Treatment Group (NCCTG) evaluating open colectomy versus laparoscopic-assisted colectomy (the COST trial) and the United Kingdom Medical Research Council (UKMRC) study of conventional versus laparoscopic-assisted surgery in colorectal cancer (the CLASICC trial). Results from both trials demonstrated that there was not a difference in the 3-year local recurrence rates or overall survival between the 2 techniques; however, there were concerns regarding the laparoscopic technique for the small subset of patients with rectal cancer who were enrolled on the CLASICC trial. The ACOSOG-Z6051 trial was designed to evaluate whether the laparoscopic technique is an acceptable alternative to conventional surgical treatment for patients with rectal cancer. Patients with stage II or stage III adenocarcinoma of the rectum will be eligible for the trial. Stratification factors for the study will include tumor location in the rectum, registering surgeon, and the type of operation planned. The primary endpoint is a composite of the oncologic parameters indicative of an adequate resection, and the expected rate of success is 90 percent. Secondary endpoints include complications, the use of pain medications, operating room time, postoperative rectal function, recurrence rates, and quality of life (QOL). The target sample size for the trial is 480 patients accrued over 4 years; however, if accrual rate better than expected, the sample size for the trial will be increased to 650 patients to increase the power of the study.

In its review, the GI Steering Committee recommended that a more homogeneous patient population be targeted, a detailed method of pathologic evaluation be required, and the trial be configured as a Phase III study with appropriate design and sample size to test whether the laparoscopic technique results in oncologic parameters that are indicative of an adequate surgical resection. Other recommendations focused on operating characteristics, stratification factors, skills verification requirements, preoperative staging requirements, and intergroup participation.

The concept was modified based on these concerns. A more homogeneous patient population was specified and a detailed method of pathologic evaluation of the resected surgical specimen based on the Quirke protocol was added. Moreover, the trial was reconfigured, as a Phase III study with appropriate operating characteristics, and a plan was developed to increase the sample size if the accrual went well. Operating characteristics of the statistical analysis plan also were modified, including addressing issues related to patient refusal of randomization and "conversion" from laparoscopic to open technique during the operation. Stratification factors were also modified, as well as the skills requirements for surgeons, particularly related to the number of colon laparoscopic resections needed.

Dr. Mooney described the timeline for the concept review and protocol development. The concept was submitted to the Rectal Task Force in March/April 2007 for discussion. The concept was submitted to and evaluated by the GI Steering Committee in May 2007. In June 2007, the Cooperative Group revised the concept and resubmitted it to the GI Steering Committee for a second evaluation, and the approval letter was issued in July 2007. The Protocol Development/Review is now in its final stages.

Questions and Discussion

Dr. Niederhuber lauded the cohesiveness of the process. Dr. Nelson agreed that the process is seamless; she said that the thoughtful and appropriate reviews also are appreciated.

Dr. deKernion said that there may be challenges in interpreting the data, as it will be influenced by the skill of the surgeon, who is performing the laparoscopy. He noted that prostate cancer investigators faced a similar issue when testing a skill set. Dr. Nelson responded that the same surgeon might be performing both types of surgery, and that all the surgeons will need to be credentialed.

Dr. Schilsky asked if the shift toward neoadjuvant chemotherapy plus radiation therapy complicates laparoscopic surgery or if it changes the assumptions that the trial is based on regarding surgical outcomes or success rates. Dr. Nelson responded that the recommendations were to use a homogeneous population and thus target those with higher risk tumors. She also said that this trial takes the field into a new era, as laparoscopic surgery allows recording and visualization as well as pathological input. Dr. Tepper added that data exist to support the assumptions. Dr. Bland wondered how conclusions were reached, regarding the validation of radiation sensitizers and the use of ≥ 1 mm metric for the circumferential resection margin. Dr. Nelson said that it was assumed that the randomization process would wash out differences, and that the ≥ 1 mm metric is currently used as an acceptable resection margin in rectal cancer.

Ms. Susan A. Leigh, Consultant, National Coalition for Cancer Survivorship, asked about the consideration of QOL issues in the trial. Dr. Nelson responded that the Dr. Jeff Schlom will be helping evaluate the instruments and study design with respect to evaluation oft QOL, rectal incontinence, and other issues.

Pancreas Cancer State-of-the-Science (SOTS) Meeting

Dr. Tepper said that the GI Steering Committee had encouraged its task forces to apply for state-of-the-science (SOTS) meetings, and that the Pancreas Task Force was selected; a Pancreatic Cancer SOTS Steering Committee was formed and met via frequent teleconferences for many months. A meeting concept evolved with a balance between laboratory and clinical science, and with the primary objective to define the NCI clinical trial agenda. Lectures included topics such as cell-associated signaling pathways as targets, tumor and host factors contributing to pancreatic cancer, and preclinical models in translational research. Workshops addressed preclinical target identification and tumor monitoring, clinical target validation and the design of therapies, the use of biospecimens to develop biomarkers, and vaccines as well as design, interpretation, and endpoints in clinical trials. The workshops also discussed adjuvant, metastatic, and locally advanced clinical trials and biomarkers in clinical trials.

Conclusions based on the meeting included that large-scale Phase III trials should not be initiated at the present time, but there should be an emphasis on Phase II studies to help define strategies most likely to succeed, and Phase II trials should be coordinated between the cooperative groups with consistent entry and evaluation criteria. Additionally, the meeting identified multiple targets of potential interest (e.g., K-ras, C-met, and Hedgehog) and the need for basic research on EMT, stem cells, and stroma. Clinical trials likely will need to combine multiple agents and be driven by preclinical data, with a major reliance on validated animal models, such as xenografts and genetically engineered models. Dr. Tepper said that, based on the SOTS meeting, appropriate animal models systems should be developed and validated, infrastructure is needed for the comparison and use of these models within the clinical research community. Based on these models, Dr. Tepper added that combination drug strategies should be developed to be tested in randomized Phase II trials.

Questions and Discussion

Dr. Abbruzzese, who also attended the Pancreas Cancer SOTS meeting, said that it is difficult to know which pathway will lead in the right direction, but that the community recognizes the need to attack multiple targets simultaneously. Participants also discussed the information that Phase II studies should yield to help Phase III studies be successful. Because advances in surgery have been limited, such as in how patients are staged or the topological evaluation of resection margins, there should be an emphasis on pathological and preoperative evaluation of patients; these issues should be included in clinical trials.

Dr. Schilsky noted that prior SOTS meetings had yielded good recommendations and asked how the new recommendations would be disseminated to and implemented to the Committee. Dr. Niederhuber said that the NCI reviews meeting comments carefully to help guide the decisionmaking process and that extramural suggestions are especially considered in the allocation of money set aside for grant exceptions; he also stated that pancreatic cancer is an example of where more science is needed. Dr. Mooney added that the CCCT is working on collaboration and coordination with the GI Steering Committee, as well as a more robust infrastructure to facilitate the implementation of recommendations.

Dr. Tepper commented that some research, such as those involving animal models, needs to be supported through other mechanisms. Dr. Hillman said that imaging could facilitate this work. Dr. Lee Helman, Chief, Pediatric Oncology Branch, and Deputy Director, Center for Cancer Research (CCR), mentioned that Dr. Terry Van Dyke has developed genetically engineered models that could be used to foster these specific research topics.

VI. CLINICAL TRIALS DATABASE UPDATE—DR. KENNETH H. BUETOW

Dr. Kenneth H. Buetow, NCI Associate Director for Biomedical Informatics and Information Technology, presented the clinical trials policy implementation plan. Dr. Buetow stated that the workflow for the clinical trials database involves four steps, as follows:

1. The trial is registered on-line via the NCI Clinical Trials Portal. Registration consists of entering a small number of data elements describing the trial into the portal, and then uploading the protocol document. Common data elements (CDEs) have been identified for protocol registration; these include the lead organization and protocol identification, PI, sponsor, protocol title and document/consent document, the trial type and phase, and the accrual status and status date. The NCI Clinical Trials Portal also supports batch upload of protocol registrations via FTP.

2. NCI staff abstract the remaining required protocol information from the uploaded protocol document into the system to support queries and reporting. Sufficient information will be entered to fulfill the data requirements for generation of NCI Cancer Center Summary 4 Reports, and protocol registration to clinicaltrials.gov according to the requirements of the FDA Amendments Act of 2007.

3. Patient-level data are submitted via the CDS Web Site (or via file transfer protocol [FTP]). The data conform to the Clinical Data Update System (CDUS)-abbreviated standard established by the NCI Cancer Therapy Evaluation Program (CTEP).

4. Reporting on the entered data is available via an analysis/reporting module.

As implied above, the system will have the ability to generate NCI Summary 4 and clinicaltrials.gov submissions.

Current policies to guide users in the proper population of the database are that additional registration or reporting is not required for trials already reported to the CTEP or Division of Cancer Prevention (DCP), and that, at the present time, reporting is required only for interventional trials. For NCI-sponsored trials, the Principal Investigator's office is responsible for reporting for all sites; for non-NCI-sponsored trials, reporting will be at the site level. Initially, new trials begun on January 1, 2009, or thereafter must be entered after that date; all active trials must be entered within 6 months (*i.e.*, by June 30, 2009). Starting July 1, 2009, the system will begin accepting the quarterly reporting of all trial updates, as well as the quarterly entry of accrual information. The first quarterly deadline for the submission of trial updates and accrual information will be September 30, 2009.

The phased deployment of the database will start with an operational pilot in July 2008. NCI is assembling educational documents and an informational web site. Potential sites for the operational pilot project will be identified and recruited, information will be prepared for dissemination to sites about pending requirements, an NCI office is being set up to perform quality assurance and protocol data abstraction staff, and help desk staff will be trained.

Dr. Buetow explained that the pilot project will target approximately five sites/grantees and be implemented in July through December 2008. The first production phase is scheduled to start in January 2009 and will include the updating of protocol detail data elements as well as the quarterly reporting of accruals and protocol updates. It is planned that a pilot of outcome and adverse event reporting will begin in January 2010.

Questions and Discussion

In response to a request by Dr. Niederhuber for additional details, Dr. Buetow said that the FDA Authorization Act will impose increasingly stricter requirements on clinical trial reporting and that the NCI is working actively with NIH to ensure that the clinical trials database is consistent with and facilitates the requirements of clinicaltrials.gov.

Dr. Laurence H. Baker, Chairman, Southwest Oncology Group (SWOG), and Professor of Medicine, University of Michigan, asked whether accrual rates would be able to be obtained from a pharmaceutically sponsored study with, for instance, 15 sites that have distinct numbering systems. Dr. Buetow replied that there are some factors, such as how blinded the investigators are, that need to be taken into consideration, but that an aggregate report will be produced.

Dr. Rebbeck, Dr. Alberts, and Mr. Gabriel M. Leung, Executive Vice President, and President, Oncology, OSI Pharmaceuticals, requested clarification about which trials must follow reporting requirements. Dr. Buetow said that data on all interventional trials that are supported by the NCI, either directly through sponsorship, or indirectly (*e.g.*, through a cancer center core grant) must be reported, and that, at this time, there are no additional requirements for reporting of closed trials. In response to a question by Dr. Runowicz, Dr. Doroshow clarified that the NCI already received information on accrual rates from industry-sponsored trials at NCI-designated cancer centers. Dr. Parkinson noted that the NCI is now tracking grant-supported funding. He also commented on pharmaceutical companies' focus on meeting FDA requirements and noted a distinction between reporting to the FDA versus to the NCI or NIH. Dr. Parkinson said that many in industry consider accrual rates to be proprietary information and suggested that the NCI consider what would be needed for public reporting in a global clinical trials system. He also observed that smaller companies likely would need to publish press releases when updating their accrual information, as accrual data could be considered "material information" and current regulations stipulate that such information must be released to everyone at the same time or be considered "insider information." Dr. Alberts encouraged the NCI to coordinate its efforts with the FDA. Dr. Buetow said that the National Library of Medicine (NLM) is holding meetings to address some of these topics. Dr. Doroshow added that the new law has the greatest effect on the NCI Cancer Centers.

Ms. Leigh asked who currently is allowed access to the information, and Dr. Nelson asked about access to information about adverse events. Dr. Buetow responded that the intent is to open the registry to the public; access to accrual data is limited. Discussions are ongoing about both accrual rates and adverse events. Dr. Doroshow said that there have been many prior discussions, and that data on adverse events would be monitored for trends only by the NCI. Dr. Schilsky commented that if the broad goal is to make information available to the research community, then it needs to be available to more investigators.

Dr. Niederhuber commended Dr. Buetow's efforts in keeping the momentum in developing the clinical trials database.

VII. NEW BUSINESS—DR. JOHN NIEDERHUBER

Subcommitee and Working Group Updates. Dr. Prindiville said that the CTAC has two existing Ad hoc subcommittees (Public-Private Partnership and Coordination) and that the Evaluation Subcommittee and Operational Efficiency Working Group have been proposed.

The objective of the Ad hoc Public-Private Partnership Subcommittee is to provide advice to the Director of the NCI on how to enhance NCI-sponsored clinical trials through collaborative interactions with the private sector. Its initial focus is on extramural oversight for the collaborative project between the NCI and the Life Sciences Consortium, CEO Roundtable, to standardize clinical trials agreement terms. This Standardization of Clinical Trials Agreement Terms project has begun and the involvement of academic medical centers, Cooperative Groups, industry, and legal advisors has been solicited, and a multidisciplinary team is compiling a list of agreement terms to be standardized (e.g., intellectual property and licensing, publishing rights, confidentiality, ownership of data, and risk and indemnification). Other work will include the analysis of agreements to develop options for harmonization, and the development of modules of potential standardized clauses and a structured approach to achieve buy-in and consensus by key stakeholders.

The Ad hoc Coordination Subcommittee provides advice to the NCI Director, regarding the promotion of collaboration among the various components of the NCI-supported clinical trials infrastructure. Its initial projects are to: harmonize program guidelines among Cancer Centers, SPOREs, and Cooperative Groups to enhance collaboration; and establish a CTAC Planning Working Group to discuss the integration of TRWG implementation into CTAC's purview.

The proposed Operational Efficiency Working Group will address Dr. David Dilts' findings on the NCI clinical trials process, which have been presented to the Cancer Center Directors. Nominations for the Working Group have been solicited from the Cancer Centers, and additional members will be solicited from Cooperative Groups, SPOREs, and other stakeholders.

CTAC Charter Changes To Accommodate TRWG. Dr. Prindiville stated that there are three proposed changes to the CTAC in light of its inclusion of translational research. 1) The CTAC will advise, assist, consult with, and make recommendations to the NCI Director, Deputy Directors, and the Director of each NCI Division on the effectiveness of NCI's translational research management and administration in meeting demands and opportunities across disease sites, patient populations, the TRWG developmental pathways, and the range of molecular mechanisms responsible for cancer development. 2) The CTAC will advise the NCI Director and Executive Committee on the appropriate magnitude for the dedicated translational research budget target and recommend allocation of translational research funding across organizational units, programs, disease sites, populations, developmental pathways, and molecular mechanisms. 3) The CTAC will ensure that the appropriate emphasis is placed on rare cancers, medically underserved populations, and historically lower resourced pathways to clinical goals.

Internal NCI Changes: CTOC and CCCT changes to accommodate TRWG. Dr. Prindiville said that the mandates of the Clinical Trials Operating Committee (CTOC) and the CCCT both are being expanded to include oversight of translational research programs. In addition, CCCT staff will be increased to manage TRWG; this includes the work of Dr. Matrisian as well as program directors, analysts, and support staff.

Future Agenda Items. Topics for future meetings include the prioritization of biomarker, imaging and QOL supplements recommended for funding; barriers to using the central Institutional Review Board (IRB); an interim report of the financial analysis of Phase III trial costs; supplemental funding program

for minority and underserved population accrual to cancer clinical trials; and an update of the activities of the Symptom Management and Health-Related QOL Steering Committee.

CTAC members also suggested the following topics: report on the NCI's theoretical physics February meeting; updates on SBIR Bridge Awards, as related to the clinical trial review process, as well as the SPOREs, NCI Community Cancer Centers Program (NCCCP), and case report forms (CRFs); and issues related to funding (or lack of funding) for translational studies.

VIII. 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 4th meeting of the CTAC was adjourned at 11:35 a.m. on Monday, February 4, 2008.