DEPARTMENT OF HEALTH AND HUMAN SERVICES
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NATIONAL CANCER INSTITUTE
13th CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE MEETING

Summary of Meeting
March 3, 2011

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

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
BETHESDA, MARYLAND
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The 13th meeting of the Clinical Trials and Translational Research Advisory Committee of the National Cancer Institute was convened on Thursday, March 3, 2011, at 9:00 a.m. in Conference Room 10, C-Wing, 6th floor, Building 31 on the National Institutes of Health main campus in Bethesda, MD. Dr. James L. Abbruzzese, Chair of the Clinical Trials and Translational Research Advisory Committee, presided during the meeting. The meeting was adjourned at 2:52 p.m.

Chair
James L. Abbruzzese

CTAC Members
Peter C. Adamson
Susan G. Arbuck
Monica Bertagnolli
Deborah W. Bruner
Curt I. Civin (absent)
Kenneth H. Cowan (absent)
Everett Dodson
Olivera Finn
Stephen S. Grubbs
Sandra J. Horning (absent)
Scott M. Lippman (via teleconference)
Nancy P. Mendenhall
Lisa A. Newman (absent)
David R. Parkinson
Edith A. Perez
Nancy Roach
Daniel J. Sargent
Richard L. Schilsky
Mitchell Schnall
Peter G. Shields
Joel E. Tepper
James L. Wade, III

***Ex Officio* Members**
James H. Doroshow, NCI
Paulette S. Gray, NCI
Rosemarie Hakim, CMS
Lee Helman, NCI
Michael J. Kelley, VA (absent)
Richard Pazdur, FDA (absent)
John F. Potter, DOD (absent)
Alan Rabson, NCI (via teleconference)

Executive Secretary
Sheila A. Prindiville, NCI

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THURSDAY, MARCH 3, 2011

I. CALL TO ORDER, OPENING REMARKS, AND NCI UPDATE—DRS. JAMES ABBRUZZESE AND JAMES DOROSHOW

Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), called to order the 13th Clinical Trials and Translational Research Advisory Committee (CTAC) meeting. Dr. Doroshow introduced the new Chair of CTAC, Dr. James Abbruzzese, Chairman, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center. Dr. Abbruzzese then reviewed the confidentiality and conflict-of-interest practices required of Committee members during their deliberations. Members of the public were invited to submit written comments related to 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. Abbruzzese reminded members that the meeting was being videocast by the National Institutes of Health (NIH) Events Management. The videocast will be available for review following the meeting at: http://videocast.nih.gov/.

Motion. A motion was made to approve the minutes of the December 15, 2010, CTAC meeting. The motion was seconded, and the minutes were approved unanimously.

NCI Update. Dr. Doroshow reminded CTAC members that there is ongoing recruitment for positions within the Office of the NCI Director. Candidate recommendations should be sent to Dr. Harold Varmus, Director, NCI.

II. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations, NCI, reported on the status of appropriations and gave an overview of the 112th Congress.

Fiscal Year (FY) 2011 Appropriations Activities. The Federal Government is operating under a two-week Continuing Resolution (CR) that expires on March 18, 2011. The CR cut $4 billion in funding from the FY 2010 budget. The reason the government is operating under a succession of CRs is because the 111th Congress, which ended in December, did not pass a budget resolution or any appropriations bills for FY 2011. The 112th Congress now has until March 18th to pass a full-year CR, which is a likely option, or pass another short-term CR. In order for the full-year CR to pass, the FY 2011 funding level must be agreed upon. The funding may be flat at the FY 2010 level, cut down 5.3 percent to the FY 2008 level, or reduced even further. The new Chairman of the House Appropriations Committee, Congressman Harold Rogers of Kentucky, has indicated that the Committee will find savings in every area of the Federal Government.

FY 2012 Appropriations Status. Despite the fact that appropriations for FY 2011 have not been set, the FY 2012 budget process has begun. The President announced his budget on February 14, 2011, which included an allocation of $31 billion to the National Institutes of Health (NIH). Of that amount,

NCI would receive $5.1 billion. There have been mixed reactions to the President's Budget. Congressman Rogers expressed concern that the budget does not go far enough in terms of spending cuts. However, several members of Congress have made public statements to suggest that exceptions to budget cuts can and should be made for biomedical research and/or the NIH budget. A list of Senate Appropriations and House of Representatives Appropriations Committee members was presented. Ms. Erickson encouraged the CTAC members to take note of new Committee members who might be educated on NCI and NIH.

New Legislation. A bill to extend the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs was signed by the President on January 31, 2011. The SBIR Extension (HR 366) temporarily extends the SBIR/STTR programs through May 31, 2011.

The Breast Cancer Patient Protection Act (HR 111) was introduced by Representative Rosa DeLauro on January 5, 2011. This bill would require coverage for minimum hospital stays and secondary consultations following mastectomy or other breast surgery.

Congressional Outreach. NCI is reaching out to the 112th Congress in a number of ways. For example, a briefing with congressional members and NCI senior staff has been scheduled to discuss the release of the NCI Bypass Budget. Dr. Varmus is also interested in meeting with members of the Appropriations Subcommittees in hopes of cultivating new champions of NIH and NCI.

112th Congress—Outlook. Priorities for the 112th Congress include resolving appropriations, increasing emphasis on oversight, and implementing or blocking the implementation of the Affordable Care Act. Last month, Representative Brian Higgins made the following hopeful comment on the House floor regarding Congressional commitment to cancer research: "Few issues are more unifying than the fight to cure cancer. As we choose our national priorities carefully, medical research, which holds the dual promise of economic and scientific growth, should be a focal point in America's rise to the top."

Questions and Discussion

Dr. Nancy Mendenhall, Professor, Department of Radiation Oncology, University of Florida Health Science Center, requested further elaboration regarding increased oversight by Congress. Ms. Erickson clarified that this priority may not have any impact on NIH or biomedical research. Congressman Darrell Issa, Chairman of the House Committee on Oversight and Government Reform, has made many statements about his intention to focus on oversight activities; however, he has not indicated where he would focus these activities or that any would be specific to NIH.

III. SPECIAL TRANSLATIONAL RESEARCH ACCELERATION PROJECTS (STRAP) IMPLEMENTATION UPDATE: IMMUNE RESPONSE MODIFIER (IRM) PATHWAY PROJECTS—DRS. SHEILA PRINDIVILLE, RENIER BRENTJENS, AND ANDREW RAUBITSCHEK

Introduction. Dr. Sheila Prindiville, Director, Coordinating Center for Clinical Trials, NCI, gave an update on the implementation of the STRAP program, which resulted from a recommendation of the Translational Research Working Group (TRWG) in their 2007 report. The TRWG recommended that NCI

establish a program to advance prioritized, early translational research. STRAPs are intended to accelerate research projects in a manner that is not possible with existing approaches and should have a high probability of significantly advancing the field. Additionally, the science of a STRAP project should be at a point where providing additional support would truly accelerate it. It was envisioned that STRAPs would incorporate project management by a group of external as well as internal NCI staff who will specifically monitor timeliness and milestones.

NCI initiated the STRAP program with the Immune Response Modifiers (IRM) TRWG developmental pathway as a pilot. The funding announcement was issued as an administrative supplement to existing grants in May 2010. Investigators had six to eight weeks to respond to the announcement. The IRM Pathway Prioritization Working Group prioritized antigens and immune-modifying agents to be included in the announcement. The Working Group of immunologists then helped identify the four focus opportunity areas for the announcement; adoptive cell therapy, antibody or "T-body" therapy, cancer vaccine targeting a viral antigen, and vaccine targeting a cellular antigen (self or tumor). Additionally, the group recommended that NCI provide key resources—those items not easily obtained in the community—including IL-12 and IL-15, should any project need them.

The submission and evaluation process was notably different from a standard grant review. The evaluators assessed whether the proposal represented a clinically significant translational research opportunity that could be accelerated with this type of funding and whether it addressed one or more of the four areas specified in the announcement. Submissions proposing research in nonpriority areas had to include a justification for doing so. The evaluators also considered whether: the proposal could easily be funded through another grant mechanism such as an R01; the proposal addressed developmental requirements envisioned by the STRAP program; there was reasonable likelihood that the project would lead to an Investigational New Drug (IND) and clinical testing; and the proposed researchers had the appropriate expertise.

NCI received 23 proposals in response to the supplemental funding announcement. It was found that half of the proposals took advantage of the identified prioritized antigen and immune modifier agents. Some applicants indicated having their own source of IL-12 and IL-15; neither of the two funded proposals used IL-12 or IL-15. Additionally, the submissions were looked at to see whether proposals followed the IRM pathway, specifically regarding clinical trial planning and informing of future clinical trials. Almost all submissions included steps along the IRM pathway.

[A summary of the Questions and Discussion for this section follow the summaries of the STRAP presentations.]

A Multicenter Clinical Consortium to Investigate the Biology and Clinical Efficacy of Autologous T Cells Genetically Targeted to the CD19 Antigen in Patients with B-Cell Malignancies. Dr. Renier Brentjens, Assistant Member, Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, described the IRM pathway studies and the project funded by the STRAP program. The study's immunotherapy approach consists of taking a patient's own T cells and, through genetic modification, redirecting those cells to target a tumor-associated antigen and a B-cell-specific antigen, CD19. This is a novel approach to treat patients with B-cell malignancies. The basic science behind this is that a T cell can be genetically modified to produce an artificial T-cell receptor or chimeric antigen receptor (CAR), one of the priorities of the STRAP award. Typically, the heavy and light chains of a mouse monoclonal antibody targeted to the desired tumor-associated antigen are linked together by a Ser-Gly repeat to produce a single-fragment antibody. That fragment is subsequently fused to a

transmembrane domain, which may or may not be biologically active, and then to a T-cell receptor signaling domain (the CD3 zeta chain). The resulting chimeric antigen receptor gene can be inserted into a viral vector for gene transfer into the patient's own T cells.

Selection of the tumor-associated target antigen is very important. CD19 is ideal because the bone marrow stem cell does not express CD19, so the risk of developing bone marrow aplasia is minimal. CD19 is one of the first antigens expressed during B-cell maturation and is expressed throughout maturation. Almost all malignancies that develop in maturing B cells (e.g., acute lymphoblastic leukemia, non-Hodgkin lymphoma, chronic leukocytic leukemia, follicular lymphoma, and a subset of myelomas) express CD19. Therefore, there is a large pool of diseases for which targeted CD19 therapy would be applicable. The intent would be to generate a chimeric receptor targeted to CD19, with a transmembrane domain and the zeta chain signaling domain. This has been done by Dr. Brentjens' team, as well as others.

The strategy is to obtain patients' T cells and generate a pseudo-clonal population of CD19 targeted T cells by introducing this chimeric receptor. Transduced cells are basically re-educated to recognize the tumor-associated antigen, CD19. *In vitro* and *in vivo* studies indicate that the transduced cells are able to target and eradicate CD19-positive tumors. In a clinical trial for patients with a B-cell malignancy, the basic paradigm would be to obtain patients' peripheral blood T cells. The T cells would then selectively be activated and proliferated; retroviral vectors containing the chimeric gene would be added as the T cells continue to proliferate; and the cell product would be formulated and infused back into the patient.

The challenge is that although there is a significant investment in this technology, it will likely be difficult to draw strong conclusions from any of the 12 or more ongoing trials that target CD19 with CAR-modified T cells. Collectively, it would be very difficult to compare the trials because the various centers in the United States and Europe have generated different variations in the approach they are using to implement this technology. There is not agreement on the best method of introducing the chimeric gene into patients' T cells (e.g., lentivirus, retrovirus, electroporation, transposons). Different centers focus on different B-cell malignancies (e.g., non-Hodgkin lymphoma, acute lymphoblastic leukemia, among others). Most trials target either only the pediatric or only the adult population. In addition, some centers use lymphodepletion to help engraft modified T cells, and others do not. The design of the CAR, either first or second generation, also varies between centers.

These factors, then, would make it difficult to reach firm conclusions on how the technology could move forward into Phase II trials and beyond. This was the impetus for the proposal that resulted in the STRAP project. The investigators agreed that they will modify the four existing trials between their institutions, which will allow for analyses of the different receptors as well as the different vectors in use between the centers. By harmonizing the trials, half of the patients will be treated with UPenn lentiviral 19-41BB cells and half will be treated with retroviral CD28 zeta cells in order to assess which cells survive longer and which vector yields a better population of modified T cells. This comparison of the two chimeric receptors would have been very difficult to make without the STRAP funding.

The exchange of vectors between the two institutions will show that the technology is exportable. It will be possible to directly compare whether one of the vectors, lentiviral vs. retroviral, is superior to the other. The STRAP funding also allows normalization of some of the variables between the clinical trials. Gene transfer techniques and immune monitoring are being harmonized between the centers.

Dr. Brentjens noted that it would have been difficult to accomplish this research with other types of funding; it costs about $30,000 per patient to produce the T cells. The clinical innovation stemming from this multicenter trial would not have been possible. He then described how this project meets the criteria for IRM STRAP funding. It is a clinically significant translational research opportunity that should be accelerated. Preclinical and clinical data suggest that this approach has significant promise in the field of immunotherapy. The project addresses two of the four prioritized areas—adoptive therapy and "T-body" or CAR therapy. He noted that significant funding for clinical development is difficult to obtain through currently available Requests for Applications (RFAs). The investigators have two open INDs, which they will cross-reference. Initiation of clinical trials will require cross-reference of INDs and to obtain IRB and U.S. Food and Drug Administration (FDA) approval of the modified, harmonized clinical trials. These processes are nearing completion and enrollment on the modified protocols will likely begin in the next three to four months. The investigators expect to achieve Phase IIa of the trial, complete enrollment, and analyze clinical and correlative data in two years. The collaborating investigators have held two meetings, and a third meeting is planned for the end of March. The Material Transfer Agreements have been put in place, viral vectors have been exchanged between the two gene transfer facilities, and the researchers are working on harmonizing their gene transfer protocols and validating them at both centers.

Dr. Brentjens' parent R01 award focuses on investigating the enhanced efficacy of T cells that have been genetically modified to express IL-12 *in vivo*. T cells secreting IL-12 appear to be more potent in eradicating tumor cells in preclinical mouse studies. The ultimate goal is to translate this approach to a second-generation clinical trial. The STRAP award will facilitate completion of the first-generation trials, providing the ability to open second-generation trials. Dr. Brentjens acknowledged several key researchers in the collaborative effort—Michel Sadelain, Isabelle Riviere, Carl June, David Porter, Bruce Levine, and Stephen Grupp.

[Questions and Discussion for this presentation are included at the end of the session summary.]

Taking iRGD through the Valley of Death. Dr. Andrew Raubitschek, Professor of Oncology, Beckman Research Institute, City of Hope, described the scientific background and rationale used to develop the STRAP proposal. He noted that this project is different from that described by Dr. Brentjens and represents a serendipitous opportunity. At the time the STRAP award funding announcement was released, a paper appeared in *Science* about a new molecule, iRGD, developed by Erkki Ruoslahti. iRGD is a cyclic peptide that targets tumors based on the RGD motif. When it binds to αvβe3integrin at the tumor site, the peptide is cleaved to expose the CendR sequence, which binds to NRP-1, causing transcytosis of any therapeutic agent that happens to be in the vascular bed at that time. Dr. Ruoslahti initially looked at iRGD's potential to increase uptake of Adriamycin, Nabraxane, and Herceptin in animal models.

Following discussions with Dr. Ruoslahti, a team—Team STRAP—was assembled to develop the STRAP as a supplement to Dr. Raubitschek's Program Project Grant to investigate whether iRGD would potentiate the uptake of antibody into tumors. The STRAP award allowed Dr. Raubitschek to put together a team consisting of Erkki Ruoslahti, David Colcher of City of Hope (animal model expert), Timothy Synold of City of Hope (clinical pharmacologist), Russell Jacobs of Caltech (magnetic resonance imaging [MRI] expert), Denny Liggitt (animal toxicologist) of University of Washington, and Vincent Chung (clinical trialist) of City of Hope.

At the start of the STRAP project, nothing was known about the pharmacokinetics of iRGD, including the molecule's half-life, optimal route of administration, or dosing strategy. A variety of drugs had been looked at with various combinations and administration schedules. No work had been performed on toxicology, formulation, or requirements for the pre-IND and IND filing. The intent of the STRAP project was to provide all of this information in record time with the goal of bringing iRGD into the clinic in 2011. The first thing that was necessary was to set up the clinical pharmacology, which was performed in collaboration with Tim Synold of City of Hope. It was important to conduct serum stability studies in mouse and human, and examine intravenous and subcutaneous multi-dosing strategies. Using subcutaneous dosing rather than intravenous dosing in humans would be of tremendous advantage. The researchers were also very interested in the interaction between iRGD and NRP-1 levels. Because Genentech is conducting clinical trials with anti-NRP-1 antibodies, the potential interaction between iRGD and NRP-1 could be of interest. These initial studies resulted in documentation of the biological activity.

The major goal of the STRAP award was to verify iRGD's ability to increase the effects of therapy. In the *Science* paper, Dr. Ruoshalti looked at administration of Herceptin with and without iRGD and found that administration of iRGD with Herceptin in the BT-474 model was able to cure nude mice. Dr. Raubitschek's research team was able to document that therapeutic efficiency in their labs.

A second goal of the project was to use a different paradigm to evaluate iRGD in the clinic. If iRGD causes a major transcytosis at the tumor site, it may be possible to detect it on magnetic resonance imaging (MRI) to evaluate patients' responses on an individual basis. Patient-specific dosing strategies could then be developed that would be dependent on follow-up with MRI. To evaluate iRGD efficacy in the clinic, Dr. Raubitschek used MRI. The initial MRI experiments were conducted in mice at Caltech in collaboration with Dr. Jacobs. The 7T MRI instrument at Caltech has a positron emission tomography (PET) insert that allows capture of MR and PET signals at the same time. MRI showed an increase in the transfer coefficient across the permeability space in tumors treated with iRGD, while the vascular space parameter remained unchanged, raising the possibility that the transfer coefficient could be a surrogate marker for iRGD activity in patients.

The next important consideration is the toxicology; Dr. Liggitt has conducted the first animal toxicology work and participated in the pre-IND meeting. The group is scheduled to discuss the parameters for the initial clinical trial with NCI.

Dr. Raubitschek described the intended focus—to look at iRGD as an individual agent in a variety of cancer populations to see which patients will respond. It is known that most tumors express NRP-1. He noted that it would be important to him that the first iRGD therapy be conducted with his group's antibody therapy, either a radiolabeled antibody or an antibody carrying a cofactor such as IL-2. The drug administration strategy will also be discussed with NCI. The parameters of the clinical trial have to be known before animal toxicology studies are performed. Good Laboratory Practices (GLP)-grade iRGD for animal studies has been synthesized. The ability of iRGD to increase anti-CEA antibody and Herceptin uptake has been confirmed in one mouse model and in the BT-474 model using MR imaging and biodistribution. The cGMP iRGD (pseudo clinical grade iRGD) has been synthesized to be used in clinical and toxicology studies. The initial stability studies and pharmacokinetics have been performed, and the analysis of rodent toxicology is in progress. The researchers are identifying the MR signature for iRGD. They have been able to show that iRGD can cure mice when used in combination with Herceptin, while either agent administered alone is not curative.

Dr. Raubitschek concluded that the STRAP funding has allowed his group to develop a team approach to take iRGD from Dr. Ruoslahti's discovery work all the way into the clinic. He credits the success of his team's application to their ability to convince the evaluators that the research team would be able to obtain an IND and take iRGD into the clinic within a year.

Questions and Discussion

[Following Dr. Prindiville's presentation.]

Dr. Richard Schilsky, professor of medicine and Associate Dean for Clinical Research at the University of Chicago Pritzker School of Medicine, commented that the large number of applications received indicates high interest in the STRAP program. He noted that 11 of the proposals did not include the prioritized antigens and immune modifier agents. Since a lot of effort was spent on the prioritization process, Dr. Schilsky posed the question of whether that effort was of value or whether STRAPs should be offered as a unique funding mechanism and the research community be allowed to decide the priorities through the application process.

Dr. Prindiville agreed that this is an important question and that NCI will have to decide on the best way of doing prioritization if they move forward with other pathways or programs. She did note that because the application time was quite short, applicants could only realistically respond in a general area where they have work ongoing.

Dr. Olivera Finn, professor and Chair, University of Pittsburgh School of Medicine, explained that the prioritization process had considered which antigens and immune response modifiers were close to being ready for clinical testing. However, as Dr. Prindiville noted, this is not a program for clinical trials and some of the prioritized agents are already too advanced for the STRAP program.

Dr. Prindiville clarified that the STRAP program offered up to $2 million in total funding.

[Following Dr. Brentjens' presentation.]

Dr. David Parkinson, President and CEO, Nodality, Inc., remarked that in his view the STRAP program was conceived to enable discovery research. He noted that investigators self-assembled to answer some of the fundamental technological issues around prioritized antigen mechanistic approaches for therapy. He suggested that a future direction of the STRAP program would be to move the field beyond discovery research to something approximating formal development, with the real deliverable of cancer treatment. He also suggested that the program think beyond having investigators self-assemble because they do not do this naturally.

Dr. Finn stated that prioritizing agents, immune response modifiers, and cancer immunotherapy approaches has been very beneficial. It might be beneficial to assemble, with the help of NCI, researchers working on the high-prioritized reagents.

[Following Dr. Raubitschek's presentation.]

Dr. Abbruzzese stated that both of the presentations were impressive and suggested that the process accomplished some wonderful things. He asked the members to focus on providing some advice to NCI on how to move forward and accomplish similar results with other pathways developed by the TRWG.

Dr. Lynn Matrisian stated that CTAC had asked the TRWG implementation team to identify translational research opportunities and develop a STRAP mechanism that is fast, facile, and flexible. This was a pilot. The TRWG implementation team chose one pathway to gain some experience. The team broke it into two parts—prioritization and a funding mechanism. The STRAP mechanism was set up so that applicants could choose to either use or not use the prioritized agents, and both types of applications were submitted. The two awarded STRAP projects expanded upon what had been envisioned by the STRAP program. CTAC had advised NCI to think about an umbrella STRAP program with all the other pathways and to think about a prioritization process as well. She asked for further discussion on insights that the pilot project has provided in terms of going forward.

Dr. Abbruzzese noted that an umbrella STRAP option, which would be a combination of the other pathways, might be more streamlined and cost-effective. On the other hand, constructing an umbrella STRAP solicitation might be very challenging due to differences between pathways. Dr. Matrisian remarked that an umbrella STRAP solicitation could facilitate individual pathways moving forward, but in order to do this, recognition that the pathways are at different stages of development would be required. It is envisioned that the various pathways would integrate at some point. It may be necessary to set up separate RFAs for some pathways.

Dr. Joel Tepper, Hector MacLean Distinguished Professor of Cancer Research, University of North Carolina Lineberger Comprehensive Cancer Center, stated that the iRGD project fits his vision of a STRAP project (i.e., bringing something from an early stage of development to the clinic quickly) more so than the T-cell therapy approach. The first project needed money to run a sophisticated clinical trial to fine-tune some issues. An important issue would be to consider what type of project would be a priority to fund. Dr. Matrisian commented that from the TRWG perspective, different fields are at different places and need different things. In the first example, there are a lot of small ("boutique") clinical trials, and the field was unable to move past that. In that particular pathway, there is a need to fill an identified gap for those agents in order to proceed to a Phase III trial. In her opinion, there should not be preconceived ideas about the extent of a STRAP. The TRWG envisioned that the pathways would be used to determine what needs to be done to reach the end of the pathway.

Dr. Peter Shields, Deputy Director of the Lombardi Comprehensive Cancer Center at Georgetown University Medical Center, remarked that the differences are the strength of the STRAP mechanism and that the argument should be about whether the mechanism will achieve progress, rather than how far along the continuum that project is.

Dr. Peter Adamson, Chief of Clinical Pharmacology and Therapeutics at the Children's Hospital of Philadelphia, commented that what has been accomplished by the STRAP projects in a remarkably short time is impressive. He asked whether the iRGD project could have been funded through the Rapid Access to Interventional Development (RAID) program. It was noted that RAID is no longer active. Dr. Doroshow remarked that NCI's Developmental Therapeutics Branch could have helped Dr. Raubitschek's activities through the NCI Experimental Therapeutics (NExT) program. However, the GMP negotiations needed to start a clinical trial will probably be as costly as the entire STRAP award. NCI will help the STRAP awardees move their projects along.

Dr. Schilsky speculated about the value of the prioritization process and whether the same two STRAP projects might have been awarded in the absence of the prioritization effort. He noted that the goal of the prioritization effort was to inform priority-setting for the STRAP program as well as across NCI overall. He inquired if any other NCI programs have paid attention to the immune modulatory agent prioritization process.

Dr. Finn remarked that investigators have started referencing the prioritized agents (the cancer research "white papers") in their grant applications, and the biotech industry has shown an increased interest in the prioritized agents and reagents. The prioritization of agents has had a much broader effect outside of the STRAP program by helping to leverage NCI funding through other means such as foundations.

Dr. Doroshow noted that due to the prioritization there have been four reports describing the agents NCI should produce and detailing how they should be produced and made available. NCI has used not only appropriated funds but also a substantial amount of American Recovery and Reinvestment Act (ARRA) funds to make materials that would have been made available for STRAP proposals. These materials will be made available in general solicitations to the immunotherapy community in response to the need.

Ms. Nancy Roach, consumer advocate with C3: Colorectal Cancer Coalition noted that one feature of the STRAP awards is that NCI will provide project management to help ensure that timelines are met. She inquired about the level of that support and whether it has been helpful.

Dr. Raubitschek stated that he would be having his first implementation meeting with NCI the next day and hoped to be able to provide a written report about how the project management aspect works. He is expecting to take advantage of NCI expertise both on project management as well as regarding issues such as toxicology and IND filing.

Dr. Brentjens commented that there has been a high degree of oversight between NCI and the group. This has been helpful in moving the project forward, including amending the timeline by three months. The proximity of the collaborating institutions facilitates having day-long meetings every two to three months, which also contributes to the success of the project. He is planning to discuss further interactions with NCI in April.

Dr. Monica Bertagnolli, professor of surgery, Harvard Medical School, commended the program team for building flexibility into the program. She noted that a strength of the program is having experts assess where the field is and where it should go, while including other directions with strong justification.

Dr. Parkinson added that prioritization of technical questions around classes of therapeutic strategy is important to move a field forward. NCI could help by bringing investigators in the field together to prioritize the current questions, overcome barriers, and work with regulators.

Ms. Roach commented that NCI's help could be especially valuable in the area of devices, given the flux in the current regulatory situation.

Dr. Abbruzzese noted that NCI will have to consider the value-added of the prioritization process vs. the complexity of the process and the time needed to do it. Only half of the grant applications

addressed the prioritized antigens or prioritized approaches, while the prioritization process was time-consuming and costly.

Dr. Bertagnolli commented that it would be useful to bring investigators together to consider how some of the highly prioritized areas might be expanded.

IV. CLINICAL TRIALS PORTFOLIO ANALYSIS FEASIBILITY STUDY—DR. JUDITH HAUTALA

Dr. Judith Hautala, Research Staff Member, Science and Technology Policy Institute (STPI), presented an overview of the Clinical Trials Portfolio Analysis Feasibility Study. The purpose of the study was to develop a procedure for analyzing the NCI interventional clinical trials portfolio for use as a management tool. This included determining the annual NCI investment in interventional clinical trials by program as well as developing processes to allocate that investment by trial type, trial phase, and organ site. STPI performed a pilot analysis of the FY 2006 NCI interventional clinical trials investment using the proposed procedures. From this pilot analysis, concise descriptions of NCI portfolio analysis tools and NCI programs supporting clinical trials were created—a reference manual for future portfolio analyses.

For NCI's intramural clinical trials program, a system is currently in place for reporting percent clinical trial relevance for project awards. There is also a system in place whereby intramural protocols are coded by trial type, trial phase, and organ site. An automated system is also being developed to link protocol data with project awards, as this task is currently a manual process. These data systems make the analysis of the intramural interventional clinical trial portfolio quite straightforward.

NCI has a number of analytic tools and databases in place to collect information on its extramural interventional clinical trials program, but these collect only some of the information needed to conduct a portfolio analysis. Each of these tools and databases was created for a different purpose and the information collected is not coded in a consistent fashion. Therefore, STPI created a new methodology to collect and link the required data for an extramural clinical trials portfolio analysis. The first step in this process is to obtain from program staff the annual budget for awards supporting interventional clinical trials. The percentage allocation to clinical trials for each program must then be estimated. Fifty percent of the clinical trials portfolio is for awards devoted exclusively to clinical trials and the other 50 percent requires award-by-award analysis for accuracy (e.g., R01/P01, Specialized Programs of Research Excellence [SPOREs], and NCI-designated Cancer Center awards). Once the clinical trials investment for each program (or award) has been determined, clinical trials funding can be allocated by trial type, trial phase, and organ site using information in existing databases and program-specific procedures. The final step is to construct a database to aggregate and report out portfolio information in a way that is useful for making management decisions.

The most difficult step of the process is the award-by-award analysis of the 50 percent portion of the clinical trials portfolio that is not devoted exclusively to clinical trials. There are two options for how to conduct this analysis. The first is to have program staff estimate clinical trial percentages (e.g., 0, 10, 25, 50, 75, 90, or 100%) for each award based on review of annual progress reports and associated budget information. For Cancer Center awards, percentages would be estimated for each core and program element. The second option for analysis is to have Principal Investigators and Cancer Center administrators include in annual progress reports an estimate of the percentage of the budget that was

spent on clinical trials; this estimate would be reviewed by program staff for concurrence. NCI staff from the Clinical Grants and Contracts Branch, the SPORE, and Cancer Centers programs have recommended option two because of its potential to provide greater accuracy.

FY 2006 Pilot Clinical Trials Portfolio Analysis. The procedures described above were used to analyze NCI's clinical trials investment in FY 2006. Dr. Hautala explained that the choice to use FY 2006 data was not due to any specific significance of data from that year, but because each of the programs presented portfolio data to the Clinical Trials and Translational Research Operations Committee (CTROC) in 2007. These data tended to be FY 2006 data and served as a starting point for this portfolio analysis feasibility project. In FY 2006, NCI invested a little less than $1 billion in clinical trials. About 80 percent of that funding was allocated to the extramural program, 17 percent (about $168 million) was allocated to the intramural program, and the remaining funds were allocated to research management support. For the intramural program, there were 96 project awards in the Center for Cancer Research (CCR) and 8 project awards and 2 contracts in the Division of Cancer Epidemiology and Genetics (DCEG) supporting clinical trials. Over 95 percent of the intramural clinical trials budget was in CCR, with DCEG at about 5 percent. Within CCR, an average of 34 percent of the project award funding was spent on clinical trials. However, approximately 70 percent of the clinical investment within CCR was not spent for project awards but for the clinical center assessment and the clinical trials infrastructure.

The FY 2006 interventional clinical trials investment of the extramural program was about $800 million, with an error bar of $47 million. Fifty percent of that investment was definitive—awards devoted exclusively to clinical trials in programs such as the Cooperative Groups and the CCOPs (Community Clinical Oncology Programs). The other 50 percent was estimated at the program level by program staff, which led to the 6 percent ($47 million) margin of error in calculation of the clinical trials investment. The extramural investment was distributed over 35 programs, 23 of which were devoted entirely to clinical trials and 12 of which were only partially in support of clinical trials (R01s, P01s, SPOREs, Cancer Centers). Only three programs individually contributed greater than 10 percent of the clinical trials investment: Cooperative Groups, including tissue banks, the Central IRB (CIRB), and the Cancer Trials Support Unit (CTSU) (21%); Cancer Centers (13%); and the Clinical Grants and Contracts Branch (13%). Looking at the distribution of extramural clinical trials funding by Division/program, 49 percent of the investment was in the Division of Cancer Treatment and Diagnosis; 30 percent, in the Division of Cancer Prevention (DCP); 13 percent, in Cancer Centers; 5 percent, in the Division of Cancer Control and Population Sciences (DCCPS); 2 percent, in the SPORE program, and 1 percent, in other programs/Divisions. Within DCTD, 60 percent of the identified programs were devoted entirely to clinical trials and the remaining 40 percent were devoted only partially to clinical trials. Within DCP, about 90 percent of clinical trial programs were devoted completely to clinical trials, with a small percentage in the grant pool.

Dr. Hautala then addressed allocation of the clinical trials investment by trial type, trial phase, and organ site. Because allocation of the intramural investment was clearly feasible, the allocation was not actually performed in the context of this feasibility study. Intramural project awards can be coded for trial type, trial phase, and organ site using existing data. The NIH clinical center assessment and the CCR infrastructure can be allocated based on relative accrual by trial type, trial phase, and organ site, which is available on a protocol-specific basis. An alternative would be to allocate the infrastructure investment by the number of trials as opposed to accrual.

For the extramural program, the feasibility of allocating the clinical trial investment by trial type, trial phase, and organ site was determined using the FY 2006 data. Allocation by trial type (treatment,

prevention, cancer control, or screening) can be done by program, with the exception of Cancer Centers and the Community Clinical Oncology Program (CCOP). The allocation for these latter programs can be determined based on relative accrual, which is currently reported by trial type. It is also possible to allocate by trial phase based on program, with the exception of Cancer Centers. The Cancer Center allocation, again, could be based on relative accrual, which is currently reported by trial phase. However, Dr. Hautala recommended that the Cooperative Group costs be allocated using two parameters, which are both currently reported by trial phase. "Fixed infrastructure costs" (including statistics, data management, and operational costs) should be allocated by the relative number of trials. Per-case reimbursements and awards to members to support accrual ("accrual costs") should be allocated based on relative accrual. Allocation by organ site is available from program staff or the Research Assessment and Evaluation Branch (RAEB) for grants (R01s/P01s) and contracts. For Investigational Drug Branch, Cancer Center, and CCOP awards, allocation by organ site can be based on relative accrual data. For Cooperative Groups, fixed infrastructure costs should be allocated based on number of trials and accrual costs, by relative accrual, both of which are currently reported by organ site.

Dr. Hautala presented some examples of the kinds of information that can be obtained from such an analysis. The analysis revealed that 58 percent of the extramural clinical trials investment was devoted to treatment trials; 11 percent, to prevention trials (including chemoprevention and nutritional trials); 21 percent, to cancer control trials (including symptom management); and 10 percent, to screening trials. Within DCP, 8 percent of the clinical trials investment was devoted to treatment trials due to CCOP accrual to Cooperative Group trials; 28 percent, to prevention trials; 48 percent, to cancer control trials; and 16 percent, to screening trials. DCP and DCTD had nearly equal numbers of early- versus late-phase trials, whereas the Cancer Centers, SPOREs, and other programs were heavily weighted toward early-phase trials.

Conclusions. Intramural clinical trials portfolio analyses can be done easily using currently available data and systems to determine the total investment and the allocation by trial type, trial phase, and organ site. However, current tools and methods are insufficient for similar analyses of the extramural clinical trials investment. Trial and accrual data are available in existing databases to perform the allocation by trial type, trial phase, and organ site. However, accurate portfolio analysis depends on an annual reporting by investigators or program staff of clinical trials funding in R01/ P01, Cancer Center, and SPORE awards.

Questions and Discussion

The FY 2006 analysis showed that NCI devoted 20 percent of its total budget to support clinical trials; Dr. Schilsky suggested that another question that might be considered is: If NCI is prepared to continue to devote 20 percent of its budget to clinical trials moving forward, what is the optimal way to allocate those funds? He suggested that such an exercise might require a working group.

Dr. Lee Helman, Chief of the Pediatric Oncology Branch and Deputy Director of the Center for Cancer Research, NCI, stated that data are needed before recommendations can be made on how best to allocate funding in order to respond to opportunities. Dr. Schilsky concurred that having such data is extremely valuable; however, the real concern is how to use the data. A grantee may not be willing to put in the effort to report additional data without a clear understanding of how the data will be used by NCI.

Dr. Edith Perez, Professor of Medicine in the Division of Hematology/Oncology, Mayo Medical School, asked whether 35 programs supporting clinical trials are really needed or whether this should be consolidated into a lesser number to allow for more transparency moving forward.

Dr. James Wade, Director of Medical Oncology, Decatur Memorial Hospital Cancer Care Institute, asked whether the intramural costs reported include treatment costs. Dr. Helman confirmed that treatment costs are included. Dr. Wade suggested that the per-unit cost of accrual in the intramural program is about 10 times higher than the per-unit cost of accrual in the extramural program and that it will be important to consider whether NCI can afford a program in which it costs 10 to 20 times more per unit for accrual than the cost in the extramural program. He noted that the difficult work of CTAC is to develop a balance for prioritization.

Dr. Mendenhall commented that the unit of evaluation must be agreed upon before revising NCI's allocation to clinical trials. Some higher-cost trials may have more intrinsic value than a large Phase III trial that may not be looking at as much correlative data. Dr. Mendenhall recommended that CTAC also look at the funding allocation for translational research.

Dr. Abbruzzese suggested that a working group might be very helpful in developing a strategy to assess how funds are being allocated over time. Following a motion by Dr. Adamson, Dr. Helman noted that it is important to evaluate not only how the portfolio is distributed, but the quality. Further points were made in the general discussion that the Committee also needs to look at whether a trial has been completed, whether trial endpoints are being met, what has been done, and the impacts.

Motion. Dr. Adamson made a motion that a working group be created to take an in-depth look at NCI's clinical trials portfolio to assess how the clinical trials budget process should be managed. The motion passed with the following votes: 22 yeas, 1 nay, and 0 abstentions.

V. CLINICAL TRIALS WORKING GROUP (CTWG) EVALUATION WORKING GROUP UPDATE—DRS. PETER ADAMSON AND DANIEL SARGENT

Dr. Peter Adamson provided an update on the work of the Clinical Trials Working Group (CTWG) Evaluation Working Group. The overall goal of the evaluation effort is to assess the performance and impact of CTWG initiatives on effectiveness of the overall NCI clinical enterprise. The CTWG Evaluation Working Group has focused on refining the proposed evaluation plan and developing a timeline for its implementation. Dr. Adamson explained that this presentation would provide an overview of the Working Group's findings and gather specific feedback from CTAC members.

In 2008, CCCT conducted a baseline study to determine the feasibility of data collection, validate measures, identify data sources, and report on selected measures of system status. The results of the feasibility study were presented to the National Cancer Advisory Board (NCAB) in February 2008 (http://deainfo.nci.nih.gov/advisory/ncab/145_0208/presentations/Wednesday/1035am_first%20Dorosho w.pdf). The CTWG Evaluation Working Group began its work near the end of 2010. Discussions were held through conference calls and face-to-face meetings, and the Working Group interviewed important stakeholders. The revised plan was reviewed and refined.

The evaluation plan is comprised of four primary components, with specific quantitative and qualitative measures developed for each component and subcomponent. The plan is limited to trials that are currently under the purview of the Scientific Steering Committees and in the Cancer Therapy Evaluation Program (CTEP) databases.

The first component, system outcomes, includes examination of trial quality, scientific importance and clinical relevance of trial results, and efficiency of trial initiation and conduct. The percentage of trials that complete accrual is an example of a quantitative measure that can be obtained. However, since failure to reach accrual goals is not always a negative outcome, examination of trial quality requires new measures that go beyond accrual completion. Scientific and clinical relevance are more qualitative measures that require expert judgment on questions such as whether trials provide definitive answers to research questions, produce novel findings, or produce knowledge with real-world consequences. Measures of efficiency of trials focus on timelines from letter of intent receipt to trial opening, concept submission, and enrollment of patients, as well as the impact of multiple amendments on efficiency. Dr. Adamson suggested that these measurements and criteria be refined and on an annual basis look at the question of whether our studies are actually changing practice.

Collaboration, the second component, is addressed by looking at changes in NCI program guidance over time; types of collaborations defined within Cooperative Groups, Cancer Centers, and SPOREs; and various incentives and disincentives associated with different types of collaborations. Quantitative measures to assess collaboration include the percentage of CTEP-funded Phase II trials that involve collaborative work across multiple institutions, and the extent of industry collaborations with NCI infrastructures, including investigational agents provided.

The third component proposes both quantitative and qualitative approaches for evaluation of the Disease-Specific Steering Committees (DSSCs). The evaluation will analyze timeliness of performance in approving concepts, as well as transparency, quality, and efficiency in prioritization; the role of the DSSC in managing the portfolio of trials; and the role of task forces. A variety of stakeholders, including DSSC members, NCI staff, and individual investigators) will be interviewed.

The final component addresses measures focused on the Investigational Drug Steering Committee (IDSC). Quantitative measures will be similar to those used with Disease-Specific Steering Committees. Qualitative measures will involve a somewhat different set of stakeholders and will require an expert panel to review the impact of the IDSC. The evaluation may delve into the literature to better understand the IDSC's productivity. Evaluation topics will include clinical development plans, prioritization, portfolio balance, collaboration, and the impact of the IDSC's reports and guidelines.

Dr. Adamson posed a set of discussion questions to CTAC members, including:
Should the evaluation be a high priority for initiation in 2011? Are the proposed areas of evaluation (system outcomes, collaboration, DSSCs, IDSCs) on target? Are there alternatives to expert judgment for assessing the scientific importance and clinical relevance of trial results? Are there alternatives to stakeholder interviews for addressing DSSC and IDSC performance? Is the extent of qualitative measures appropriate to achieve the goals of the evaluation? Should CTAC form a standing subcommittee to monitor the evaluation process?

Dr. Daniel J. Sargent, Director of Cancer Center Statistics at the Mayo Clinic College of Medicine, added that the Working Group discussed the need to consider the multiple changes in progress, but that these are not only difficult to identify but also difficult to further assess in terms of the impact of

specific changes. It was agreed that the evaluation should be initiated, based on the charge to the Working Group, to evaluate the impact of the CTWG. It is possible to identify what is important to measure, although it might not be possible, ultimately, to identify the specific changes that have moved the system.

Questions and Discussion

Dr. Mendenhall suggested that data on the adoption of guidelines, such as those developed by the National Comprehensive Cancer Network (NCCN), and information on insurance reimbursement policies would be useful indicators of whether trial findings have modified clinical practice. Dr. Adamson replied that this is a good idea as long as the bias is avoided by using only data from well-recognized entities. Dr. Sargent added that Medicare and Medicaid coverage was included as a metric.

Dr. Parkinson noted that the FDA encourages companies to interact with Cooperative Groups. However, companies are ultimately responsible for trial completion and subject to penalties if trials are not concluded by agreed-upon dates. He pointed out that these are important considerations for companies in making decisions to put agents in Cooperative Group trials.

Dr. Mendenhall commented that in looking at the roles of stakeholders such as task forces and advocates, it will be important to focus not only on the roles they play but also on whether interactions with them are valuable. It is important that interviews rather than surveys be used to collect this information.

Dr. Finn asked for clarification of the discussion question asking whether there are alternatives to expert judgment, pointing out that DSSCs have members with expertise in relevant areas. Dr. Adamson said that this relates to evaluation of the DSSCs outside of the DSSC framework.

Dr. Abbruzzese asked whether the CTWG Evaluation Working Group feels that it has obtained enough input from CTAC to begin preparing a report for presentation in July. Drs. Adamson and Sargent stated that the CTWG Evaluation Working Group needs to know whether there is a level of comfort with metrics that rely heavily on qualitative data and limited "hard" data. Qualitative measures require more resources than do quantitative measures and are more difficult to implement. Dr. Stephen Grubbs, Chief of Oncology, Medical Oncology Hematology Consultants, agreed that there is always a concern that qualitative measures may not lead to useful information, but this uncertainty cannot be addressed until after the measures have been tried.

Dr. Deborah Bruner, Independence Professor in Nursing Education, School of Nursing, University of Pennsylvania, suggested that due to the level of uncertainty, it might be worth considering the upcoming report as a second preliminary or interim report within an ongoing process. It will be difficult to measure the effect of guidelines because of the time required to move trials into alignment with them. It may turn out that adding additional levels of review, such as evaluating DSSCs, will not result in system improvements.

Dr. Abbruzzese reiterated the informational intent of the presentation to allow the Working Group to get feedback and commented that no vote would be required. He noted that the comments and suggestions from CTAC members will be very helpful.

Dr. Helman expressed interest in learning the percentage of Phase II and Phase III trials that meet their primary objectives. Dr. Adamson agreed and suggested that this is an example of why a pilot study should be conducted for a single year (2008) to determine whether meaningful data can be collected.

Dr. Bruner noted that it would be good to consider the cost-benefit to determine whether the high cost of qualitative evaluation is justified. Dr. Prindiville added that the cost-benefit assessment would also need to include the feasibility of incorporating the proposed data elements into current databases.

Dr. Sargent noted that the Working Group will focus on prioritizing the proposed data elements to include those that are most critical.

Dr. Tepper said that it is important to do this because the data are needed. He noted that one of the things that is being evaluated is the process—whether the process is working and whether or not the Task Forces and Steering Committees are adding to the process. He also suggested that percentages of trials that succeed in influencing practice should be treated as baseline data and that subsequent studies every five years should be conducted to measure progress. It will be necessary to learn how to use the data, for example, to understand what the right percentage is of Phase III studies that lead to practice change.

Ms. Roach noted that gathering qualitative data on processes is difficult to do retrospectively. She seconded Dr. Bruner's concern about the cost of qualitative research. Dr. Adamson said that the CTWG Evaluation Working Group shares this concern and is seeking CTAC's advice on how to limit the number of qualitative measures and interpret qualitative data.

Dr. Tepper stated that in terms of approval and disapproval of concepts, it might be easier to speculate on whether these decisions were wise after several years have passed.

Dr. Hautala suggested that the current list of qualitative measures should be pilot-tested before any are eliminated; otherwise, potentially important measures might be left out of the evaluation.

VI. TRANSFORMING NCI'S CLINICAL TRIALS SYSTEM—DR. JAMES DOROSHOW

Dr. Doroshow moderated the discussion of proposed changes to NCI's clinical trials system. CTAC members were provided with a list of discussion points prior to the meeting. The discussion points focused on NCI's infrastructure, optimization of translational research opportunities, clinical trials in rare diseases, and oversight.

How do we ensure that the network is able to develop clinical trials to move research to patients quickly across the full spectrum of cancers? Dr. Mendenhall expressed concern over the potential integration of the Radiation Therapy Oncology Group (RTOG) into another Cooperative Group. She emphasized that RTOG has done an excellent job in designing and completing important trials that guide clinical practice in all major tumor sites. The clinical questions that radiation oncologists deal with are very different from those faced by medical oncologists and surgeons. If RTOG merges with another Cooperative Group, there is concern that the radiation oncology field will be greatly hindered. Dr. Tepper concurred with Dr. Mendenhall's remarks but noted a greater concern in combining two disparate Cooperative Groups such as RTOG and the National Surgical Adjuvant Breast and Bowel Project

(NSABP); a new structure would need to be developed to facilitate and ensure that modality-specific questions are being addressed.

Dr. Bertagnolli stated that she is in favor of having multiple multidisciplinary disease-oriented committees available to address a particular scientific question, especially for complex, challenging diseases. Having multiple committees or groups brings more expert opinions to the table and allows more creative ideas to enter the system. However, Dr. Bertagnolli expressed her opinion that there needs to be a central coordinating body that prioritizes research areas and study ideas. Dr. Mendenhall asked how discipline-focused research questions, such as the degree of axillary node dissection or dose fractionation schemes in radiation oncology, would be answered by a multidisciplinary committee.

Dr. Schilsky commented that all of the relevant clinical and scientific oncology disciplines must be represented in a new Cooperative Group program, whatever that new configuration may be. He noted that all of the radiation oncologists who are currently participating in the Cooperative Group program will, hopefully, be able to continue to do so productively in the new program. With regards to the reorganization, NCI is not mandating any particular configuration of the Cooperative Groups. Therefore, if RTOG and NSABP choose to combine into one new group, it will be incumbent upon the leaders of those two Cooperative Groups to devise a new plan as well as a new structure for the group and not merely combine the two existing groups to maintain their same missions.

Dr. Helman commented that there was a successful Children's Oncology Group (COG) study that quickly and definitively answered a radiation therapy question related to hyperfractionation in rhabdomyosarcoma. Dr. Helman asked for Dr. Mendenhall's input on how this one COG study was able to successfully answer a radiation-focused question and whether there are lessons to be learned. Dr. Mendenhall responded that the number of patients available for pediatric trials is much lower than the number of adults available to participate in clinical trials. Since there are not as many children, there are fewer opportunities to conduct studies, perhaps resulting in more focused trials. With regards to the adult oncology groups, the pool of potential clinical trial participants is greater than the pediatric pool of participants, resulting in increased opportunities to conduct studies and answer a multitude of scientific questions.

Ms. Roach stated that NCI must provide incentives (i.e., funding dollars and support) to ensure progress on the revitalization of the clinical trials system. She also commented that transparency is needed. Regular updates related to the progress made as well as the barriers within the system need to be regularly presented at advisory committee meetings so that investigators have a platform to discuss these issues.

Dr. Adamson commented that there needs to be room for innovation in the new clinical trials system. It was suggested that the initial phase of the restructuring system should be considered a pilot phase, and that more than one system (i.e., Cooperative Group structure) should be tested to determine how to best organize the Cooperative Groups.

Dr. Mitchell Schnall, Matthew J. Wilson Professor, University of Pennsylvania Medical Center, said he supports the formation of multidisciplinary teams but warned that it will be difficult to create a structure that makes the best use of each specialist's time.

Dr. Bruner disagreed with Dr. Schilsky's earlier comments and noted that new alliances are being formed without sufficient discussions on how best to restructure the Cooperative Groups. Dr. Abbruzzese

questioned whether the Funding Opportunity Announcement (FOA) for the new Cooperative Groups could be general enough to allow for innovation in the group structure and fostering of collaboration among investigators.

Dr. Parkinson suggested that the new groups be structured in a way that separates scientific strategy from implementation. Currently, the Cooperative Groups are not equally efficient at both elements. Dr. Sargent responded that separating operations from science is extremely risky. However the new system is structured, it must be made clear that the driver of clinical trials is the science, not operations. Dr. Sargent also commented that there needs to be competition within multi-disease Cooperative Groups. Having single-disease-specific Cooperative Groups creates a monopoly on research in a particular disease and does not allow for the flow of new ideas.

How do we incentivize the participation of Cancer Centers in the Cooperative Group system/network? Dr. Doroshow stated that much, if not all, of the scientific input for the Cooperative Group system comes from Cancer Center members. Cooperative Groups play an important role in some Cancer Centers, but less of a role in many others. A critical issue to address is how to incentivize Cancer Centers, not just their members, to become an integral part of the Cooperative Group network.

Ms. Roach inquired why NCI would fund a Cancer Center that does not participate in a national clinical trials network. Dr. Linda Weiss responded that almost 100 percent of Cancer Centers conducting clinical research do participate in a Cooperative Group; the concern is the level at which they participate. The Guidelines Harmonization Working Group report has incorporated review criteria on leadership and participation in the Cooperative Group system. The next version of the clinical trials guidelines will include review criteria specific to Cancer Center participation in NCI clinical trials programs. A major disincentive for Cancer Center participation in Cooperative Group trials is the minimal financial support available to Cancer Center investigators. Dr. Bertagnolli stated that the Cancer Centers have been incentivized to participate in the Cooperative Groups and provide academic input, leadership, and feedback on how to structure trials. Cancer Centers should receive credit when they are willing to truly invest in Cooperative Group research.

Dr. Schilsky commented that for many years the highest accruing institutions in CALGB have been Dana Farber and Ohio State—two exceptional Cancer Centers. If these two Cancer Centers can productively participate in the Cooperative Group system, any of the Cancer Centers have the ability to do so. At a recent Board of Scientific Advisors (BSA) meeting, a number of laboratory scientists commented that they did not understand how to access the resources of the Cooperative Groups. Dr. Schilsky commented that this represents a failure of Cancer Center leadership and a disconnect between leadership and its scientists. There needs to be a discussion on the role of Cancer Center leadership in participation in the Cooperative Groups. Dr. Schilsky also stated that every Cancer Center has access to patient populations that are best served by being offered Cooperative Group protocols. Cancer Centers have unique roles in laboratory-to-clinic and clinic-to-population translation and should be able to support publicly funded randomized clinical trials that are addressing potential practice-changing questions, while maintaining a robust portfolio of early-phase investigational trials.

Dr. Wade stated that the clinical trials network is in a state of crisis. He views the transformation of the clinical trials system as a Phase II study. The five-year outcome of the restructuring may be positive, with an improved number and quality of studies, or it may be negative, with a 25-50 percent drop in trial accrual. The Committee needs to address what the outcome of this "experiment" should be. Dr. Schilsky commented that the worst-case outcome of this "experiment" is that it is uninformative.

Given current budgetary issues, it is inevitable that there will be fewer trials and lower accrual. He feels that these are poor metrics to measure success. Better metrics may be whether trials are launched and completed more quickly.

Dr. Bruner suggested that a funding program similar to the STRAP awards be offered to Cancer Centers to further incentivize them to work with the Cooperative Groups.

How will cancer prevention and control be integrated into the network? Dr. Bruner noted the existence of the CCOPs and stated that it is important that the priorities of the CCOPs match the priorities of the new Cooperative Groups. She also commented that minority populations need to be better incorporated into survivorship and symptom management trials.

Dr. Schnall stated that the Cooperative Groups need to address the entire spectrum of the disease pathway, from early detection through treatment of metastatic disease.

Dr. Wade commented that the restructuring of the Cooperative Groups should be deemed a success before the structure is expanded to other areas of NCI's cancer prevention and control network. Dr. Shields disagreed, saying that prevention and control should be mandated across the entire clinical trials network as part of the initial restructuring process.

What purpose/function will the Strategic Oversight Panel serve? Dr. Doroshow stated that CTAC was created to oversee all of the clinical trials processes that have been discussed thus far and that any cross-disease Strategic Panel should be under the auspices of CTAC. Substantive input is needed from participants across the clinical trials network—Cooperative Groups, Cancer Centers, SPOREs, and basic scientists—to help set a strategic vision and make the best investment decisions. The Strategic Panel could be created as a subcommittee of CTAC. Dr. Paulette Gray, Director of the Division of Extramural Activities, NCI, noted that if the Strategic Panel is a CTAC subcommittee, its meetings will have to be public. However, the subcommittee could establish smaller working groups to address different issues in a nonpublic forum.

Dr. Schilsky commented that before any Strategic Oversight Panel is created there needs to be a discussion of criteria to determine what types of trials a publicly funded clinical trials system is uniquely suited to run.

Ms. Roach noted that it is important to include global expertise on the Strategic Panel.

How can we optimize translation and incorporate modern science in a network that will be able to adapt as new knowledge is introduced? Dr. Tepper stated that NCI's clinical trials program has not done a good job of being innovative or quickly translating laboratory science into clinical applications. The Steering Committees and Task Forces have been isolated from progress in the scientific realm. If every Phase III trial is a success, then NCI is doing a poor job of being innovative and taking chances. Dr. Abbruzzese agreed with Dr. Tepper, stating that as a member of the Gastrointestinal Cancer Steering Committee (GISC), it has been difficult to obtain scientific input and convince investigators to incorporate innovative scientific questions into their studies. Dr. Tepper offered suggestions to address this issue, including educating Steering Committee members to increase their awareness of current science and involving laboratory scientists at the Steering Committee and Task Force levels.

Dr. Helman commented that there needs to be a discussion on the prioritization of early-phase trials to ensure that innovative trials are supported. Additionally, CTAC needs to address how Cooperative Groups can quickly move forward successful early-phase trials.

How do we best encourage Cooperative Groups to do trials in rare diseases? Dr. Tepper shared a model used by GISC to address gastrointestinal stromal tumors (GIST). None of the current Cooperative Groups specifically address GIST, so a GIST Task Force was created under the auspices of GISC. This Task Force functions in a way similar to a Cooperative Group disease committee and has been successful in putting together scientific panels. Addressing rare diseases requires leadership.

Dr. Adamson commented that for pediatric cancer, there is a Rare Disease Committee that is used as a platform to address any rare disease for which there is a compelling clinical question. To address adult rare diseases, there will need to be international collaboration and a common platform to share and leverage experiences.

Ms. Roach commented that when analyzing the clinical trials portfolio, there will likely be an imbalance in the amount of funding allocated to different diseases/organ sites. She noted that it will be a challenge to level these imbalances and suggested that this issue should be addressed. Dr. Helman responded that it is difficult to ensure a balanced portfolio. When a compelling clinical opportunity arises, it must be considered regardless of whether it is in a rare disease or in a disease that is a major public health problem.

Dr. Grubbs asked how the transformation of the clinical trials system will fit in with health care reform. The issue 5 to 10 years from now will not be the quality of clinical trials, but whether the Center for Medicare and Medicaid Services or private insurers will be willing to spend as much money for patients to participate on a trial.

Other Comments or Issues. Dr. Susan Arbuck, President, Susan G. Arbuck, M.D., LLC, asked whether there have been enough discussions about restructuring the system that have involved all stakeholders in the clinical trials system, as noted by the Institute of Medicine (IOM) report. Dr. Schnall commented that the most informative discussions will be within the Cooperative Groups. Dr. Schilsky stated that there is an upcoming workshop sponsored by the American Society of Clinical Oncology and IOM to which all of the stakeholders affected by the recommendations of the IOM report have been invited.

VII. NEW BUSINESS—DR. JAMES ABBRUZZESE

CTAC Function and Role. Dr. Abbruzzese asked for input and suggestions on how CTAC could function better, better advise NCI, and have more impact moving forward.

Ms. Roach recommended that more time should be set aside for discussion at future CTAC meetings. Presentations are informative but could be done in other forums and may not be the best use of time.

Dr. Finn commented that there are multiple NCI initiatives that are open to public comment via the Web and asked whether those comments are being read. Dr. Doroshow affirmed that all comments are

read. Dr. Finn then suggested that some of those comments be presented to CTAC, which could act as a forum for community viewpoints to be expressed.

Dr. Tepper recommended that a subcommittee of CTAC be established to set meeting agendas. This would ensure that the most pertinent issues are addressed at CTAC meetings and would also be helpful in gaining input from NCI. Dr. Abbruzzese expressed his agreement and asked members to contact him or Dr. Prindiville if they would like to be involved in the agenda-planning calls.

Dr. Schilsky commented that the only way for a committee such as CTAC to be effective is if it has specific actions to take; otherwise, it is just a forum for information sharing. Dr. Schilsky recommended that the charge to CTAC be revisited to clarify the specific actions of the Committee. Dr. Abbruzzese responded that the formation of a working group to analyze NCI's clinical trials portfolio will be a good starting point.

Dr. Wade commented that his term on the Committee is coming to an end and that he is impressed with the work CTAC has achieved over the past few years. He suggested that the Committee should consider identifying the endpoints of the new clinical trials enterprise—points at which it is clear the new system is successfully working or is failing. If the system is failing, other techniques need to be implemented to keep NCI's clinical trials system afloat.

VIII. ADJOURNMENT—DR. JAMES ABBRUZZESE

There being no further business, the 13th meeting of CTAC was adjourned at 2:52 p.m. on Thursday, March 3, 2011.