Multi-Center Phase III Clinical Trials and NCI Cooperative Groups: Workshop Summary

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WORKSHOP SUMMARY

Margie Patlak, Sharyl Nass, and Christine Micheel, *Rapporteurs*

National Cancer Policy Forum

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Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Jan C. Buckner, M.D., Mayo Clinic
Gwendolyn Fyfe, M.D., Genentech
Heidi Nelson, M.D., American College of Surgeons Oncology Group and Mayo Clinic
Ellen Stovall, National Coalition for Cancer Survivorship
Marcy Waldinger, M.H.S.A., University of Michigan Comprehensive Cancer Center

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the final draft of the report before its release. The review of this report was overseen by **Melvin Worth, M.D.** Appointed by the Institute of Medicine, he

was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the rapporteurs and the institution.

Contents

Introduction

The National Cancer Institute's Cooperative Group Program for clinical research was established in 1955 and has grown to include 12 cooperative groups, representing 1,700 institutions and the collective recruitment of roughly 22,000 patients to cancer clinical trials each year. Cooperative groups are made up of comprehensive cancer centers, cancer centers, academic medical centers, community hospitals, and private research institutions, and they are supported by 10 biostatistics centers and a clinical trial support unit at the National Cancer Institute (NCI). The Cooperative Group Program enables pooling of public resources available for the study of cancer prevention, detection, and treatment. Because of the public and academic nature of the collective groups, it has been possible for them to conduct clinical trials that extend beyond the usual focus and capacity of pharmaceutical companies, including trials on methods of cancer prevention and early detection, the comparative effectiveness of treatments, and how treatments affect patients' quality of life or long-term health, as well as trials that use new trial designs for combination therapies and proof-of-concept studies. In addition, the cooperative groups' infrastructure provides a valuable resource for industry to use for the clinical evaluation of commercial drug candidates.

In the first 50 years of their existence, the cooperative groups contributed to substantial gains in the quality of treatment for many types of cancer, including breast, ovarian, colorectal, and childhood cancers. Cooperative group research has been instrumental in establishing nearly all of today's standard adjuvant therapies as well as combined-modality

treatments. Despite this record of success, cooperative group trials today are facing a number of issues that limit their effectiveness. The trials must deal with cumbersome and complex processes, including trial planning and start-up; scientific, regulatory, and ethics review; staff participation; patient accrual; trial monitoring; and financial management. Inefficiencies in these processes, which greatly prolong the period of trial design and approval as well as erode financial support and increase regulatory burdens, have hampered the ability of the cooperative group Phase III trials program to achieve its goals. Many clinical research programs and individual cancer patients choose not to participate in the program or to participate modestly. For example, while the Cooperative Groups Program recruits around 22,000 patients every year, this represents only a small fraction of cancer patients eligible to participate in trials.[1] To compound the problems of lack of institutional and patient participation, the results of some cooperative group trials are never published after many years of hard work and patient participation.

There is great concern that the process of moving new cancer treatments into Phase III trials and then into regulatory approval within the NCI Cooperative Group Program has become inefficient, underfunded, and underutilized by oncologists and cancer patients. Despite NCI-sponsored internal and external reviews, the NCI Cooperative Group Program has remained largely unchanged over its existence, except for the gradual increase of regulations and oversight. Thus, the National Cancer Policy Forum (NCPF) chose to convene a workshop entitled "Multi-Center Phase III Clinical Trials and NCI Cooperative Groups," which was held in Washington, DC, July 1–2, 2008. As explained by the workshop chair, Dr. John Mendelsohn, president of M. D. Anderson Cancer Center, the purpose of the workshop was to outline the challenges faced by the public clinical cancer research enterprise and to identify potential approaches for addressing these challenges. He opened the conference by throwing out what he called a "big, audacious goal." This goal is to slash in half the amount of time that it takes to progress from the conception of a clinical trial to actually starting the trial.

The agenda for the workshop can be found in Appendix A. At the conference, experts and major stakeholders offered presentations in four sessions:

- Organization of the NCI clinical trials system and operation of Phase III clinical trials;

[1]The American Cancer Society estimates that there will be 1,437,180 new diagnoses of cancer in the United States in 2008 (ACS, 2008). Of these individuals, not all would be eligible to participate in clinical trials, but the percentage eligible would be estimated to be higher than the 1.5 percent that currently participate.

- Patient recruitment and physician participation;
- Data collection standards to establish safety and efficacy; and
- Costs and payments within clinical trials.

Across the various sessions, many of the presentations touched on similar issues, with speakers identifying shared problems and potential solutions for improving the quality and efficiency of trials undertaken by the cooperative groups. At the end of this document is a section titled "Summary and Wrap-Up." This section spells out the common themes heard at the workshop, as summarized by Dr. Mendelsohn.

This document will serve as one input to the deliberations of an Institute of Medicine committee that will develop consensus-based recommendations for improving cancer clinical trials and the operation of the NCI Cooperative Group Program. The committee will also consider other issues that may warrant exploration and analysis. Some of these were mentioned by the NCPF chair, Dr. Harold Moses of the Vanderbilt-Ingram Comprehensive Cancer Center. He pointed out that a number of other topics relevant to the discussion on how to improve the Cooperative Group program had been addressed at a complementary workshop, "Improving the Quality of Cancer Clinical Trials," that was held by the NCPF in October 2007. This workshop covered clinical trial design, molecular imaging, predictive markers, clinical trial costs, and regulatory issues. The workshop summary has been published and will also be used as input to the deliberations of the committee (IOM, 2008).

In general, this workshop summary follows the order of the speakers at the conference, although some speaker comments have been grouped to maintain the summary's primary organization by topic. The views expressed in this summary are those of the speakers and discussants, as attributed to them, and are not the consensus views of workshop participants or NCPF members.

ADAPTING THE COOPERATIVE GROUPS IN A CHANGING CLINICAL ENVIRONMENT

Dr. John Niederhuber, director of the NCI, focused his introductory remarks on the recent paradigm shift in cancer treatment from "search and destroy" nonspecific and broadly toxic treatments to "target and control" combinations of therapies that are specifically targeted to the genetic or molecular defects that underlie a patient's cancer. Using lung cancer as an example, he noted that researchers discovered specific genetic mutations of the epidermal growth factor receptor that are linked to how well a patient responds to the targeted cancer treatments gefitinib and erlotinib; researchers have also identified the mechanisms of resistance

to these treatments (Paez et al., 2004; Kobayashi et al., 2005; Yun et al., 2008). These findings have led to promising clinical results in a cancer that is traditionally difficult to treat. "It represents that transition we are making to identify more specifically a target and match that patient in a much more specific way to that target," Niederhuber said.

He then said that the main focus of the NCI's Cooperative Group Program has been to test new anticancer agents from the NCI's drug development program (Dignam, 2004). For most of the program's duration these agents have been toxic, nonspecific chemotherapies, used singly or in combination. "In an era of targeted therapy, the system is geared toward the testing of nonspecific regimens," he said. "It lacks the capacity to highly characterize each patient and carefully match that patient profile to targeted therapeutic combinations." As he noted in his cover letter to forum members and workshop participants, "the clinical trials system must be structured today to meet the challenges and requirements of tomorrow" (Appendix C).

The main challenge in this regard will be to design a trial structure that can obtain drug approval and demonstrate safety and benefit in this new kind of environment—an environment in which patients can be characterized according to the molecular defects that underlie their cancers so as to better match them to the experimental therapies under evaluation. Such characterization may be done within the cancer genome characterization centers, which are currently part of the Cancer Genome Atlas pilot project of the NCI and the National Human Genome Research Institute, or within a similar setup, Dr. Niederhuber suggested.[2] He also referred attendees to two relevant documents published by the NCI. One is on restructuring the NCI's clinical trials enterprise, and the other is on overhauling the process whereby biomedical discoveries are translated into useful interventions for patients.[3]

Dr. David Parkinson, president and chief executive officer of Nodality, Inc., concurred with Dr. Niederhuber's comments: "We have enormous opportunity related to biology and technology around cancer therapeutic solutions. We also have very significant inefficiencies in translating those opportunities into clinical reality."

[2]See http://www.cancer.gov/newscenter/pressreleases/TCGAcancertypes.

[3]See http://spores.nci.nih.gov/public/ctwg_finrpt_June2005.pdf and http://www.cancer.gov/aboutnci/trwg/executive-summary.pdf.

Session 1A: Organization of the NCI Clinical Trials System

THE NCI'S CLINICAL TRIALS SYSTEM

Dr. Jeffrey Abrams, associate director of the NCI's Cancer Therapy Evaluation Program (CTEP) began the first session of the conference by describing how the Cooperative Group Program fits within the context of other NCI clinical trial programs, discussing the improvements that have been made within these programs in recent years, and outlining the challenges that still lie ahead.[4]

In addition to its intramural Clinical Center, Dr. Abrams said, the NCI has a large, multi-faceted extramural clinical trials program. The NCI has grants that can support either investigator-initiated studies or the cancer centers at which trials are conducted, as well as cooperative agreements, such as those that underlie the Cooperative Group Program and the Community Clinical Oncology Program (Box 1). The NCI's CTEP[5] currently supports about 250 Phase I clinical trials, 400 Phase II clinical trials, and between 100 and 150 Phase III clinical trials. In addition, the NCI's Division of Cancer Prevention currently has 123 active trials. These provide financial and logistical support for both patients and physicians within a large national and international network for their participation in clinical trials sponsored by the NCI. Cooperative agreements also provide support for a Phase I treatment program, a program directed at treating

[4]See http://www.cancer.gov/cancertopics/factsheet/NCI/clinical-trials-cooperative-group.

[5]See http://ctep.cancer.gov.

BOX 1
NCI Clinical Trials Program: Multi-faceted

Extramural Research Activities

- **Grant mechanisms**—R01, R03, R21, R37, and P01 grant-supported trials in treatment, control, and prevention
- **Cancer Center Support (Core) grant**—partial support for trials at NCI comprehensive cancer centers
- **Research contracts**—prevention and treatment trials
- **Specialized Programs of Research Excellence (SPOREs) (P50 grants)**—treatment and prevention
- **Cooperative agreements**—Community Clinical Oncology Program research bases, cooperative groups, Phase I treatment and central nervous system tumors (adult and pediatric), Blood and Marrow Transplant Clinical Trials Network

Intramural Research Activities

- **Clinical Center**

SOURCE: Abrams presentation (July 1, 2008).

central nervous system tumors, and a bone-marrow transplant cancer treatment network.

With the program's participating sites, which are scattered throughout 50 states, Puerto Rico, and Canada, cooperative group trials accrued about 20 percent of all the patients at NCI-designated comprehensive cancer centers in 2007, Dr. Abrams said. This percentage is about the same as the percentages accrued by industry at these cancer centers. To further boost participation, the NCI established the Community Clinical Oncology Program (CCOP) and the minority CCOP to feed into the cooperative group trials.[6] These CCOPs make up a large network of community-based physicians, including those based in populations with sizable numbers of minorities, which receive financial support from the NCI so that their patients can participate in cooperative group or other NCI-supported clinical trials. CCOPs provide accrual to protocols, which is the enrollment of qualified patients into clinical trials, and some data management and quality control, while affiliate cooperative groups or cancer centers are responsible for developing protocols, data management and analysis, and providing quality assurance.

[6]See http://prevention.cancer.gov/programs-resources/programs/ccop.

Dr. Abrams said that the Cooperative Group Program is unique among NIH-supported clinical trials programs in that it consists of researchers at institutions affiliated with the cooperative groups who jointly develop and conduct trials in multi-institutional settings. It also has a clinical trials infrastructure that is available at any time to test new therapeutic strategies as well as a flexible research agenda that can respond to changing scientific opportunities and new discoveries. Also unique to the Cooperative Group Program is the volunteerism on the part of researchers who support it. "Not everybody is getting their own particular grant to do this work," he said. "In fact, many centers that contribute mightily only get their per-case reimbursement, which is not sufficient to support this work. So volunteerism has been a keystone of this project."

Currently there are 12 cooperative groups, which are listed in Box 2. In addition, there are related NCI-sponsored groups that provide radio-

BOX 2
NCI Cooperative Group Program 2008

The NCI Cooperative Group Program is composed of 12 groups. Seven are classified as multimodality groups, while the others specialize in various cancer sites or treatment modalities.

Multimodality:

- Cancer and Acute Leukemia Group B (CALGB)
- Children's Oncology Group (COG)
- Eastern Cooperative Oncology Group (ECOG)
- European Organisation for Research and Treatment of Cancer (EORTC)
- NCI of Canada-Clinical Trials Group (NCIC-CTG)
- North Central Cancer Treatment Group (NCCTG)
- Southwest Oncology Group (SWOG)

Specialty:

- American College of Radiology Imaging Network (ACRIN)
- American College of Surgeons Oncology Group (ACOSOG)
- Gynecologic Oncology Group (GOG)
- National Surgical Adjuvant Breast and Bowel Project (NSABP)
- Radiation Therapy Oncology Group (RTOG)

NOTE: NCIC-CTG funding is limited to participation in intergroup trials.
SOURCE: Abrams presentation (July 1, 2008).

therapy or imaging quality assurance reviews and aid with imaging data management. The cooperative agreement that funds the cooperative groups is a cross between a grant and a contract, Dr. Abrams said, so that government scientists and grantees can work together to achieve the best outcome (CTEP, 2008). A financial award is given to support the infrastructure of the cooperative groups. This funding is used to support their operations, statistical analyses, offices, investigators, and committees. Some cooperative groups use this funding as a source of reimbursement of per-patient costs at their sites, once patients are accrued onto a clinical trial. But for many cooperative groups, the NCI provides per-patient reimbursements to individual cooperative group sites in addition to the funding for the cooperative group's infrastructure.

The NCI coordinates protocol review of all the cooperative groups and provides quality assurance and pharmaceutical management programs. The NCI and the cooperative groups work jointly on data and safety monitoring boards, meeting organization, and development of intergroup relationships and arbitration procedures. Cooperative groups are also permitted to accept funds from non-government sources for research not supported by the NCI (NCI, 2000). Via this mechanism the cooperative groups can accept support for their trials from industry or from charitable contributions. Despite some industry involvement, the cooperative groups have maintained their independence. Company partners are not involved in the monitoring of the trials and are informed of the trial results at the same time that the public is informed.

These public–private partnerships are valuable, Dr. Abrams said, especially as they assist with some of the regulatory compliance needed to pass drugs through Food and Drug Administration (FDA) review. He added, however, that private funds are usually used for specific trials and not for maintaining the infrastructure of the cooperative groups. Consequently, private funds cannot always compensate for insufficient public funding, as these funds often cannot be rapidly used to support trained personnel at a large number of sites.

The NCI, including the cooperative groups, tends to run trials focused on the best management of disease and not on specific agents, Dr. Abrams said. Such trials might compare two or more novel approaches with an accepted standard treatment or assess predictive markers for selecting individualized therapeutic approaches. The NCI also conducts trials generally neglected by industry, such as those of rare diseases or of cancer-prevention interventions, and carries out studies aimed at improving upon commercially available agents or determining their safety and effectiveness at lower doses or in the pediatric community (Mauer et al., 2007).

Between 1998 and 2007 the number of Phase III cooperative group

trials decreased, which may reflect the fact that funding for the program declined after 2002 and has currently leveled off at around $145 million a year. This figure reflects a 20 percent decline in funding when the effects of inflation are considered, Dr. Robert Comis, president and chairman of the Coalition of Cancer Cooperative Groups and group chair of the Eastern Cooperative Oncology Group (ECOG), pointed out in a later presentation (NCI, 2008b). Since 1999, Dr. Abrams said, the reimbursement for sites has remained fixed at $2,000 per patient on the treatment trials, which is about one-third to one-quarter the amount of financial support needed to support the cost of these studies (Schmidt, 2007). To counter insufficient funding the NCI increased per-case reimbursements to sites by $5 million last year. It has also set aside $1.6 million for biomarker studies run by the cooperative groups. But Dr. Comis later noted that, by way of comparison, industry often pays more than $15,000 per case in Phase III studies. "Cooperative group trials are an incredible bargain for the public. It's almost unbelievable that we can do the work that we do at $145 million a year and still provide the kinds of data and information that continue to drive the field forward," Dr. Comis said.

Dr. Abrams described a number of improvements the NCI has made to its Phase III clinical trials programs over the past 10 years, which have made them more efficient and brought them up to date with the current state of the science. One such improvement, for example, was establishing a centralized Institutional Review Board (IRB) so as to avoid multi-center trials having to be reviewed by hundreds of IRBs throughout the country.[7] Currently 329 institutions are enrolled in the central IRB, and 183 studies have been approved through this process, Dr. Abrams reported. But he said that although more than half of the pediatric sites participate in the central IRB, only about one-quarter of the adult sites do. Barriers to an increased use of the central IRB include individual institutional concerns about legal liability and having a separate process for cancer trials as opposed to other trials, as well as an unwillingness by these institutions to give up control in this area (McNeil, 2005). Those institutions hesitant to participate in the central IRB can participate in a "facilitated review," which allows the local IRB to monitor the initial work of the central IRB. If the local IRB agrees with the central IRB's review and finds it acceptable, the local IRB can then let the central IRB take over the review functions for the trial from that point on.

The NCI also established the Clinical Trials Support Unit (CTSU), which is essentially a virtual administrative assistant.[8] The CTSU created a single online menu of trials for the Cooperative Group Program, which

[7]See http://www.ncicirb.org.
[8]See http://www.ctsu.org.

includes all the required documents for physicians and their patients to participate in a trial, as well as data management and regulatory documents. The online menu makes it possible for any cooperative group member to participate in any Phase III trial suitable for his or her patients, rather than only those trials within the specific geographical cooperative group of which they are a part. "We have gotten away from only ECOG members working in ECOG and only NSABP [National Surgical Adjuvant Breast and Bowel Project] members working in NSABP," Dr. Abrams said. "We have really opened the system up quite extraordinarily." CTSU also recently created a new system called the Open Oncology Patient Enrollment Network, which will be a single site for all cooperative group enrollments for Phase I through Phase III trials. Physicians can register and enroll their patients through the same system. "We think that will be a big boost for investigators to only have to deal with one system regardless of what cooperative group trial they choose to enroll a patient in," Dr. Abrams said.

These CTSU accomplishments have speeded the accrual of cooperative group clinical trials, according to Dr. Abrams. It also appears to have boosted the number of non-cooperative group affiliated sites now participating in clinical trials, and it may be a way for them to develop a track record and improve their clinical trials participation.

In addition to creating CTSU to make participation in cooperative group trials more user-friendly and cost-effective, the NCI has also put together state-of-the-art scientific meetings and established disease-specific steering committees comprised of experts, cooperative group and CCOP members, patient advocates, and community representatives. The steering committees determine the best questions to be addressed by the cooperative group's Phase III trials and the best ways to design those trials. Before the creation of the steering committees, CTEP reviewed the cooperative group studies. Finally, the NCI hopes to create in the near future a single remote data-capture system for all the cooperative groups.

"We have developed what I think is an integrated priority-driven system," Dr. Abrams said. "Hopefully, the pieces are now in place to make the system hum. I also think we could do a lot better and embrace Dr. Mendelsohn's goal that we could improve by 50 percent [the time it takes to go from conception to the start of a clinical trial]. But there is a learning curve, and I think we have managed to get the pieces in place now to be able to be more efficient."

He added that in an era of flat budgets, "we do have to become more efficient and have to prioritize the trials we are doing. We cannot have hundreds of trials circulating through the system that are not of top priority." He also suggested developing and nurturing more partnerships with

industry and adding screening components to trials to meet the patient assessment needs of targeted therapies.

He said that industry is increasingly outsourcing its trials to overseas institutions. While stressing that such testing will not adequately reflect how well a drug will do within the medical environment of the United States, he added that the NCI cooperative groups have to partner with international groups so as to participate in the multinational trials being run by industry. He finished his talk by mentioning the importance of the cooperative groups forming partnerships with advocacy and community organizations. "We have to make sure that advocates are included early in the process, not as an afterthought," he said.

After Dr. Abrams' talk, Dr. Robert Califf, professor of cardiology, vice chancellor for clinical research, and director of the Duke University Translational Medicine Institute, noted the disparity between the costs of running cooperative group clinical trials and the amount of reimbursement from the NCI. He raised the question of whether it is ethical to attempt to do a clinical trial when those who are running it are not getting paid enough to do it well. Dr. Abrams responded that sites try to meet their cost burdens by balancing trials that are better reimbursed because of industry partnerships with those that receive lower reimbursements. He added that funds are also donated from cancer centers that see running national cooperative group trials as in their best interests. "But as times have gotten tougher, that interest has declined," he added. Some cancer centers have capped the number of accruals that can go to cooperative group trials, because they feel it is too much of an economic burden, he said, agreeing with Dr. Califf that the economic situation is currently a crisis and is causing the numbers of cooperative group clinical trials to drop. "The costs have gone up dramatically, yet the cap on the amount reimbursed per patient has not changed since 1999," Dr. Parkinson said (Schmidt, 2007). "So somebody is paying the price, and the issue is what trials are actually making a difference. It would be interesting to see performance metrics related to information per unit patient and whether some clinical trials are more productive than others."

Also concerned about the quality of clinical trials, Dr. Burger, associate professor of clinical obstetrics and gynecology at the University of California, Irvine, School of Medicine, suggested considering mandatory online educational course work for institutions that are not actively attending specific cooperative group meetings in cases where those trials have been initiated. He also suggested adding quality assurance representatives to each Phase III clinical trial done in the cooperative groups, in addition to the traditional study co-chairs.

MAYO CLINIC AND NORTH CENTRAL CANCER TREATMENT GROUP

The next speaker, Dr. Jan Buckner, professor of oncology at the Mayo Clinic College of Medicine and the group chair of the North Central Cancer Treatment Group (NCCTG), spoke about the academic-community partnership between Mayo Clinic and the NCCTG, which has existed for the past 30 years. Although originally established as a way for Mayo Clinic to reach patients in sparsely populated nearby regions, the NCCTG now has 43 member networks that treat patients in more than 340 locations within 33 states, Canada, and Puerto Rico. More than three-quarters of its patients are enrolled from community practices.

Mayo Clinic serves as the research and administrative base for the NCCTG and also supports other cooperative groups via its biospecimen bank and its statistics and data center. The centralized, integrated support that Mayo Clinic provides to the NCCTG is extensive and includes:

- *scientific leadership*, with experts in therapeutic interventions, laboratory correlative studies, statistics, epidemiology, and quality of life supporting the design, implementation, and analysis of clinical trials;
- *administrative support*, including grant preparation and management, budgeting, contracting and legal support, accounting, communications, and publications;
- *statistics and data management*, including safety monitoring, data analysis, statistical design of studies, data collection, quality assurance and control, and abstract and manuscript preparation; and
- *operations support*, including regulatory support, protocol development, information technology, site and meeting management, data collection, and quality assurance and control.

Dr. Buckner noted that although the quality control of the trials begins with concept and protocol review both internally at Mayo Clinic and externally by the NCI, the relevance and feasibility of a proposed trial are enhanced by having industry sponsors, the FDA, patient advocates, and community oncologists provide their input in protocol reviews. Each protocol is also reviewed by disease- and modality-specific committees at Mayo Clinic and an independent Mayo Clinic research committee.

There are multiple mechanisms for quality assurance, including automated web-based data monitoring that generates alerts when there are serious adverse events (SAEs), when data are overdue, or when data are questionable. On-site audits are conducted by the NCCTG, the NCI, and the FDA. Protocols are highly specified for imaging technique and assessment criteria, and a central review of images plus on-site audits also help

to assure image quality. Dr. Buckner noted that pathology quality assurance has become more important with the advent of targeted therapy. This is done with protocol-specific specimen submission kits, consensus review of problem cases, and centralized laboratory confirmation of protein or gene targets.

There are also guidelines for ensuring the ethical integrity of the cooperative group's clinical trials. All investigators undergo training on the ethical conduct of human subjects research and must disclose any conflicts of interest. Because of the pivotal role that Mayo Clinic investigators play in the process, the Mayo Clinic Conflict of Interest Review Board also reviews all Mayo Clinic participants.

All these review processes ensure that the cooperative group's clinical trials are high quality and scientifically rigorous, Dr. Buckner said, but they also cause protocol development times to be entirely too long. Protocols can be as long as 150 pages and sometimes require as many as 150 weeks for approval. "Certainly each cooperative group has its own internal inefficiencies that need to be addressed," he said, "but the extensive external review creates a set of inefficiencies in and of itself. Often the reviews are sequential and not concurrent, and there is a lack of standardization of the processes." Industry sponsors may also cause delays with their complex internal decision-making process and their contract and budget issues, while IRB reviews delay the process further still. "Whether it is an NCI central IRB review, a regional central IRB, or an individual institutional IRB, there is lack of consistency among the IRBs in terms of criteria and process," he said.

In addition to start-up inefficiencies, Dr. Buckner said, regulatory processes also impede cost-effectiveness. Site and investigator credentialing is excessive and lacks standardization across the country. Adverse event reporting is redundant and inconsistent across organizations. Many industry and government policies add administrative costs but have questionable added value, he said.

Dr. Buckner ended his talk by suggesting that external inefficiencies be improved by standardizing information technology infrastructure as well as data elements, collection, and reporting. He also suggested simplifying and harmonizing regulatory methods, such as the adverse event reporting required by both the NCI and the FDA. He then described Mayo Clinic's attempt to improve its internal inefficiencies by using the *lean process* to eliminate steps that do not add value.

This process was led by the Mayo Clinic Quality Academy and involved protocol development unit staff and legal and budgeting staff. The staff focused on reducing the number of steps and time taken between drafting the first protocol and submitting it to the NCI or the IRB, because these steps were under the control of the clinic. The steps were mapped

out, and those that did not add value to the process were eliminated. For example, redundant reviews and delays caused by waiting for e-mail responses were eliminated. "We cut out a part of the e-mailing by saying you must appear on a certain date for protocol planning meetings or your protocol will not go forward," Dr. Buckner said. "That gave some accountability to the timeline." A review of seven protocols submitted since the streamlining process revealed that development time from the time the protocol was first completed until it was submitted to the NCI or the IRB dropped by 75 percent.

After Dr. Buckner's talk, there was some discussion of how many clinical trials a given institution participating in the Cooperative Group Program can run simultaneously in a high-quality manner. Dr. Buckner noted that there is adequate training available for both new and established data management experts and that clinical research associates and research nurses attend semiannual meetings not only for the NCCTG but also for other cooperative groups in which they participate. In addition, because the same institutions have been running these clinical trials for 30 years or longer, there is expertise at the institutional level that is transmitted from one study to another.

There are also a number of quality control tools that enable consistency and quality across participating institutions, Dr. Buckner added. These tools include remote data-capture system methods that require participants to fill out every field and the availability of quality assurance personnel to answer questions.

"There are multiple mechanisms by which we can have multi-center trials of high quality if we [are diligent] in training the people and then supporting them after the protocol is open," Dr. Buckner said. He also noted that the quality of studies tends to rise with the number of trials run at each site. "If you are talking about three or four trials at a given site, that is maybe a yellow flag that the quality may not be good. If it is 8 to 10 trials and people put on 5 to 25 patients a year, I think that generally is enough for staff to be able to do good quality research with adequate support," he said.

RADIATION THERAPY ONCOLOGY GROUP

The next speaker, Dr. Walter Curran, professor and chair of the Department of Radiation Oncology of Emory University School of Medicine, chief medical officer of the Emory Winship Cancer Institute, and chair of the Radiation Therapy Oncology Group (RTOG), discussed how the RTOG cooperative group is organized. This multi-center cooperative group systematically tests novel radiotherapy approaches against cancer and pursues fully integrated translational research to support and further

this effort, Dr. Curran said. He added that because RTOG investigators are located at nearly every academic center in the United States and Canada, patients throughout those two countries can participate in RTOG clinical trials. Because of a new international membership initiative (Corn et al., 2008), there are several international RTOG members, including members located in China, Hong Kong, Israel, Korea, Peru, and Russia. RTOG also runs clinical trial collaborations with other organizations, including the European Organisation for Research and Treatment of Cancer, Southwest Oncology Group (SWOG), Cancer and Acute Leukemia Group B (CALGB), the NCCTG, the American College of Radiology Imaging Network, and Specialized Programs of Research Excellence (SPOREs).

RTOG is administered by the American College of Radiology. RTOG has an elected chair and both elected and appointed vice-chairs. A 15-member steering committee with elected and appointed members meets monthly. An executive committee includes those 15 members plus 13 additional members. There are also disease-site committees and working groups as well as scientific core committees, which are listed in Box 3. Some of these core committees are unique to RTOG's mission, such as an Advanced Technology Integration Committee, which examines how to test and evaluate the available technologies specific to radiation oncology. Dr. Curran noted that a Clinical Trials Education and Recruitment Working Group is embedded in every clinical trial and is particularly useful. This group consists of patient advocates and various experts who evaluate every trial concerning its ability to accrue and the likely difficulties of running the trial.

BOX 3
Radiation Therapy Oncology Group's Scientific Core Committees

- Advanced Technology Integration
- Health Services Research and Outcomes
- Translational Research Program
- Biospecimen Resource
- Pathology
- Medical Oncology
- Medical Physics
- Surgical Oncology

SOURCE: Curran presentation (July 1, 2008).

According to Dr. Curran, RTOG is unique in that its biostatisticians, data managers, headquarters staff, quality assurance center, protocol developers, and group chair's office are all housed in Philadelphia within an integrated office layout. "The work-flow efficiency with this model has really been outstanding," he said. Decisions about which studies to run are aided by the disease-site committees and working groups and the scientific core committees, which define research priorities, Dr. Curran said. The steering committee then reviews and approves all research proposals and adjudicates among competing research priorities.

Much of the research run by RTOG focuses on how to improve the physical and molecular targeting of radiation therapy, with or without chemotherapy, so that it is less toxic and more effective, Dr. Curran said. Among the innovations being tested are the use of image-guided radiation therapy and functional imaging to improve the physical targeting of tumors, the combination of targeted chemotherapies with radiation therapy, and the use of molecular biomarkers such as the epidermal growth factor receptor to target radiation therapy or identify those patients most likely to benefit from such therapy. RTOG also conducts translational and analytic research with its unique and interlinked clinical biophysical, biologic, and outcomes databases that enable powerful biostatistical and medical informatics approaches.

The strategic themes of RTOG, which emphasize radiation therapy, are not duplicated by other cooperative groups, Dr. Curran said. Because of this emphasis RTOG is the lead cooperative group in studying primary and secondary brain tumors, head and neck cancer, and non-operative therapies for localized and locally advanced prostate cancer (Chung et al., 2007).

About half of RTOG's funding comes from its core cooperative group agreement, with additional funds coming from corporate foundations and other grants. Sixteen percent of its funding comes from a Pennsylvania state tobacco settlement. Dr. Curran added that RTOG relies heavily on investigator volunteerism. Recently RTOG nearly doubled the amount of funding it receives from private foundations, and it has substantially expanded its membership and volunteer member efforts. This has resulted in a 28 percent increase in accrual over the most recent grant period and an increase in the number of publications and abstracts on RTOG studies, Dr. Curran said. He added that the accrual failure rate of RTOG has decreased from 33 percent in 1996 to 9 percent currently.

Dr. Curran summarized his talk by saying, "We have an organization customized to our mission and strategic aims and a unique niche among the cooperative groups. I think that would be true of all of the cooperative groups, and that is why the system probably is as complicated as it is."

After Dr. Curran's talk, there was discussion of how to handle the

regulatory, quality assurance, and funding aspects of international membership. Dr. Curran said that this is a challenge and that every country is different, but he added that the initiative from the NCI on international cooperation will be helpful in this regard.[9] "You really need someone who is an advocate at the institution," he said. He also pointed out that there are no differences between the international and the domestic criteria for being an RTOG member, which helps with quality assurance across international boundaries. But he added that the support for radiation quality in the American sites is greater than that for international sites.

IMPROVING CLINICAL TRIAL START-UP TIMES

The next speaker, Dr. David Dilts, professor in the Owen Graduate School of Management and the Vanderbilt University School of Engineering and co-director of the Center for Management Research in Healthcare, discussed organizational shortcomings in developing clinical trials and ways to overcome them. An expert in operations management, Dr. Dilts has shown with his research that it takes about the same amount of time to set up a cancer clinical trial as it does to run one. His detailed analysis found that it takes about 810 steps to open a Phase III cooperative group clinical trial, with 68 of those steps having an opportunity for looping that would involve additional revision and review steps. As many as 38 separate groups or individuals can be involved in a study before it receives its first patients, Dr. Dilts said. Dr. Dilts has mapped these steps and process loops: in 8-point font, the process map for CALGB was 35 feet by 5 feet, ECOG's was 50 feet by 5 feet, and CTEP's was 45 feet by 5 feet. There is no evidence that many of the steps in the development process improve the value of the study, he added (Dilts et al., 2006, 2008). "There is a ton of redundancy," he concluded.

Part of that redundancy is due to what Dilts termed scope creep, which occurs when one group or organization expands the scope of its authority or power beyond what was originally intended. An example would be an IRB reviewer that reviews not just the ethical design of a study but the scientific design as well. "Everybody wants to add something to make it a little bit better by tweaking a study, but the minute you add something, you may add months to the development process," Dr. Dilts said. Time is also wasted, he added, when there are extraneous reviews in the development process rather than a comprehensive review.

When Dr. Dilts analyzed the development process for clinical trials, it became apparent that there was not one step or one individual or group in the process that was the bottleneck. There were inefficiencies across

[9]See http://ctep.cancer.gov/guidelines/nci_clin_intl_guidelines.pdf.

the board, and each step contributed to the delay in opening a clinical trial. Rather than a single bottleneck, there was what is referred to as a "floating" bottleneck in the system. As soon as one bottleneck is corrected, another bottleneck arises to take its place. Dr. Dilts also said it was interesting to note that each individual or group took about the same amount of time to complete its step in the process.

The problem is not how much time each step takes, Dr. Dilts said, but how many repetitive steps there are with looping such that the same person or institution keeps reviewing the same study after minor alterations were made that other reviewers required. "Only by working together can we make major improvements," he said. His computer model found that if individual cooperative groups or CTEP singly try to improve their processes, they will each cut only a few days off the trial development timeline, but if they work together to improve the entire process, the timeline will be substantially shortened. The desired outcome is to decrease the amount of time to open a study from being discussed in terms of years to being discussed in units of days, Dr. Dilts said.

Dr. Gordon Bernard, professor in the Department of Medicine and assistant vice chancellor for research at the Vanderbilt University Medical Center, later added in his talk that much time is wasted, because many of the steps in clinical trial development are conducted serially rather than in parallel. He noted that his group can predict when they will be finished with a protocol and be ready for a protocol review committee to review it. But the National Heart, Lung, and Blood Institute will not set up a protocol review committee until the final protocol is in hand, and that can take an additional three or four months to set up.

The median time it takes to open a Phase III cooperative group clinical trial currently is 2.5 years, but that time can vary from 1.25 years to almost 7 years, Dr. Dilts reported (Dilts and Sandler, 2006; Dilts et al., 2006, 2008). The science can change tremendously during the time it takes to approve a clinical trial. As a result, when the trial starts accruing patients, it may happen that it is no longer testing the "popular" experimental treatment or that the protocol is no longer relevant, Dr. Dilts pointed out. During the following presentation, Dr. Richard Schilsky, professor of medicine at the University of Chicago and chairman of CALGB, gave a telling example of this: A clinical trial aimed at assessing whether the addition of cetuximab to standard chemotherapy improved the survival of patients with previously untreated metastatic colorectal cancer (Clinicaltrials.gov, 2008). During the several years of protocol development and initial accrual phase of the study, bevacizumab was approved by the FDA for the treatment of metastatic colorectal cancer, and another study showed the importance of testing colorectal cancer tumors for genetic mutations (in the *ras* gene) that predict whether patients will respond to cetuximab. This required

rewriting the protocol twice and subjecting it twice to the same lengthy review process it went through initially so that bevacizumab could be part of the standard of care given in the trial and so that patients' tumors were screened for the *ras* mutations prior to receiving treatment with cetuximab.

The length of the development process for a clinical trial appears to affect the accrual success of the trial. The longer trials take to be developed, the less likely it is that they will meet their minimum accrual goals, Dr. Dilts reported (Goldberg, 2008a). He stressed that the ultimate inefficiency is a clinical trial that is never completed because of insufficient patient accrual, and this happens far too often with cooperative group trials. Sixty-four percent of all Phase III studies sponsored by CTEP between 2000 and 2007 did not meet their minimum accruals. Only about one quarter of all cooperative group trials accrue five or more patients, and nearly 40 percent do not accrue any patients at all. "All those 800-plus steps it takes to develop a clinical trial are wasted and useless if nobody shows up," Dr. Dilts said.

In the remainder of his talk, Dr. Dilts discussed ways to remedy the inefficiencies that cause long development times for clinical trials and affect their success in meeting minimum patient accrual levels. He suggested analyzing existing data—and collecting additional data—to assess how long it takes to develop various clinical trials and to determine what factors affect those development times. Redundant, non-value-added steps in the process should be eliminated. Dr. Dilts noted later during discussion that, to facilitate such data collection, a clinical trial should be identified by the same tracking number as it goes through the different review steps. "In the four comprehensive cancer centers we studied, there was an average of eight different tracking numbers for exactly the same study—you had an IRB number, a finance number, a grant number, etc., and so you could not track it," Dr. Dilts said. "If you cannot track it, how do you know what is happening to it?"

During his presentation, Dr. Bernard agreed that it is important to create metrics around the clinical trial development process in order to determine much more readily when and where in the process problems are happening. He also recommended sharing those metrics within cooperative groups and providing comparative metrics to local organizations. "We plan to list our metrics on the CTSA [Clinical and Translational Science Awards[10]] website, to the embarrassment of some of our sites," he said. Dr. Califf also recommended publicly reporting metrics during his

[10]See http://www.ncrr.nih.gov/clinical_research_resources/clinical_and_translational_science_awards.

presentation. "Just the public shame of how pathetic this is will lead to improvement," Dr. Califf said.

Dr. Dilts also suggested not trying to run every feasible or scientifically worthy trial that is conceptualized but rather to limit trials to those prioritized as being among the top 10 per institution. Dr. Bernard concurred with this approach in his presentation, noting that otherwise "you just bury the organization in protocols that are not accruing, and they really do use up the infrastructure of the institution." Priorities can be set based not only on scientific merit but also on operational complexity, which determines how likely trials are to succeed, Dr. Dilts said. The optimal studies are those that have the highest scientific merit and the lowest operational complexity, he added (Figure 1).

During the discussion period, Dr. Joseph Aisner, professor of medicine, chief medical officer, and director of the Thoracic Oncology Program at the New Jersey Cancer Institute, raised his concern that streamlining the number of clinical trials will adversely affect research on rare or pediatric tumors, where there are now three protocols activated institutionally for every patient accrued. Dr. Bernard noted that this was a valid concern and suggested that another funding mechanism, perhaps one akin to that for research on orphan drugs, could be set up to make sure clinical trials on rare cancers continue. "The central protocol could become a much more automated process so that you can get a study up and running within a week as soon as you discover you have a patient to enter it," he suggested.

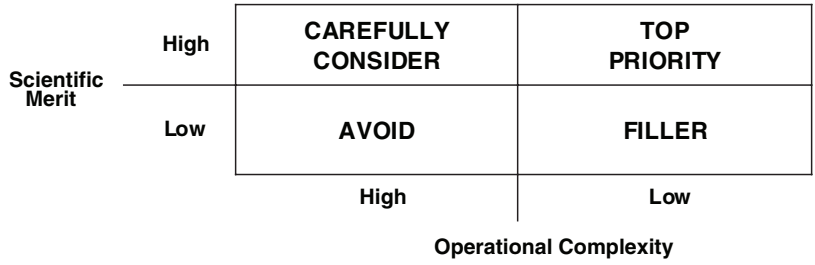

FIGURE 1 Scientific triage: A technique for determining which trials should be pursued. Prioritizing the conduct of clinical trials should take into account both scientific merit and operational complexity, according to Dr. Dilts. The most straightforward studies to undertake are those high in scientific merit, but low in operational complexity.
SOURCE: Adapted from Dilts presentation (July 1, 2008).

One key to prioritizing and limiting the number of clinical trials run at each institution is eliminating what Dr. Dilts called the "entitlement culture" that currently exists among the investigators of cooperative groups. This culture encourages people to think along the lines of "the cooperative group is responsible for opening my study because I am part of the cooperative group," Dr. Dilts said. "Suppose that the *New England Journal of Medicine* had that—I'm a doctor, so you should publish my paper because I am a doctor."

Clinical trial review committees or institutions are not only reluctant to "just say no" to proposed trials, but when they do say no, their denial often is not meaningful, Dr. Dilts said. He found that 14 disapproved concepts were still developed into protocols, and 11 of these were activated. Seventeen withdrawn concepts were developed into protocols, 8 of which were activated. "No should mean no," he said.

In addition, there should be strict adherence to review deadlines. "If the only penalty for being late is getting more time, then why do something on time?" he said. He also suggested developing and using standard terminology as well as administrative standards, noting that critical scientific issues can vary, but administrative processes can be standardized.

His final suggestion was to create focused Phase III teams composed of cooperative group and CTEP members and pharmaceutical representatives, which could activate a Phase III protocol within 90 days. The incentive for meeting the 90-day deadline could be providing the grant money to run the study, Dr. Dilts suggested.

Dr. Dilts concluded his presentation with a quote from Peter Drucker, author of *The Effective Executive*: "Unless a decision has 'degenerated into work' it is not a decision; it is at best a good intention" (Drucker, 2007). He added, "We do not have time to make good intentions. We have to make the system better."

Following Dr. Dilts's talk, Dr. Maurie Markman, vice president for clinical research at the M. D. Anderson Cancer Center, raised the possibility that there was a link between the high costs of running clinical trials and low accrual rates. "The cost is somewhere between $6,000 to $8,000 per patient now for some single trials, because you are following the patients for several years," he said. "I believe that is a large explanation for why the accrual is the way it is. You have got to pay the people to do the work, and there is not money for it. We do not have the funds at the institutional level to support this increasingly expensive enterprise."

Dr. Dilts agreed about the high expenses for running clinical trials, many of which are not reimbursed. But he reiterated that there is great expense in developing clinical trials that are never run to completion because of poor accrual. "If you really cut down the number of trials run, then perhaps there will be enough money to pay for what you need," he

said. He added that industry studies, which provide better reimbursements, do not accrue better than investigator-initiated studies, and that there is no funding source–dependent time difference in how long it takes comprehensive cancer centers to open a study. "I do not know whether money makes a difference in the eventual accrual. I know it does not make a difference in the time it takes to open trials," Dr. Dilts said.

Also discussed was whether increased government involvement in cooperative group trials is causing unnecessary delays in clinical trial start-up times. Dr. John Ruckdeschel, president and chief executive officer of the Barbara Ann Karmanos Cancer Institute and Cancer Center and associate dean of cancer affairs at Wayne State University's School of Medicine, noted that in 1981 cooperative groups stopped being funded by NCI grants and instead were funded by a cooperative agreement that boosted government oversight (CTEP, 1996). "The cooperative agreement meant that at every step of the way the government was involved," he said. "CTEP primarily, but you can count multiple other sources and committees and progress review groups. We have to reexamine whether that was the right change, because what it has imposed is a whole lot of this back and forth business. In addition, it has become just like the emergency room physician who orders test after test because he is worried about being sued. Cooperative groups spend an inordinate amount of time redesigning studies so they are more likely to get approved by CTEP and others." In response, Dr. Dilts noted that usually in business there is what is known as disintermediation, which raises the question, Why do I need the middle layers at all? "Why do we need intermediation of both CTEP and the cooperative groups?" Dr. Dilts asked. "If they do not add value, why do we need them?"

Following the discussion, Dr. Schilsky offered a presentation on how to rise to the challenge of rapid protocol activation. He began the talk by pointing out the many stumbling blocks that cooperative groups face when taking on this challenge. One of these impediments is the "all-volunteer army" of investigators that run cooperative group trials. Referring to CALGB, which he chairs, he said "None of the investigators in the CALGB work for me, so I do not control how they spend their time." This poses problems when these investigators are hard pressed to find time to review protocols, because their other responsibilities must take precedence.

Dr. Schilsky also reiterated some of the problems that Dr. Dilts pointed out, such as having "too many cooks in the stew" when generating and reviewing protocols, and too much tinkering by each of these parties. "Often the study gets discussed in different venues without exactly the same people around the table," Dr. Schilsky said. "So somebody comes in who has not seen the discussion in the last six months and says, 'We ought

to change the eligibility criteria, or we ought to include a new drug,' and before you know it, you have got the study being redesigned five different times, and each time it gets changed, it has to be re-reviewed." This is exacerbated by the frequent turnover among collaborating industry staff. "We will start a discussion about study design, and a year later suddenly it is a whole new group of people, and they do not seem to have any corporate memory," Dr. Schilsky said.

He described a particularly frustrating review process for one study. After this study was approved by CTEP, it underwent a lengthy three-round review process at the central IRB, which finally approved the protocol, so they assumed they could begin the trial. But then the NCI disapproved the protocol because of one of the changes made to satisfy the IRB, which required yet another several rounds of revision and reviews at both the NCI and the central IRB. "We are striving to strike the right balance of a controlling culture versus an enabling culture," Dr. Schilsky said, "and one might argue that we are too heavy on the control side and not heavy enough on the enabling side to allow these studies to move forward more quickly." He noted that the NCI cooperative agreements "provide very little flexibility for the cooperative groups and how we do business. Why does the NCI provide 50 percent of the funding but retain 100 percent of the control for the cooperative groups?"

Dr. Schilsky also repeated the need for communication and synchronization of the development team. "In my organization we have the protocol development going on in one office, and the forms development going on in a different office," he said. "I will be first to admit that we have had many times where the protocol is ready to go, but the forms are two months behind, or vice versa." Other impediments to speedy trial development are overburdened statistical centers and questions about who will own the data generated from the study.

Of increasing importance is the bigger question of who will pay for the study. The NCI pays only for some expenses involved in running a clinical trial and often does not pay for research-related tests that health insurers are also not likely to reimburse. "Say the protocol requires a PET scan every two weeks, a research-related biopsy, or frequent ECG monitoring to assess the QT interval prolongation," Dr. Schilsky pointed out. "You cannot bill those out as standard of care because they are *not* standard of care." He noted that the last review of CALGB recommended an annual budget of $33.8 million per year, but instead it was awarded $14.4 million per year—43 percent of the recommended level of support. This has prompted CALGB to seek industry support for many of its studies, but this support adds lengthy negotiations with the participating pharmaceutical companies, which do not have the best interests of the cooperative group at heart. "It is abundantly clear to me that the company

attorneys are hired to protect the company's interest. They are not hired to negotiate favorable contracts with the cooperative groups," said Dr. Schilsky.

He finished his talk by discussing ways to improve the clinical trial development process. To counter tinkering and repetitive reviews, he suggested a "two strikes and you're out" policy. "Our investigators send in a concept to the executive committee," he explained. "We will either vote it up or down or table it. If we vote it down, it is done, and we do not entertain a resubmission of the concept. If we think there is a salvageable problem, we will table it, but it then must be voted up or down the next time through." To avoid excessive tinkering, Dr. Schilsky also asks his committee chairs not to discuss protocols once they are in development, because "the more they talk about them, the more people want to change them."

CALGB also uses Dr. Dilts's approach to prioritizing studies based on both scientific merit and operational complexity, and Dr. Schilsky noted that they raised the bar for a priority score such that there are few concepts coming through the system. Once the executive committee approves new protocol concepts, they are added to a master priority list for the entire cooperative group. "So all parts of our organization know what are the high priority protocols at any point in time," Dr. Schilsky said. This has helped improve synchronization because both the people in the protocol and the statistical center know, for example, what the top five protocols on the priority list are. His organization is currently also developing a web-based protocol tracking system that can easily be accessed to see where a protocol is in its development life cycle.

Following Dr. Schilsky's presentation, Dr. Scott Ramsey, full member of the Cancer Prevention Program in the Division of Public Health Science at the Fred Hutchinson Cancer Research Center, suggested that when evaluating clinical trial protocols, in addition to considering the scientific merit and operational complexity of the study, that a third category he called "clinical relevance" also be considered. Determining the clinical relevance would involve surveying the landscape of clinical trials that are currently being run in order to avoid redundancy or to delay protocol approval based on the results of some of these trials that might affect study design. Dr. Schilsky agreed that this was important and added that CALGB tries to incorporate such information into the initial conception of the protocol. "We do have lots of experts who are involved in designing these trials who, generally speaking, know what the landscape is, but sometimes they do not know everything, things change, or unexpected data comes out, the impact of which no one fully appreciated," he said.

Dr. Schilsky also gave numerous suggestions for what other groups involved in reviewing clinical trials can do to improve efficiency. He sug-

gested reconsidering whether it is necessary that the NCI review protocols for which they do not hold the Investigational New Drug (IND) approval or if FDA review of those protocols might be sufficient. When the NCI does have the IND, he suggested combining NCI and FDA review within 30 days. If there are no INDs being tested in a clinical trial, he suggested that an NCI review should be sufficient and that the FDA should not have to review the protocol as well. Eliminating NCI reviews might make industry more willing to collaborate with cooperative groups, Dr. Schilsky pointed out. He suggested modifying the terms of the NCI cooperative agreements so that they have more flexibility with regard to NCI reviews of protocols.

Another suggestion by Dr. Schilsky was that the FDA specify a minimum data set necessary for New Drug Application (NDA) submissions and that the agency assess the value added of Special Protocol Assessments, because they add considerable time to the FDA review process. Dr. Schilsky also suggested having the Centers for Medicare and Medicaid Services (CMS) cover all clinical care costs for patients on trials and also having them modify their physician billing codes so that doctors can bill at a higher rate for their patients on clinical trials, as these patients require more complex management.

IRB ISSUES

Dr. Schilsky also said that it might be wise to reexamine the value of a central IRB. Although he thinks it is a great idea, he said it has been difficult to implement. Because just 20 percent of the cooperative group sites in the United States ascribe to only the central IRB, the remaining 80 percent are "essentially being held hostage to the central IRB review, because they have to wait for that process to be completed before they can send the protocol to their own local IRB," Dr. Schilsky said (Ledford, 2007). In a later discussion, Dr. Califf noted that Duke University seldom uses central IRBs for its clinical trials but instead often uses commercial IRBs, which "just do the job without all the rigamarole we typically have inside the academic centers." He continued, "I think the facilitated IRB is a much better approach, because if you turn over everything to one central IRB and if it does a stupid thing, the entire machine is shut down, whereas beaming people in by teleconference, etc., gives everybody the benefit of expert review without totally giving up local control."

During a later presentation, Dr. Renzo Canetta, vice president of oncology global clinical research at Bristol–Myers Squibb, concurred that "the central IRB is not the magic solution in terms of time saved. Sometimes it helps, but sometimes it does not and is something that needs to be revisited." But Dr. Alan Keller, chairman of clinical research at Cancer

Care Associates in Tulsa, Oklahoma, noted later in his presentation a number of reasons why central IRBs are advantageous (McNeil, 2005).

During a later discussion, Dr. Markman pointed out that federally funded research falls under the regulation of the Office for Human Research Protections (OHRP), but non-federally funded research, such as clinical trials sponsored by industry, does not fall under OHRP's mandate. "So when you talk about the NCI central IRB, that is OHRP-related, but the for-profit IRBs have nothing to do with OHRP. We really are talking about different languages when we talk about the pharmaceutical companies that do not necessarily have to use OHRP," Dr. Markman said. Dr. Abrams concurred and added that "the major difference between the commercial IRBs and the NCI's central IRB model is that the commercial system comes in and takes over the entire IRB for an institution and there is not a local IRB—there is only the commercial IRB that serves that institution. The NCI's model is more of a shared model that still uses a local institution IRB, which provides local context, but the central IRB taking over certain responsibilities for the study."

Later in his talk, however, Dr. Keller deplored the fear of lawsuits and provincialism on the part of local institutions and the perceived importance of "local context," which he calls an unnecessary sacred cow. "We are a monolithic country when it comes to oncology treatment guidelines, FDA approvals, approved Medicare coding, national payor reimbursement standards, judging the standard of care," he pointed out. "I am not judged by the standard of care in Oklahoma. They will bring in New York attorneys if I get sued." Even informed consent forms are determined to a large degree by NCI specifications. To further emphasize his point, Dr. Keller pointed out that no drug has ever been denied approval because of geographic, political, cultural, religious, or ethnic differences. "So I would get rid of the local context requirement and then give some backup to our local IRBs to not do this," he said. He suggested insisting that institutions receiving federal funds use the NCI's central IRB. He noted that a central IRB reduces redundancy, costs, variability, and time, while increasing oversight and safety.

Dr. Mendelsohn suggested requesting that OHRP have all IRBs adhere to the same standards to simplify the review process for those clinical trials that use several IRBs. Dr. Abrams concurred with this suggestion. Dr. Markman said later in his talk that the FDA regulations on patient safety need to be congruent with those of OHRP. "There are multiple organizations and agencies at the federal and state levels that are responsible for patient safety, and they need to get on the same page," he said.

Session 1B: Lessons from Non-Cooperative Group Multi-Center Clinical Trials

The next portion of the first session of the conference was devoted to lessons that can be learned from those who run multi-center clinical trials outside the Cooperative Group Program. The speakers for this portion of the workshop were a cardiologist, an industry scientist, and a community physician.

ORGANIZATION OF MULTI-CENTER CLINICAL TRIALS

Dr. Robert Califf is a cardiologist, vice chancellor for clinical research, and director of the Duke University Translational Medicine Institute. He addressed organizational and operational issues that affect all clinical trials, not just those focused on cancer. He then discussed efforts that his university made to improve the efficiency of its clinical research efforts, and he made general recommendations for the clinical research enterprise at large. Dr. Califf began his talk by noting the complexity of clinical trials, but he pointed out that this complexity is to be expected given that a clinical trial is a transaction between the health care provider and the patient. "This by nature is a complicated and complex interaction, in which the investigator side of that equation has very split loyalties and obligations in terms of the requirement to function under a certain set of rules of the trial, and in trials that deal with sick people, also having a major obligation to put the welfare of the subject first," he said. "This leads to an underestimation of the number of transactions that have to occur and overly ambitious expectations of how well this can occur. . . . We would

be better off if we had more realistic expectations of what a clinical trial can accomplish in the first place."

In general, there are three models for clinical trials: the NIH model, the hybrid model, and the industry model. Dr. Califf noted that industry trials are regarded as being more efficient than publicly funded trials, while NIH trials are regarded as keeping the patients' best interests as the top priority. He suggested that the primary task is to develop a functioning hybrid model, and that lessons can be learned from both the NIH and the industry models. Dr. Califf concluded that there should be a balance of power, because clinical trials involve a set of human interactions in which there is no single right answer in regards to how best to run or oversee a trial. He also emphasized that there is a complex tradeoff between efficiency and ethics. "The degree to which you are willing to tolerate imperfection is a key decision that needs to be made," he said.

Dr. Califf noted that the coordinating centers for clinical research can be academic medical centers, which tend to be inefficient and have limited operational capabilities, or contract research organizations (CROs). The CROs essentially work as extensions of their sponsors, which typically are pharmaceutical companies (Shuchman, 2007). Nonprofit corporations or academic research organizations can also coordinate clinical research studies, and they aim to combine the efficiency of the CRO with an academic or "public good" mission. He pointed out that while academic centers do not do clinical trials to generate additional income, there are other benefits of doing such research, including enabling delivery of innovative therapies to patients, aiding in determining the best medical practices, and providing extra care to patients without additional cost. More fundamentally, however, academic research centers conduct clinical research because research itself is a core mission of the institution, Dr. Califf said.

Decision making in a clinical trial is a complex process, Dr. Califf pointed out, and although it is done by consensus within executive committees, ultimately the sponsor "holds the trump card over withdrawing the funding." Industry sponsors also hold the trump card when it comes to publication of the study's findings, he added. "Our most prestigious academic centers, when they sign up to be a site in an industry clinical trial," he said, "do not require that the results of the trial be published, routinely sign agreements to keep the plans for human experiment secret, and do not require a trial architecture that insures protection from suppression of negative results" (Davidoff et al., 2001; Schulman et al., 2002). What academic centers do require, he said, is the right to publish the data on their own patients in a trial. But if there are 100 centers participating in the trial, "it is statistical malpractice to publish the data from your own patients about the primary result," Dr. Califf said.

"Why don't we put our foot down?" he asked. "The answer is because

if I say no, the industry sponsor will just go to the next academic center that says yes. None of our physicians want to lose access to the cutting-edge drugs that industry has to offer." As an example within his own field of cardiology, Dr. Califf pointed to a study that found that conflicts of interest went unreported in more than 80 percent of clinical trial results examined (Weinfurt et al., 2008). "We have real problems in terms of the architecture of trials and the results of contracts that we sign," Dr. Califf stressed. One of these major problems is that many clinical trial results are not reported, especially if they are negative results. The registering of all clinical trials on ClinicalTrials.gov and the World Health Organization's registry is helping in this regard, Dr. Califf noted.[11] He added that academic bureaucracy can also impede the reporting of clinical trial results.

He then went on to discuss the costs of clinical trials and how to reduce them. Dr. Califf noted a recent conference and subsequent publication on sensible clinical trial guidelines and recommendations to reduce bureaucracy in clinical trials (*Sensible guidelines for the conduct of clinical trials*, 2007; Eisenstein et al., 2008). At that meeting, which was attended by industry, government, and academic representatives, it was stressed that industry and others spent billions of dollars on clinical trial research (Moses et al., 2005). This suggests that there are probably sufficient funds for clinical research and that the problem is that those funds are being spent inefficiently. When the attendees calculated the costs of doing a specific clinical trial protocol by various methods of organization, they found massively different cost estimates for the same trial generating the same results that would pass FDA scrutiny (Figure 2).

Dr. Califf reported on recent efforts by his own university to reduce the costs of its clinical trial operations. Duke University set up a task force that recently evaluated its clinical research to assess how to make it more efficient. As is true with all academic medical centers, the task force found that Duke's clinical research was historically more of a "mom and pop" undertaking, according to Dr. Califf. "Each investigator was on his or her own, trying to make it without much organization or infrastructure support," Dr. Califf said. He described the core principles of the task force: first, a reaffirmation that clinical research is an important function of an academic medical center, and second, that efficiency in clinical trials is important. The task force identified a number of ways to make clinical research more efficient. One option was, for instance, to remove the responsibility for such research from individual clinical departments and place it within groups of clinical research investigators in a particular therapeutic area to form site-based research units that would be supported by a clinical research support office.

[11]See http://www.clinicaltrials.gov and http://www.who.int/ictrp/en.

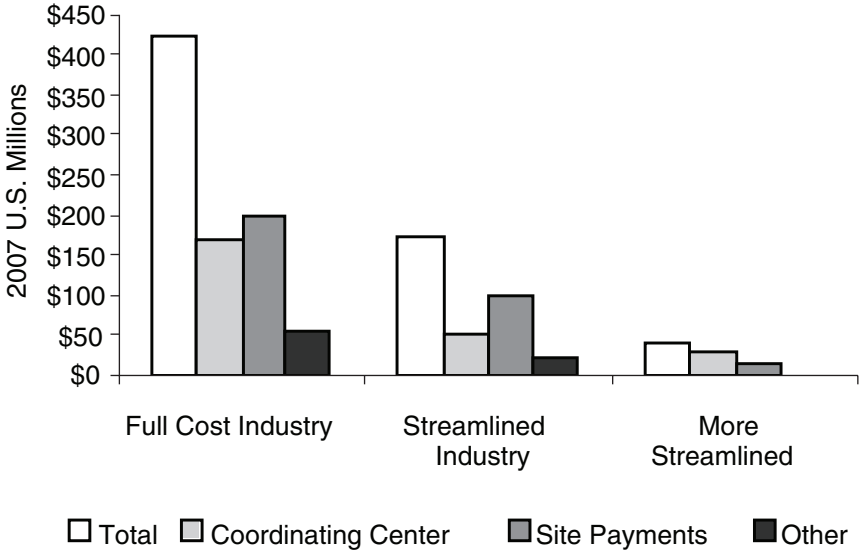

FIGURE 2 Patient trial costs. At the Sensible Guidelines for the Conduct of Clinical Trials Conference, representatives from academia, industry, and government agencies convened to discuss approaches to reduce bureaucracy in clinical trial design and conduct. Attendees reached massively different cost estimates for a specific clinical trial protocol that would generate the same results and still pass FDA scrutiny.
SOURCE: Califf presentation (July 1, 2008) and Eisenstein, E. L., R. Collins, B. S. Cracknell, O. Podesta, E. D. Reid, P. Sandercock, Y. Shakhov, M. L. Terrin, M. A. Sellers, R. M. Califf, C. B. Granger, R. Diaz. 2008. Sensible approaches for reducing clinical trial costs. *Clinical Trials* 5(1):75–84, copyright © The Society for Clinical Trials. Reprinted by permission of SAGE.

The research units function like small businesses embedded within the medical center, Dr. Califf said. Their responsibilities include acquiring economic approval for each planned and ongoing study, scientifically reviewing such studies, providing human resources for all non-faculty research staff as well as for orientation and oversight, and conducting the trial. The research units are led by a faculty member, the lead clinical research associate, and an administrator. The support office for these research units provides what Dr. Califf called the "rules and tools," including information technologies and an understanding of the reimbursement rules that enables the office to effectively manage Medicare billing. Operational oversight is done jointly by the medical school and the university health system.

Dr. Califf concluded his talk by providing lessons and suggestions for improving the clinical research enterprise. In addition to publicly reporting start-up metrics, he suggested applying business practices to the organization of clinical trial operations. Such practices include structural alignment, financial accountability, and appropriate rewards for site-based investigators. He also recommended developing more effective mechanisms for public–private partnerships that do not have conflicts of interest or compromise the academic mission.

Other mid-term recommendations were to do "research on research" in order to develop evidence to support improved federal and global guidelines and to build capacity through reengineering the clinical enterprise. Efforts in this regard have been started by the Clinical Trials Transformation Initiative.[12] A more long-term goal is to develop a national learning system that would continuously record clinical practice data in electronic health records and disease registries. With such data, randomized controlled trials could be conducted by inserting randomization into the data already being collected, Dr. Califf noted. For example, the Society of Thoracic Surgeons has a national database that keeps the records of about 80 percent of the patients who have cardiothoracic surgery in North America.[13] Clinical trials can be run using this registry data without collecting much additional data, Dr. Califf said.

INDUSTRY-SPONSORED MULTI-CENTER CLINICAL TRIALS

Next, Dr. Renzo Canetta of Bristol–Myers Squibb gave the industry perspective on industry-sponsored multi-center clinical trials, which, as he noted, have increasingly become multinational clinical trials. A survey of FDA-registered investigators reveals that although slightly more than half are from the United States, an increasing number are from European countries, Russia, India, and Argentina (Parexel International Corporation, 2008). Even more telling is the patient accrual to Bristol–Myers Squibb oncology pivotal trials between 1992 and 2007, which revealed a striking decline of accrual in the United States and an increase in accrual in other countries throughout the world (Table 1). Dr. Canetta noted that of the 10 oncology drugs Bristol–Myers Squibb introduced into the United States over the past 25 years, 5 were also approved for sale in other countries. The globalization of trials has been driven by the increasing international commercial interests of many pharmaceutical companies, he said, and by the difficulties that face patients and investigators who wish to participate in clinical trials in the United States.

[12]See http://www.trialstransformation.org.

[13]See http://www.sts.org/sections/stsnationaldatabase.

TABLE 1 Accrual to Bristol–Myers Squibb Oncology Pivotal Trials

	% Pre-2000	% Post-2000
United States	70.8	40.5
Western Europe	18.6	26.8
Canada	5.8	9.5
Eastern Europe	2.9	4.7
Japan	1.6	1.3
Latin America	<1.0	6.4
Asia/Pacific	<1.0	5.8
Oceania	<1.0	4.0
Africa	<1.0	0.5

NOTE: Includes >20 trials, >20,000 patients.
SOURCE: Canetta presentation (July 1, 2008).

Dr. Califf pointed out during his presentation that the cost for each person in a clinical trial is three to four times as much in the United States as it is in India or China (Lustgarten, 2005). This greater cost is due, in part, to the added layers of bureaucracy linked to conducting clinical trials in the United States, and it is leading to an increase in overseas trials, he said. He also expressed concern about the "massive shift in clinical trial participation that is currently occurring away from the United States," (Agres, 2005; Getz, 2005) and added, "What is particularly disturbing about recent trends is that when you look at the dropout of clinical investigators in the United States compared to the dropout of the rest of the world, we are losing our most experienced clinical investigators. Very experienced clinical trialists are beginning to say 'It is just not worth it any more—I am losing money, I am at risk of being vilified in my local newspaper for experimenting on people, and the regulatory risk is just too high.'" Later during the conference, Dr. Califf underlined this point by saying, "In the last six global clinical trials that we have been approached to coordinate by industry, the only major question industry [asked] us was how few patients do we have to put in the United States to be credible with the FDA. In other words, there is a mandate to not enroll patients in the United States because of the dynamics."

The globalization of clinical trials has had several consequences, including the need to fulfill numerous different local regulations in study activation, monitoring, and adverse event reporting, which results in the generation of extensive final clinical study reports that can be 1,000 pages long. Essentially, there is global auditing of the data generated. "Our data are the most scrutinized, regulated, audited, and [corrected] that you

might dream of," Dr. Canetta said. "We have been audited by the FDA, European health authorities, and the Japanese Ministry of Health." There are complexities involved in integrating multiple study databases from several different countries, he added, and occasionally study materials and tools, such as patient-reported outcomes instruments, must be translated into different languages.

Dr. Canetta then gave a breakdown of the costs involved in running a multi-center industry-sponsored clinical trial. As others have noted, about 40 percent of the money and time spent on these trials is involved with the start-up phase of the trial. Start-up activities include negotiations with investigators and institutions, internal review by the sponsor, fulfillment of local regulations, IRB approval, and special protocol assessment. There can also be 34 or more internal reviews within Bristol–Myers Squibb, Dr. Canetta said. On average, across all therapeutic areas, it takes his company eight months from the time that a protocol is conceived to the time that the first patient is treated in the trial. The company currently hopes to achieve five-month review times that might be accomplished by aligning review cycles so some are run in parallel rather than sequentially.

Once a protocol is approved, there are numerous costs to industry involved in running a multi-center clinical trial, Dr. Canetta said, including funding for the personnel and infrastructure needed to run the trial; the fees of adjudication committees, IRBs, and data management centers; travel and meeting costs; and the costs of additional tests and procedures that are not reimbursed by insurers. The independent, blinded radiologic or other data review done by adjudication committees is becoming common for trials with non-survival endpoints, Dr. Canetta said. This involves procuring the data or images—not all of which are digital—from other hospitals and then shipping them and storing them at a central location. "We are talking about patients that are on treatment for longer amounts of time. They basically have a life, and their life brings them to other places so procuring their X-rays and computed tomography (CT) scans costs money," Dr. Canetta said.

Other major costs for industry are those linked to producing and providing the drug tested and the placebo or other comparators. Dr. Canetta noted that industry will provide an experimental drug to patients who take part in a study for as long as they wish to remain on the therapy, even after the conclusion of the study. Although this was not a major cost during the previous era of cytotoxic chemotherapy, it certainly is a significant cost in today's era of chronic prolonged treatment, Dr. Canetta said. "What that means is that now we are still dosing free of charge patients who started receiving a drug in the Phase I trial started in November of 2003," he said. The relabeling of a comparator, as is required by certain countries, or the masking of a placebo can also be costly, he added.

Another type of increasing cost is that involved in sample processing and sample shipment, which in the current era of genomics and population pharmacokinetics is done on a global scale. There also is the cost of maintaining records for a number of years after the conclusion of the study or after the submission of the registration dossier. "This time changes from country to country," Dr. Canetta noted. "It is not 5 years only because FDA says so. It is more because there are other countries that want more."

A final clinical trial cost Dr. Canetta mentioned is the cost of advertising for proactive recruiting of patients to trials. "We have been able to improve accrual to some of our trials by having advertisement campaigns about the existence of a particular trial in a particular geographical area," he said. "That is something that in the past did not exist."

All these costs add up to a stunningly large figure of over $1 billion spent by industry on research and development for each new drug (new molecular entity) approved in the United States (DiMasi and Grabowski, 2007), Dr. Canetta said. He added that the costs linked to failed experimental drugs account for three-quarters of the cumulative drug development costs (DiMasi et al., 2003; Parexel International Corporation, 2008). These costs rise as an experimental drug passes through the various phases of clinical testing.

Dr. Canetta concluded his talk by pointing out the irony of the public outcry for independent research that ignores the reality that industry-sponsored trials are the most regulated, intensively monitored, and scrutinized experiments in biomedical research. He noted that it is in industry's interest to continue to collaborate with capable investigators and organizations, wherever they are. The increasing globalization of the industry makes multinational collaborations attractive, he added, pointing out that the increasing need to identify and treat patients with specific genomic characteristics makes it necessary to access patients across a wider geographic area.

Dr. Canetta suggested mixed partnerships with cooperative groups whereby the cooperative group uses its own members and industry provides additional international investigators that industry takes the responsibility to monitor. "This has worked out very well in terms of the timeliness and the accrual. I think it is time that the NCI cooperative groups started thinking in these terms as well, because it is a reality," Dr. Canetta said. Dr. Schilsky added during the discussion that his cooperative group is currently involved in such a mixed international partnership with Novartis for the testing of a leukemia drug within select genetic populations. "CALGB is the IND holder for the United States and essentially all of North America," he said. "Novartis is the IND holder for the rest of the world. They have organized the extra U.S. sites and we

have organized the North American sites. The protocol is activated and is working."

In the discussion following Dr. Canetta's presentation, Dr. Califf postulated that industry databases are "too clean and that a huge amount of money is spent on irrelevant study and that the NIH databases do just as well at getting the right answer." Dr. Canetta responded by acknowledging that industry probably does collect too much data, but he added that much of the data industry collects in excess of what would be collected by a cooperative group is used to satisfy the diverse regulatory demands of the various countries in which industry's trials are run.

In the same discussion Dr. Comis noted that cooperative group studies are often used for supplemental New Drug Applications (sNDAs) or supplemental Biologic License Applications. "So in the United States at least, there is this symbiosis between what companies do and what the publicly funded system does," he said. "It really benefits the whole nation and all cancer patients, so what would happen if our side went away?" Dr. Canetta responded that without cooperative group partnerships, the costs of industry doing investigations would increase and this would probably end up reducing the number of sNDAs that would be submitted. "But I think what will go away is probably more diffuse rapid access to experimental agents and getting physician investigators familiar with novel treatments," Dr. Canetta said. "That will be really detrimental to the public interest." Dr. Schilsky added that there probably would be fewer adjuvant therapy trials, fewer combined modality clinical trials, and fewer comparative effectiveness trials, "and lots of other things that the cooperative groups do that are important to patients," he said.

PRIVATE PHYSICIAN PERSPECTIVE ON MULTI-CENTER CLINICAL TRIALS

The next speaker, Dr. Alan Keller, chairman of clinical research at Cancer Care Associates in Tulsa, Oklahoma, addressed multi-center trials in the community and gave the perspective of a network of private physicians who participate in clinical trials. Dr. Keller began his talk by giving a number of reasons for private physician networks to participate in clinical research, including being able to provide the best care for their patients by accessing cutting-edge drugs, playing a proactive role in drug development, and getting good exposure for the group, which helps in patient and physician retention and local marketing. He added, however, "If anybody is in this to make money, they are in the wrong business, even on the private side." Typically Phase I or investigator-initiated trials do not generate income for private groups. There is some potential for that

in large Phase III registration trials, Dr. Keller said, but these larger trials are also more labor intensive.

Part of the reason it is difficult to generate income from clinical trials is that the fixed costs for the infrastructure needed to develop and oversee the trial are high, but the capital investment is low. Patient accrual also is unpredictable and often unbalanced from study to study, and this affects the financial feasibility of running trials. Although some had hoped that enhanced information technology making clinical trial information accessible via the Internet would improve patient accrual, Dr. Keller said this has not been the case in his experience. He noted that the fixed costs involved with the development and regulatory and quality-assurance oversight of a clinical trial make up one-quarter of the costs of running a trial. Practice costs, study operations, and management account for about half the cost, and the remaining quarter is spent on direct research expenses and physician compensation, which in Dr. Keller's group was $100 per patient. Most of the funding for privately run clinical trial networks is from drug sponsors, although Dr. Keller noted that increasing numbers of participating investigators are members of CCOPs, which are funded by the NCI Division of Cancer Prevention through a competitive peer-review grant program.

Dr. Keller noted that the basic infrastructure of private multi-center clinical trials is essentially the same as that of the cooperative groups (Box 4). Quality assurance of the trials is managed through frequent

BOX 4
Multi-Center Trials: Private Group or Network

Infrastructure
- Leadership group
- Committees
  - Monthly teleconferences
  - Meetings with industry
- Administrative staff
  - Protocol writing
  - Central data management (investor initiated)
  - Data and Safety Monitoring Board
  - Finance/budget
  - Statistical support
- Office space

SOURCE: Keller presentation (July 1, 2008).

audits by the drug industry or CROs. As is the case with cooperative groups, private research groups are subjected to numerous IRB reviews and a great deal of regulatory paperwork, he said.

Dr. Keller then went on to describe what works and what does not work for private multi-center trials. On the list of what works he included pre-study involvement that allows investigators to participate in the study design and also initiation meetings, as long as they are done by teleconference or some other long-distance means so that investigators do not have to travel and lose a day of work to attend them.

Dr. Keller was a strong advocate for central IRBs, although his group does not use the NCI central IRB. His group uses a private, commercial central IRB that meets frequently. "They help us from an economic standpoint in that in my practice we are in at least 17 different sites of service, so I do not have to do 17 different local IRBs," Dr. Keller said.

As for what does not work, Dr. Keller pointed to the excessive paperwork required by the FDA. "If we can cross-file drug INDs, why not cross-file investigators? How many 1572s[14] and curriculum vitae does the FDA really need?" he asked, noting that when his group joins a trial with the pharmaceutical industry, it has to ship about four boxes of forms, many of which had been filled out for previous studies. To alleviate this excessive paperwork, Dr. Keller suggested setting up a national Web-based database for investigators that would contain all of an investigator's relevant FDA forms and that could be accessed with a personal identification number. E-mail reminders could be sent every two years requesting online updating, and trials could be open only to eligible investigators who have up-to-date registrations in the system.

Dr. Keller also suggested retooling financial disclosure requirements. Although he recognizes that such disclosure is important, it often is not relevant, as in the case of double-blind studies or studies in which an individual investigator does not manage the study data or contributes a small percentage of the cases and cannot block publication of negative data. He recommended requiring financial disclosure only for physicians who author the study report and contribute more than 10 percent of the patients in non-blinded studies or who own 5 percent or more of company stock. Financial disclosure should also be required of those who are on the data and safety monitoring board of a study. "I do not think you need a financial disclosure in every instance," Dr. Keller said. "It is just another piece of paper that goes in the box and gets sent in."

Dr. Keller was also critical of extensive auditing procedures. "You

[14]The 1572 is a federal form and is the statement of the investigator that he will abide by the federal guidelines set forth in the Code of Federal Regulations for the use of drugs in an investigational setting. It is available at http://www.fda.gov.

are in trouble when the number of appointments you have with auditors exceeds those that you have with your patients," he said. In addition, he pointed to shortcomings in the reporting of SAEs. "I must spend maybe an hour a day as the [principal investigator] signing SAEs that come from Poland or somewhere else," he said. These piecemeal reports do not put the SAEs within a meaningful context, Dr. Keller said. For example, the reports do not indicate on a global or a national multi-center scale how frequently the SAE is occurring within the trial. He was also critical of the frequently required follow-up burden of some clinical trials that requires the costly storage of records for long periods of time.

Sites with insufficient accruals and low or non-accruing physicians also are problematic, Dr. Keller said. He presented an analysis of a group of about 800 physicians that found that about 60 percent of the physicians accrue less than one patient per year per study and about half of all research sites also have low accrual rates. Not only are low-accruing sites and physicians an economic drain on the system, Dr. Keller pointed out, but they also affect the quality of studies. "Poor accrual equals poor data," he said, and he suggested closing sites that do not accrue enough patients.

At the same time, Dr. Keller noted that as screening of patient volunteers moves from phenotype to genotype, the patient pool is getting smaller and spread out across a larger geographic area. "We need everybody to participate in clinical trials," he said. "If we are looking for a target that is only in 20 percent of the patients and we only get 2 percent of eligible patients into clinical trials, it will take us forever to finish these trials. So we need to open this up across the country and make the system a lot simpler." The increasing availability of more effective cancer drugs for second- and third-line indications for patients who did not respond or are no longer responding to initial treatment also limit patient accruals for experimental drug trials.

Poor Medicare reimbursement for prescription drugs is also limiting patient participation in clinical trials and physician willingness to undertake these trials. As a result, many physician groups, including Dr. Keller's practice, are limiting the number of their new patients on Medicare and are requiring those on Medicare who cannot afford their drug copayment to be treated in the hospital. Dr. Keller's physician group recently decided that, due to this Medicare situation, it would no longer enroll Medicare patients in NCI-supported clinical trials. "We have cost-shifted for the very last time—I do not think there is anything left to shift," Dr. Keller said. "We are under water, and the research was the first thing to fall here."

In the discussion after Dr. Keller's presentation, Dr. Ronald Herberman, director of the University of Pittsburgh Cancer Institute, noted that his

patients who are on Medicare fee-for-service plans do not have a burdensome amount of medical bills. But in his area there are a number of patients who rely on Medicare HMO Advantage programs. "This has become virtually an absolute negative for any such patient to be able to afford to go into a clinical trial," he said (Lin et al., 2008). "I believe that this is something that needs to be vigorously addressed at the national level," he added.

Another participant raised the question of how to deal with the inertia of private practitioners who are accruing a patient or less a year, given that "there is no carrot or stick to offer them." Dr. Keller responded that they tackle this at the site level by explaining to investigators there that it is not financially feasible to keep the site open and then they close the site. In a later presentation, Dr. Laurence Baker, professor of internal medicine at the University of Michigan Medical School and chairman of SWOG, reiterated this approach, noting that this group's policy is that a member in good standing with the cooperative groups must accrue 50 patients a year from its institution, not including patients accrued from affiliates under its supervision. "We also made it clear to our leaders, including committee chairs, that leadership in the group meant that there was accrual from your institution," he said. "We spend a lot of time talking about reducing the number of institutions and how we should police ourselves and reduce institutions that insufficiently participate."

Session 2: Barriers to Patient Recruitment and Physician Participation

Following Dr. Keller's presentation, there was a great deal of discussion concerning how to boost patient accrual and achieve greater physician participation in clinical research. Dr. Keller said, "In my experience, people either like doing clinical investigations or they hate it and will not do it. I'm not sure you can change that." Dr. David Johnson, professor of medical and surgical oncology, director of the Division of Hematology/Oncology, and deputy director of the Vanderbilt-Ingram Cancer Center, suggested that more money should be spent on the doctors who are doing most of the accruing—the 20 percent who accrue 80 percent of the patient population. "Then," he said, "patients will seek these individuals out, and it might also change the behavior of those physicians who find it burdensome to participate in the clinical trials process." Dr. Keller agreed with this approach, as did Dr. Gwendolyn Fyfe, senior staff scientist in clinical hematology/oncology at Genentech. "It makes a lot of sense to pay sites that recruit a lot of patients more so that they can have excellent infrastructure," she said. "It also makes sense to take community sites and make it easier for them by collecting less data. Do we really need to know where grade one toxicities happen at every site? Why not collect [just] deaths and SAEs at community sites and make it easy for them to participate in a trial?" Dr. Keller agreed and added, "There are virtually no incentives in this country for any doctor to enroll a patient on a clinical trial, and there are huge disincentives. Every portion of the clinical trials program has to look at how they can eliminate the disincentives that they contribute to the process."

Dr. Ruckdeschel countered that both his research on accrual to patient trials at the physician level and also data from Dr. Comis suggest that the high degree of variability in patient accrual is caused by individual investigator behavior (Albrecht et al., 2008; Comis et al., 2003; Lara et al., 2001). "It is the physicians and not the complexity of the IRB," he said, "so if we are going to give people in institutions more, we need to get down to the physician level, because it really is individual physician behaviors that guide this, and much less the nuisance work that is part of that." In response, Dr. Keller said, "In my practice it falls to just a couple of individuals to interact with the IRB and do all that regulatory stuff. Therefore, it is a big deal." Another participant suggested that the difference between clinicians and clinical researchers should be clearly defined and that academic rewards or a cost structure that supports and encourages clinical research should be built into the system.

Dr. Califf ended the discussion on an ominous note by adding that clinical research is now being subsumed by an economic measurement system that constrains the "impassioned doctor." "He gets outvoted by his own practice partners because he is hurting the financial status of the practice," he said. "You probably cannot fix this incrementally but rather need to do radical surgery, which is very risky. But the sense I am getting is that things are moving very fast in the wrong direction."

Continuing in the same vein as the previous discussion, the second session was devoted to understanding barriers to patient recruitment and to physician participation in clinical trials. Accrual of sufficient numbers of patients into clinical trials is a major barrier to the timely completion of clinical research. Accrual is affected by both patient and provider attitudes about participation in clinical research. Several surveys have found that the single most important factor affecting accrual is whether a provider offers a clinical trial to the patient (Albrecht et al., 2008; Cox and McGarry, 2003). But many issues can affect patients' decision making, including the informed consent process, unwillingness to receive a placebo treatment, and perception of personal benefit (Llewellyn-Thomas et al., 1991; Wright et al., 2004). Health care providers have to consider the time and resources that must be devoted to clinical trial participation and the liability of participation in the current regulatory climate. In addition, the recent acceleration in the development of new cancer treatments and medical technologies demands more clinical trials, compounding the challenges that limit physician participation and patient recruitment. Beyond patient and provider attitudes, accrual is affected by strict eligibility criteria (George, 1996), and there is controversy on what criteria are necessary to obtain results applicable to the general population.

Academic clinical researchers face additional challenges when making decisions about participation in cooperative group clinical trials. These tri-

als take a significant time commitment, but cooperative group trials are collaborative by nature, making it difficult for faculty whose primary research activity is participation in these clinical trials to succeed in the traditional academic system that rewards independent work. Deans in academic medical colleges must look after a host of career development issues for their academic research faculty, including teaching competencies, committee service, research effectiveness, the ability to obtain research funding, and the tenure process (Hait, 2006).

Dr. Mendelsohn opened the session by outlining his perception of the barriers to patient and physician participation in clinical trials. He cited issues in patient recruitment, including concerns about experimentation and randomization versus access to what is seen as the best treatment and also a failure to effectively communicate with patients about the trials. He also cited overly stringent eligibility requirements, which exclude many potential participants. As for the issue of what is preventing physician participation in clinical trials, Dr. Mendelsohn agreed with previous speakers' assessments that there is inadequate payment and frustration with excessive paperwork. He suggested that ethical concerns that place a current patient's welfare before the need to gather knowledge for future patients and inadequate real-time prompting on protocols appropriate for patients both play a role as well. Finally, he stressed that another barrier to physician participation is a lack of recognition for their efforts, which impedes career advancement. "Publications of collaborative clinical trials have lots of middle authors[15] who do not get much credit when promotion and tenure are being discussed," he said.

ACADEMIC CHALLENGES

The session began with a panel discussion about academic challenges to the effective conduct of clinical trials. The panelists included Dr. Laurence Baker of SWOG, Dr. Gordon Bernard from Vanderbilt University, Dr. Michael Caligiuri of Ohio State University, and Dr. Alan Lichter of the American Society of Clinical Oncology (ASCO). Prior to the discussion, each panelist opened with a 10-minute overview of his perspective on the challenges. The first panelist, Laurence Baker, professor of internal medicine at the University of Michigan Medical School and chairman of SWOG, began by saying that the single most important barrier to a

[15]There is a great deal of variability in the contributions made by authors of scientific publications. While the roles of the first and last authors are relatively standardized, the contributions made by the so-called middle authors can range from virtually nothing to equivalent to the first author's. This ambiguity causes problems for tenure and promotions committees.

more successful cooperative group program was a lack of harmonization among cooperative groups, medical and cancer centers, and SPOREs. Instead of cooperation there is competition fueled by limited financial resources and a lack of the sort of communication that would foster more efficient alignment. "We say we are interested in cooperating, but we do not quite live up to that," Dr. Baker said. "I do not think the system needs to be blown up. It does need to be reengineered pretty quickly, though."

Most major medical and cancer centers strive to be top-tier research organizations, he noted, but they recognize that grant support is insufficient to run a research enterprise and that they have to rely also on philanthropy and patient care to underwrite their research costs. "Our cancer centers have become addicted to the revenue of clinical activities," Dr. Baker said. "Clinical investigators are encouraged to increase patient care activities through increased utilization of chemotherapy, laboratory, imaging, radiation, and surgical services, so that revenue can be obtained, sustained, and grow in this research enterprise."

With this fiscal tightening has come a lessening of support for cooperative group trials and, subsequently, insufficient patient accruals, Dr. Baker said. He gave an example of one medical center that joined SWOG in 1990 but resigned in 2003 because its executives claimed they could not afford to do cooperative group trials that only reimbursed $2,000 per patient. Another center has had four different principal investigators in the four years it has been part of SWOG. The previous principal investigators said they resigned because the center director could not provide sufficient support for their research activities. The center has not reached the minimum number of patient accruals—50 patients—that SWOG set for their clinical trials. Another medical center, Dr. Baker said, had established priority criteria for the center that placed cooperative group trials fifth on the list and behind contract trials funded by pharmaceutical companies, even if the cooperative group trial was authored by one of its own faculty. This is in contrast to the experience of another cancer center and SWOG member, which had a center director and faculty committed to research. This cancer center substantially improved its low patient accrual rate after recognizing its problems and committing itself to rectifying them.

The conclusion that can be drawn from these examples is that "money is necessary, but it is not sufficient," Dr. Baker said. "We need to have cancer and medical center leadership that is committed to research." He added that the goals for cancer centers, cooperative groups, and SPOREs need to be aligned regarding therapeutic clinical trials.

One way to improve the system and the goals alignment would be to increase the NCI's $2,000 cap on per-patient reimbursements, Dr. Baker suggested. He also recommended providing salary support to investigators who design and conduct studies so as to permit a reduction of the

time they spend in the clinic. In addition, he suggested providing career development awards for new and mid-level faculty members doing outstanding clinical research.

Unlike Dr. Mendelsohn, Dr. Baker did not think a lack of recognition of the participation in clinical trials stifles career promotion. Instead, he said, the problem is department chairs or center directors who want their clinicians to earn more clinical revenue. "We need to better recognize the downstream revenue created by these clinical investigations," he said.

Later in his talk, Dr. Michael Caligiuri, director and chief executive officer of the Ohio State University Comprehensive Cancer Center, concurred. "The bottom line is that cancer does make money," he said. "It is clear that the oncology product can be profitable and that you need a certain armamentarium to attract patients at an academic medical center." That armamentarium includes clinical trials, he pointed out, so efforts in this regard should be appreciated by department chairs who are making salary and tenure decisions. "We have developed a transparent culture between what I will call the suits in our hospital doing the administration and the physicians who are doing the research. We've tried to embrace a culture where our administrators understand that protocol-driven research brings the kinds of patients we want into our cancer center. That has created a whole new perspective for our administrators in dealing with salaries, bonuses, etc., for clinical investigators."

Dr. Schilsky added that the U10 grant[16] recognizes the clinical leader of a cooperative group, because that individual is listed as the principal investigator on an NCI-funded grant. "It gives that person credibility, respect, authority, infrastructure, and an ability to leverage local institutional funds," he said. He added, however, "That whole part of the process has just been progressively eroded, and I think it is putting the stability of our major institutions in jeopardy." Dr. Baker pointed out that department chairs should recognize clinicians who receive a fraction of their salaries from federal funds that support their clinical research, just as bench scientists who receive federal grants for their research are recognized.

Dr. Baker gave several suggestions for improving patient accrual to clinical trials, including eliminating unnecessary exclusions. An example of an unnecessary exclusion is when the patient has had prior treatment regimens; this was necessary in the cytotoxic chemotherapy era, when there was justifiable concern about the effect of several successive treat-

[16]The U10 grant is the NIH Cooperative Clinical Research award mechanism. Under this cooperative agreement mechanism, the principal investigator retains the primary responsibility and dominant role for planning, directing, and executing the proposed project, with NIH staff being substantially involved as a partner with the principal investigator.

ment regimes on the bone marrow of the patient, Dr. Baker said, but this exclusion is no longer relevant today. Another exclusion that is no longer relevant is having had a prior cancer. "I am one of 11 million cancer survivors, but we know that hundreds of thousands of us will develop a second cancer," he said. "Don't we deserve to be included in studies of potentially important new agents?" During the discussion, Dr. Johnson described additional barriers to patient accrual, including consent forms that require patients to pay for their clinical care if their insurance does not provide adequate reimbursement and also patients' concerns about having to pay for their own medical care if the experimental treatment causes any injuries.

Dr. Baker also questioned the wisdom and ethics of placebo-controlled trials for metastatic cancer. Although placebo-controlled studies are considered a scientific way to prove the value of a new treatment, this design is always the lowest hurdle a pharmaceutical company must achieve for regulatory approval. "Certainly it makes no sense to have sham IVs and [pharmacokinetic] studies and multiple venipuctures," he said. "That is what makes our patients upset. We would be better off recognizing that cancer clinical trials should primarily serve the needs of patients, not those of society."

Dr. Baker concluded his talk by saying, "We should recognize the strength of the U10 mechanism and consider expansion of it. Our U10 sites are the most important sites of our group for science, accrual, and leadership." He noted that of SWOG's current 48 studies, 44 have been authored by a member faculty from a U10 institution, and the average accrual from these institutions is more than 70 patients a year. Later in the discussion, Dr. Schilsky agreed: "When we look at the statistics on our U10 holders, all of whom are at major academic medical centers like SWOG, they account for essentially all of our committee leaders, and the majority of our protocol chairs and committee members, as well as provide a substantial fraction of our patient accruals."

The second panelist, Dr. Gordon Bernard, professor in the Department of Medicine and assistant vice chancellor for research at the Vanderbilt University Medical Center, discussed some challenges faced in academic medical centers regarding physician participation and patient recruitment. He highlighted many of the topics that had already been discussed: the need for standardized definitions and metrics for evaluation across institutions, protocol design and Medicare reimbursement issues, the need to reduce the number of non-value-added steps, the need to make it easier to conduct steps in parallel, and the fact that too many trials harm an institution's ability to conduct efficient clinical research.

Dr. Bernard suggested that "The consent forms that come out of the NCI IRB are lengthy, complicated, wordy documents that are difficult

for my committees to swallow." Dr. Stephen Grubbs, medical oncologist at the Helen F. Graham Cancer Center and principal investigator of the Delaware Christiana Care CCOP, agreed with this point during his presentation. "My average consent form is now 30 to 35 pages long," he said. "Anybody who thinks that my patients are reading 35 pages of a consent form is out of their mind. I go through those consent forms in summary, page by page with the patients. But I do not believe that they ever go home and read the whole thing."

Dr. Bernard suggested standardizing consent and contract language and having a "short form" approach to consent forms. He noted that the Association of American Medical Colleges has a working group currently trying to develop a short form that can be layered on top of a long, complicated consent form. The short form states in a few words what is going to happen to the patient, with links to the rest of the document for those who want more detail. He also suggested expedited study approval and review of consent language at secondary sites once an accredited IRB has given approval. "You would not need a full committee to review it—just the chair could look at it," Dr. Bernard said.

Finally, Dr. Bernard discussed his viewpoint on the challenges facing academic medical centers with respect to physician participation and patient recruitment in cooperative group clinical trials. He has had clinical investigators ask him to direct institutional funding to make up the deficit for the cooperative group trials, but it was not possible to justify that these trials should be given priority over other clinical research. Their clinical trials office, like others, rely on revenues generated for its survival, but it always operates on a deficit. Dr. Bernard also discussed academic rewards, and started by explaining that Vanderbilt has two categories of faculty: physician scientists, whose primary income is to come from academic grants, and clinician educators, whose primary income is to come from seeing patients. While clinician educators do the patient recruitment, there is not a sufficient incentive for them to recruit because their evaluations do not depend on it. Dr. Bernard recommended more effort in addressing these issues, and he added that Vanderbilt is trying to find ways to allow young investigators to succeed.

INSURANCE BARRIERS

The third panelist, Dr. Michael Caligiuri, director and chief executive officer of the Ohio State University Comprehensive Cancer Center, said that his experience as a director of a comprehensive clinical cancer center led him to believe that lack of insurance reimbursement is an impediment to patient accruals (Lara et al., 2001; Mattel et al., 2004), estimating that such a lack of insurance prevented about one-quarter to one-third of the

patients at Ohio State University's Comprehensive Cancer Center from participating in clinical trials. Dr. Caligiuri explained that commercial health insurers often refuse to pay for routine care costs associated with a clinical trial, even though those same costs would be reimbursed if the patient were not receiving experimental treatment. These costs are substantial and include physician visits, blood work, and X-rays.

A lack of such reimbursements affects many patients, Dr. Caligiuri said, because they reside in states where there are no laws that require commercial health insurers to pay. Even the 23 states that currently have clinical trial coverage laws do not necessarily require insurers to cover all cancer patients, such as patients on Phase I or II trials or those with employer self-insured plans,[17] in which a large company self-insures its employees (NCSL, 2008). "So without a federal policy, cancer patients cannot be guaranteed that if they enroll in a potentially life-saving clinical trial there will be someone there to pay for the process," Dr. Caligiuri said. "This is a huge impediment for most patients giving any further consideration of an experimental agent." After a lobbying effort by Dr. Caligiuri and his colleagues, the Ohio legislature passed a bill, ultimately signed into law by Governor Ted Strickland, obligating health plans to pay for routine costs of care when a cancer patient enrolls in a clinical trial.[18]

Dr. John Feldmann, medical director at the Moses Cone Regional Cancer Center, noted later in his presentation that many large companies now self-insure their employees. Any self-insured plan that is offered as part of a benefits package is covered under Employee Retirement Insurance Security Act (ERISA) (Butler, 2000; DOL, 2008). This is the federal law that sets forth the minimal standards that must exist in any independent health plan; it currently does not require covering the routine care costs linked to clinical trials. Furthermore, this act has a section that preempts all state laws. "So if you have a self-insured plan, no state law about clinical trial coverage will be applicable," Dr. Feldmann said. This is a major problem, given that in some areas, such as North Carolina, about half of patients now have self-insured plans offered by their employers.

To overcome this impediment, Dr. Caligiuri suggested requiring

[17]A plan offered by employers who directly assume the major cost of health insurance for their employees. Some self-insured plans bear the entire risk. Other self-insured employers insure against large claims by purchasing stop-loss coverage. Some self-insured employers contract with insurance carriers or third-party administrators for claims processing and other administrative services; other self-insured plans are self-administered.

[18]*To amend sections 1739.05 and 1751.01 and to enact section 3923.80 of the Revised Code to prohibit insurers, public employee benefit plans, and multiple employer welfare arrangements from excluding coverage for routine patient care administered as part of a cancer clinical trial,* SB 186, 127th General Assembly of the state of Ohio.

ERISA plans to provide coverage for the routine costs of participating in clinical trials. This was pursued by two members of Congress, Representative Deborah Pryce and Senator Sherrod Brown, and led to the introduction of the Access to Cancer Clinical Trials Act of 2007 (H.R. 2676 and S. 2999).[19]

Dr. Caligiuri noted later in discussion that getting political action in this regard was relatively easy, because there is bipartisan support for ensuring that the routine costs of care linked to participating in clinical trials be reimbursed and because requiring this does not require a financial commitment on the part of the state or the federal government. "You have a paying customer who is not getting what is due," he said, "so it was really easy to get support for it from both Republicans and Democrats." He suggested fostering a grassroots effort by clinical trialists and patients to support the passage of the federal law.

A workshop attendee noted that there are a number of cancer organizations, including ASCO, that have been working with Senators Edward Kennedy and Kay Bailey Hutchison on legislation that addresses coverage of routine care costs linked to cancer clinical trials as well as other cancer care concerns. "Given the congressional interest in some sort of comprehensive cancer omnibus bill, there might be an opportunity there," the participant said. The same discussant also noted that there is debate about whether CMS should codify its Medicare clinical trials coverage policy. Currently there is a national coverage decision to reimburse the routine care costs linked to clinical trials with therapeutic intent, but individual contractors with the Medicare program can opt not to cover this cost. Dr. Leslye Fitterman, epidemiologist in the Office of Clinical Standards and Quality at CMS, agreed that contractors at the local level have the authority to determine what is reasonable and necessary, and she said that this is why there is so much disparity in interpretations of therapeutic intent in terms of understanding what is actually needed and what is considered standard of care. That disparity could be rectified with a federal ruling in this regard.

Dr. Ruckdeschel noted that in Michigan there is only one major health insurer—Blue Cross and Blue Shield—and it has a "Don't ask, don't tell" policy about reimbursing routine costs linked to clinical trials. "We do not see this as an issue," he said, "and when we have discussed this in other forums, a lot of states have said they do not want to stir this up with

[19]Although the legislation was referred to committee, it was not acted on during the 110th Session of Congress. U.S. Congress, House of Representatives, 2007. Access to Cancer Clinical Trials Act of 2007. H.R. 2676. 110th Cong., 1st sess. (June 12, 2007). U.S. Congress, Senate, 2008. Access to Cancer Clinical Trials Act of 2008. S. 2999. 110th Cong., 2nd sess. (May 8, 2008).

a piece of legislation because they have a similar *modus operandi*, where they do not tell the insurance company the patient is on the study, the insurance company does not ask, and things just proceed as if it were a normal bill." But Dr. Feldmann cautioned that the "Don't ask, don't tell" policy carries certain risks: "If you have a supply drug and you bill for the infusion without an associated J-code because the drug has been supplied, the insurance company will detect the fact that the patient is on an experimental trial, and then everyone is at risk because the costs will be enormous at that point."

One participant pointed out that in his area of the northwestern United States, about 12 percent of patients on Phase III trials or Phase II clinical trials with therapeutic intent are denied reimbursement of routine care costs. And Dr. Mendelsohn pointed out that there is even less reimbursement for patients in Phase I trials. "We have lots of patients that turn down a chance for a Phase I trial and take the standard old 5FU [5-fluorouracil] because the insurance company will pay for that," he said. "That is a new phenomenon in the past year." Dr. Bernard noted in his presentation that if protocols for Phase I and Phase II trials are redesigned so that clinical response is the clear primary objective, Medicare might be more likely to pay for the costs linked to patient participation in the trials. "Of course a Phase I study explores a lot of safety issues and the like," he said, "but I do not think you would give it to somebody if you did not think it had a prayer of affecting the tumor size or whatever it is that you are measuring as your surrogate marker of disease."

ACADEMIC RECOGNITION FOR CLINICAL TRIALISTS

The final panelist, Dr. Allen Lichter, executive vice president and chief executive officer of ASCO, addressed the pitfalls of career advancement for the clinical trialist. A former medical school dean and clinical researcher who worked for many years in the Cooperative Group Program, Dr. Lichter has found that working in oncology clinical cooperative groups is frequently not well rewarded with academic recognition and advancement. He said that this is caused by a number of factors, including:

- a lack of awareness by promotions committees of what such research entails;
- the collaborative nature of the research, which makes it difficult to mark individual accomplishments;
- the time factor involved in clinical research; and
- the under-funding of much of this effort.

Clinical research is not well understood by academic promotion committees, Dr. Lichter noted. There is no other specialty that has a clinical research infrastructure similar to oncology, he said. Furthermore, the work is done largely off-site with investigators from other institutions who are largely unknown to the committee, and many committees assume that most clinical trials are performed by industry, so they believe that there is not much academic productivity or thought that goes into it.

Clinical trial research is also undervalued, Dr. Lichter added. "There is very little sense of the intellectual rigor and complexity that goes into trial design and protocol execution," he said. "The assumption is, 'This is Tylenol against aspirin for headaches and can be designed in about 10 minutes and carried out by anybody.'" There also is no sense of the intense time commitment involved nor an appreciation for the critical role these studies play in advancing the field, Dr. Lichter said. "We should probably bring in those 30-foot process maps [prepared by Dr. Dilts][20] and say this person deserves promotion, because they negotiate this every day." In the discussion, Dr. Curran did note, however, that there is some prestige involved in having committee leadership appointments in cooperative groups and that this prestige can result in opportunities or promotions in the investigators' own institutions.

Another problem making it difficult to attain recognition and promotion from such collaborative work is that it is not independent. "We stand up as academic leaders and talk about the importance of team science," Dr. Lichter said, "and then we sit down in promotions committees and ask what has this person done that is independent. I have said to the faculty when I was dean that if Abbott and Costello were trying to get tenured for comedy, we would turn them down because they did not have independent comedy routines. If we value team science, we have to figure out how to reward it."

As others had noted already, much of clinical research time spent by investigators is not funded, and division directors and department chairs are clamping down on uncompensated time. "To maintain salaries in most clinical departments today," Dr. Lichter said, "there is a very much 'eat what you kill' salary structure. If you are not seeing patients and generating revenues, you are not going to have your salary supported. Many promotions committees flip to the grant page and look for grant funding in your name, yet grant funding in the name of the investigator is either lacking or is as a co-investigator." Another problem is that clinical trials can take years from conception to publication, "and in most academic medical centers today, the tenure clock is not calibrated to this time scale," Dr. Lichter said.

[20]See Dilts et al., 2006, 2008.

He concluded his talk by offering suggestions for how to improve this situation in academia, given the major disincentives against physicians participating in clinical research. He suggested that the leaders of cooperative groups should communicate to academic medical centers the role that individual investigators play in these groups and what their accomplishments and impact have been. Lichter noted, however, that this may not be practical to carry out. He also suggested that funding agencies should emphasize the important contributions made by clinical trialists, even when their work is funded indirectly. A new nomenclature should be created and publicized that recognizes this indirect funding. He suggested that tenure should be available to clinical researchers in oncology and that the tenure clock be modified to accommodate the nature of this research. Finally, he suggested that when faculty members apply for promotions they should use an annotated bibliography to explain their work to those who are unfamiliar with it and to detail what their exact roles were for each published paper.

During the discussion, Dr. Mendelsohn and Dr. Lichter both noted that in other fields like physics and astronomy, collaboration in large teams is the norm. Dr. Lichter said, "We in medicine are well behind that curve," because we haven't figured out how to recognize or reward individual contributions to team science. As an example, Dr. Mendelsohn said, "If we do a cooperative group or any kind of trial, it is very rare for a pathologist or a radiologist to be a first or last author, so they get little credit for the work they contribute."

Dr. Johnson noted that unless you are the principal investigator of a cooperative group trial, you will not get listed in the CRISP (Computer Retrieval of Information on Scientific Projects) database of government research grants. But entering all the investigators participating in such a trial in the CRISP or some other database should not be difficult to do, he said, and it would give promotions committees something to go by. Dr. Lichter agreed with this suggestion, noting that "writing a protocol and getting it approved and activated is about 20 times harder than getting a paper published in a journal, yet the latter is the currency of academic productivity, and the former is often unknown or disregarded."

Dr. Baker reminded attendees that protocol submission is at an all-time low. "That should not be ignored as a simple phenomenon of this year, as I think it represents a much more serious set of problems," he said, recommending that more salary support should be provided to investigators to stimulate clinical research. As an example of such stimulation, he described the young investigator financial awards his institution provides for individuals proposing clinical trials. This program had 29 applicants this year, up from 19 the previous year, Dr. Baker noted. Dr. Caligiuri added that The Ohio State University has incentives built into

the payment of its clinicians who conduct clinical research. "Participation in clinical research gets you points that affect your salary," he said.

Dr. Curran pointed out that the NCI provides salary support for investigators who lead a Phase III trial, with the amount being determined by milestones such as finishing a protocol and other steps in a clinical trial process. "This financial support is not always recognized," Dr. Curran said. "Sometimes the money disappears not into the individual pocket but into the coffers of that group and is not recognized as federal dollars. That is something that we can do more about. If it is $10,000 a year for two years, then it should be recognized as the equivalent of being a co-investigator in a grant in federal dollars and should be respected as a percent of the effort." He added, "We have increasingly tried to use the idea that if you get 20 percent of your salary from federal dollars, you should get 20 percent of your time relieved to do that effort. That would be the case if you were doing wet bench research and is one of the things I think we could endorse." In a later presentation, Dr. Alan Benson, professor of medicine at the Northwestern University Feinberg School of Medicine and associate director for clinical investigations at the Robert H. Lurie Comprehensive Cancer Center, returned to the subject and said, "We are fearful that there will be increased schisms between laboratory and clinical medicine in terms of the competition for very scarce resources. This is probably an area where the IOM could help, in terms of challenging our academic centers to recognize the value of clinical research by their faculty."

The final topic of discussion concerned the fact that because there are fewer cooperative group Phase III trials being run and because those that are run often stop midway due to lack of accrual, it is likely that there are cities and centers all over the country that do not have a trial open in a particular tumor type at any given time. So, one participant asked, how can members of a cooperative group work better together to participate in these trials and build on the infrastructure of an already established trial? Dr. Curran answered that the trials of all the cooperative groups are now listed in the Cancer Trials Support Unit (CTSU) database. "Therefore, if your group does not have a trial in the specific disease, you can easily switch to another group and do the trial via the CTSU just by being a member of a single cooperative group," he said. To make it worthwhile, cooperative group guidelines were changed so that there is recognition not only for leading trials, but also for accruing to important trials that are prioritized in the national system. Steering committees for many disease types are also up and running, while those for other disease types should be active soon, Dr. Curran said. These committees should foster more cooperation between different members in the Cooperative Group Program and subsequently more patient accrual.

CCOP PERSPECTIVE ON PATIENT ACCRUAL

The final session of the first day of the workshop began with Dr. Stephen Grubbs, medical oncologist at the Helen F. Graham Cancer Center and principal investigator of the Delaware Christiana Care CCOP, discussing the contributions, benefits, and challenges of the CCOP program. CCOPs contribute one-third of the total patient accrual to NCI treatment and prevention trials, Dr. Grubbs said, including a large number of early-stage patients, to which the community physicians have more access (NCI, 2003). Dr. Grubbs noted that only half of the participating physicians are medical oncologists or hematologists—the others are primary care physicians, surgeons, radiation oncologists, or urologists. By participating on cooperative group committees and other NIH committees, CCOP members also provide a community perspective in trial design. And because CCOP is a national network with members spread throughout the United States and Puerto Rico, it allows relocated patients to continue their participation in a clinical trial—something that proved invaluable, for example, when Hurricane Katrina forced many Gulf Coast residents to move.

There are also benefits to the community physicians who participate in CCOP, including the opportunity to provide state-of-the-art cancer treatments to their patients and to design and participate in research studies. The physicians also benefit from the training of their research staff, investigator mentoring, and peer review that the cooperative groups provide, Dr. Grubbs said.

He then went on to discuss what factors affect participation in clinical trials. Studies on a national scale show that the top two reasons that patients do not enroll in clinical trials are that physicians do not offer clinical trial information to the patients or that there is no protocol in which the patient can participate. Other factors high on the list are age and performance status requirements of the trial, the patient's desire for standard therapy, and barriers that prevent patients in underserved communities from participating (Albrecht et al., 2008; McCaskill-Stevens et al., 1999; Mills et al., 2006). When he conducted a study of barriers to patient accrual at his CCOP in Delaware, he found that three-quarters of the 1,000 patients studied were not eligible to participate in a clinical trial.[21] Among those who were not eligible to participate in the clinical trial, there was no trial available for 54 percent, 20 percent could not participate because of poor performance status, 6 percent were denied participation because of a prior cancer history, and 5 percent could not participate because of abnormal laboratory results.

[21]S. S. Grubbs, Delaware Christiana Care CCOP, unpublished data, 2008.

Of the patients who were eligible for a trial, 38 percent enrolled and 62 percent declined to enroll in clinical trials. Two-thirds of those who declined did so at the advice of their physicians, many of whom thought the patients were too old to participate in a clinical trial. An age of more than 70 years was the biggest factor against enrollment in a clinical trial, followed by gender, with women less likely to participate than men (with the exception of participation in breast cancer treatment trials). "I think there is a silver lining in there," Dr. Grubbs said. "We were successful in getting women on the breast cancer trials because of the publicity and patient advocacy that is going on in our country. When women get breast cancer, they already have it in their heads that clinical trials are a positive thing."

Other Delaware CCOP accrual barriers that Dr. Grubbs discussed are a lack of a dedicated recruitment effort for medical and non-medical oncology clinical investigators and infrastructure resource limits, which have become especially pressing with the declining CCOP budget. "Our budget to run the CCOP only covers about two-thirds of the cost of my hospital, which kicks in a third to cover it. That does not even include the in-kind giving that the private practices do," Dr. Grubbs said. Other barriers are regulatory and documentation burdens, a lack of clinical research associate retention, and the insurance restrictions mentioned by other speakers. "Our problem in our state is the ERISA exemption," Dr. Grubbs said.

Another major barrier is the constraint that participating in clinical trials places on a physician's time—a constraint that is exacerbated by the increasingly more complex trials and required consents, Dr. Grubbs said. "I give double bookings for my average patients on a complex trial like one with two targeted molecules for colon cancer chemotherapy," he said. "It takes me that much time to sort through all the toxicities and do the dose adjustments for each drug." Nontraditional physician investigators, such as radiologists and pathologists, also find their time overburdened conducting the tests and analyses required for clinical trials, and so they often resist doing them, especially since they are not paid to do these extra tests and procedures, Dr. Grubbs said.

Dr. Grubbs suggested several ways to overcome some of these accrual barriers, including providing adequate funding for the CCOP infrastructure and offering third-party reimbursement for oncology care linked to participating in a clinical trial. He also suggested developing more clinical trials for the majority patients for whom there is no appropriate protocol or who cannot participate in available protocols because of ineligibility. In addition, he suggested easing regulatory burdens and simplifying consent forms.

Dr. Grubbs said he would like private insurers and CMS to recog-

nize the value of clinical trials and to reimburse the associated expenses more readily, and he stressed the need for public education about the importance of participating in clinical trials. He suggested that there be fellowship training tracks to train and encourage community clinical investigators and also ways to publicly recognize those community physicians who regularly participate in oncology trials so the patients seek them out. He also suggested establishing a mentoring program for new and underachieving community research sites.

To improve patient accrual in his CCOP, Dr. Grubbs said, the organization recently started requiring a minimal annual patient accrual amount from its participating physicians as well as attendance at a cooperative group or research meeting at least every other year. He is encouraged by how physicians in his group have been responding to the new requirements, he said. "I have got four physicians that have put two people on trial in the last five years that have each accrued three to four patients so far, and the requirement has only been around for six months," he said. "But there will be gnashing of teeth at the end of the year, because some physicians are going to be stripped of their ability to participate in trials."

Dr. Grubbs also showed how CCOP participation has transformed the quality of cancer clinical care in Delaware. It spurred the development of one of the most advanced state cancer control programs in the United States today, he said. This program includes a state cancer consortium, a statewide colorectal screening program with funding for the uninsured, and funding for uninsured patients for up to two years of cancer control, including cancer clinical trial activity. CCOP participation has also raised the cancer standard of care in the state, which has resulted in a significant drop in cancer mortality in Delaware. Delaware, New York, and Maryland lead the most improved category in cancer mortality rates, with drops of more than 12 deaths per 100,000. In addition, Delaware's cancer mortality is dropping at a rate double that of the national average (DCC, 2007). He attributes much of that drop in cancer rate to the CCOP and the clinical trials it runs in the state.

Dr. Grubbs concluded by stressing the importance of the CCOP program. "CCOPs produce high quality and quantity clinical research and are the vehicles that elevate community quality cancer care," he said. "The CCOP program is robust now but under the same multiple pressures experienced by academia and private practice medicine."

The next speaker, Dr. John Feldmann from the Moses Cone Regional Cancer Center in North Carolina, presented a perspective from a much smaller CCOP. He began his talk by noting that about 80 percent of patients still receive care in community practices. "It is clear that academic centers alone cannot produce the number of patients we need for

timely completion of NCI studies," he said. "And community physicians, not only through CCOP, but also independently, need to remain in the process somehow." However, Dr. Feldmann noted a peculiar distribution of open protocols among participating CCOP sites in North Carolina. More than three-quarters of those sites have less than 10 protocols open, and nearly half the sites currently have no protocols open. "Obviously, there are a large number of sites doing a small or moderate amount of research throughout the state, which is a problem," he said. He raised the question of whether these sites would do more research if they had more resources.

Dr. Feldmann then discussed the pressing issues that are limiting the participation of patients and physicians in cooperative group clinical trials, including reimbursement and funding issues, regulatory burdens, competition from industry trials, and problems with trial publicity. He noted that, traditionally, a sizable portion of the revenue that supports community oncology practices is the profit margin made on chemotherapy. But because of recent changes in reimbursement by CMS, that margin has been shrinking, and some small practices that do not have enough volume to receive a discount on the drugs are actually having difficulty making any margin at all, Dr. Feldmann reported. Hospitals with a significant indigent load can purchase chemotherapy drugs at a reduced price because of a Health Resources and Services Administration (HRSA) program called 340B.[22] So marginal payors are increasingly being referred to hospitals, Dr. Feldmann noted, as are Medicare recipients who cannot make their drug copayments.

The recent 10 percent cut in Medicare reimbursements[23] puts more financial pressures on private practices, fostering cuts in personnel and patient time that make it less likely they can afford to participate in clinical research. "Everyone in private practice is trying to cut personnel, and those personnel needed for good data collection or to deal with the regulatory burdens of clinical trials are going to be among the first to go," Dr. Feldmann said. In addition, practitioners, who now have less time to spend with patients, are less likely to explain to patients their clinical trial options and to do consents; nor are they likely to have the time and willingness to fulfill other obligations of a primary investigator. One way to deal with this is for the private practitioner to work with local hospitals that can provide data management services. But this is difficult for rural

[22]See http://www.hrsa.gov/opa/introduction.htm.

[23]The 10 percent Medicare payment reduction that went into effect July 1, 2008, was rescinded when both Houses of Congress overrode a July 15 presidential veto to maintain current funding levels for the rest of the year, while providing a 1.1 percent payment increase in 2009. *Medicare Improvements for Patients and Providers Act of 2008*, P.L. 110-275, 110th Cong., 2d sess. (July 15, 2008).

practices to carry out, because the hospitals are often smaller and do not have the financial resources to provide this type of service, Dr. Feldmann said.

As had been previously mentioned, Dr. Feldmann noted that NCI funds are insufficient to address the financial insufficiencies faced by CCOP physicians, which increasingly rely on hospital partners to subsidize clinical trial costs or on industry trials revenues. But hospitals are also facing increasing financial pressures, and Dr. Feldmann was skeptical that the new partnerships between the NCI and industry could solve these financial problems. Most of the industry trials involve INDs, and the trials are much more complex and require more time. "The payments may be threefold higher, but in our experience, the increased work has been out of proportion to that increase in reimbursement, and these trials have not improved the financial situation," Dr. Feldmann said.

Industry clinical trials also compete for the same limited pool of patients seen by community physicians, he added. Patients are more likely to accrue to industry trials, because they usually involve a Phase II component that does not require randomization. Other competitors for NCI cooperative group trials are industry-only networks. "These are being sold to smaller practices and even to some practices currently in CCOP as a way to do research in the office without as much financial risk," Dr. Feldmann said. The network handles the regulatory burden centrally, and the design is more efficient for industry partners, because they can often contract directly with these networks and not have to contract with all the individual practices involved. But for financial reasons almost all of these networks now exclude NCI cooperative group trials, Dr. Feldmann said.

He also expressed concern about the studies being done as part of CMS's new Coverage with Evidence Development program.[24] These studies use CMS's extensive database to determine the effectiveness of certain treatments and whether they should be covered by the insurer. "Our concern is that this will take the place of support of clinical research eventually by CMS because it is a faster and more effective way of getting data," Dr. Feldmann said. "From a research standpoint, this is probably not the ideal way to advance medical knowledge."

He then discussed clinical trials publicity. He noted that a Harris poll (Harris Interactive, 2001) showed that only 16 percent of cancer patients were aware of clinical trials, although they generally had a favorable impression of them. He also pointed out the difficulties in searching for appropriate clinical trials for patients. Although there are multiple trial searching sites, the information on them is often inaccurate, outdated, or

[24]See http://www.cms.hhs.gov/CoverageGenInfo/03_CED.asp.

incomplete. In addition, many of the trials are not regionalized, with the result that "studies from 2,000 miles away are mixed in with those next door," he said. "It can be very difficult for the patients to find them." Some states, such as Georgia and North Carolina, are trying to regionalize their search engines and to make the clinical trials information more accurate and up to date, he noted, but more needs to be done in this regard.

Dr. Feldmann concluded his presentation by stressing that community participation is essential for timely trial completion, but it is going to need increased outside support in the community, possibly via partnerships between practices and hospitals. "Increasing industry trials at the expense of NCI trials is a huge threat," he said, and much needs to be done to resolve the reimbursement and insurance issues that he discussed. "We are going to need some joint regional efforts, which may include expansion of the CCOP program or local partnerships with a state between practicing groups and local medical centers. Something is going to have to be done to shore up this effort."

PERSPECTIVE FROM A NATIONAL HEALTH CARE SYSTEM

The next speaker, Dr. Richard Kaplan, associate director of the National Cancer Research Network (NCRN),[25] discussed the United Kingdom's recent successful initiative to boost patient participation in clinical trials. The United Kingdom has a national health care system called the National Health Service (NHS) for which all its citizens are eligible. The system includes the NCRN, which is a single national network for cooperative cancer clinical trials. This new network funds research nurses and data managers as well as the expertise of radiologists, pharmacists, pathologists, and other clinicians to a limited extent. The funding that was put in place for this was brand new money, and funded personnel were charged with doing research—they could not be diverted to meet the ordinary clinical loads of a very busy, overburdened system, Dr. Kaplan said. The data coordinating centers that are also managed under the NCRN are funded separately. The network also supports cancer steering committees composed of scientific experts and consumer representatives. These committees oversee existing studies, consider new research questions, develop new proposals, and provide expert advice.

The NCRN was established in 2001 with the goal of doubling patient participation in clinical trials within its first four years. It has exceeded this goal: within six years, patient accruals rose from 3 percent of the annual incidence of cancer to 13 percent. The NCRN recruits 28,000–32,000 patients per year in treatment studies, plus another 30,000–40,000

[25] See http://ncrn.org.uk.

on screening or prevention trials, numbers roughly equal to the annual patient accruals in the NCI Cooperative Group Program, even though the United Kingdom's population is about one-fifth the size of the U.S. population. The expansion in enrollment was seen more in the community hospitals than within academic medical centers, which already had good participation in clinical trials. The growth in randomized trials is leveling off, while the growth in nonrandomized trials continues to expand. This is in part because more genetic epidemiology studies are being done, Dr. Kaplan said, but it is also because the workforce put into place at NCRN's start now has about the maximum number of large complex trials it can effectively handle.

The main reason that the NCRN has been so successful in boosting patient accruals, Dr. Kaplan said, is the availability of increased funding dedicated to research staff involved in clinical trials. "The biggest driver of success was that new research nursing staff was put in place: if you get enough personnel out there, you can—up to a point—put more patients on clinical trials."

Although there might be some lessons that U.S. clinicians can learn from the NCRN experience, Dr. Kaplan noted a number of ways in which health care in the United Kingdom and the United States differ that can affect patient accrual to clinical trials. For example, people in the United Kingdom generally do not have access to innovative drugs or new uses of drugs outside of academic or industry-run clinical trials run within NHS. This restricted access makes government clinical trials more attractive to British patients and physicians than they are in the United States, where off-label use of drugs is prevalent. Dr. Kaplan claims that U.K. physicians are especially well motivated to support clinical trials as a way to be more evidence-based in their practices. "There is a genuine belief that it is their job to try to put patients on a study and to look for evidence of a treatment's effectiveness," Dr. Kaplan said. Patients in the United Kingdom are often more accepting of being randomized in clinical trials than are those in the United States, he added. They typically follow clinician advice, even if the advice is to be randomized, and they infrequently seek multiple additional opinions.

Another factor increasing patient and physician participation in clinical trials is the fact that in principle all extraneous standard health care costs linked to patients participating in clinical trials are automatically covered by the national health care system in the United Kingdom, although Dr. Kaplan noted that individual NHS Trusts (regional medical services) sometimes have insufficient funds to cover these extra costs, and access to a trial may be limited or capped. On the other hand, there is a strategic alignment of charity and government funding of cancer clinical research in the United Kingdom, the National Cancer Research Insti-

tute,[26] with charities "very committed to the work of the cancer research network," Dr. Kaplan said. If more resources are needed—for the data centers, for example—the Institute partners work out which amongst all the government agencies and funders can provide the cash or other support necessary, he said.

Dr. Kaplan added, however, that the NCRN may not be able to maintain its momentum in boosting patient accruals to cancer clinical trials in the face of the trials nearing full capacity and the economy starting to falter, which makes increased resources unlikely. Furthermore, the increased burden of following patients on established trials will interfere with physicians' ability to take on new ones. "The burden of following up on something close to 200,000 patients now is beginning to add up," he said.

Dr. Kaplan ended by noting that the NCRN is not a perfect system. Some of the most important studies are work-intensive, and with capacity now fully occupied, some local networks are declining to conduct them. Also, most of the studies are done on common cancers, with rare diseases being at a disadvantage in the system. In addition, accrual has been slow for studies that need to recruit from primary care or non-oncology clinics. There also need to be specific mechanisms of support for imaging, pathology, and pharmacy resources. New resources and new incentives have to be built in to fine tune the success so far. He also suggested that improved alignment of clinical trials internationally during the development phase would provide more complementary and synergistic research data and would prevent trials being duplicative except where that was desirable.

PATIENT PERSPECTIVE

The final speaker of the day was Ms. Deborah Collyar, cancer patient advocate and founder of the PAIR (Patient Advocates in Research) international network, who spoke about patient perspectives regarding participation in clinical trials. She began her discussion by debunking common myths perpetuated about clinical trials, including the idea that patients join clinical trials for selfless altruistic reasons. "I have not met anyone who enrolled in a clinical trial to help future patients," she said. "They enroll based on the lottery concept. They hope for the best, for that winning ticket, but they realize it is probably not going to happen."

Instead of curing patients, clinical trials often simply offer them more time, Ms. Collyar pointed out. Thus patients have to decide if that extra time is more beneficial than the costs linked to pursuing the treatment. Those costs are not just financial but may also include pain or discomfort

[26] See http://www.ncri.org.uk.

beyond what the patient would experience with the cancer alone as well as impairment of lifestyle. Other factors that influence the decision to participate in a clinical trial include whether a patient has insurance and whether the patient has a support system. "It's a life decision, not just a medical one," Ms. Collyar said.

She was critical of the informed consent process, noting that any procedure done in a hospital or clinic often requires patients to sign a consent form. From the patients' perspective, in order to receive the experimental therapy offered in a clinical trial they have to sign a consent form. "They do not understand the difference between what we are talking about in research versus a medical procedure," she said. She added that another common patient misconception is that research is the equivalent of treatment. And even with all the regulations that are currently in place concerning informed consent, problems can still arise, she noted, offering as an example the case of Jesse Gelsinger, who died in 1999 from complications related to receiving an experimental gene therapy (Gelsinger and Shamoo, 2008; Somia and Verma, 2000; Wirth and Yla-Herttuala, 2006). Patients also often erroneously assume that placebos are not given in cancer trials, and this misconception needs to be honestly addressed. Another myth, this one on the part of health care workers, is that patients do not want to be told that they are dying, Ms. Collyar said. She argued that most patients *do* want to know they are dying so that they can focus on what is most important to them for the remainder of their lives.

Another common misconception, according to Ms. Collyar, is that a lack of patient awareness about clinical trials is impeding their participation in them. Patients do not pay attention to clinical trial awareness campaigns until they are afflicted by a condition for which there is not adequate treatment, she said. In addition, as others had pointed out, she noted that half of all patients are not eligible for clinical trials (Lara et al., 2001). "If we tell more people that clinical trials are the greatest thing since sliced bread, and they find out that they are not eligible for one, that creates a larger problem than what we have today." She added that "low enrollment is not their fault, it's our fault—we have to fix the system so people can get more involved in it."

Ms. Collyar offered several suggestions for improving clinical trials from a patient perspective. She suggested having informed consent templates that are written in plain language that patients can easily read and understand. Patients should also be given easy-to-read summaries of research results and be acknowledged for their valuable contributions to research when they participate in clinical trials. "People want to know that their contributions are making a difference," she said. Ms. Collyar also suggesting doing a better job helping patients not just with their medical treatment but with making decisions that fit their lives and

with making clinical trials a normal part of the decision-making process. Patients need help navigating their therapy and their clinical trial options, she said.

Ms. Collyar was critical of the Privacy Rule[27] developed under the Health Insurance Portability and Accountability Act (HIPAA), stating that the rule needs to work for the patients and not against them. HIPAA has created paperwork nightmares and made it difficult for patients to acquire their own records. HIPAA also can keep researchers from obtaining critical biospecimens and information that could further research. Often patients want access to their own biospecimens and information when new tests and treatments become available, yet the way in which institutions interpret the privacy rule or intellectual property agreements prevent that access. To avoid these constraints, Ms. Collyar recommended creating universal standards for data sharing.

She also said that the NCI's role in clinical trials should be to facilitate them and to provide oversight but that the institute should not be involved in regulating clinical trials. She suggested that the NCI should sponsor a yearly public meeting between the NCI director and the clinical trial leaders and the cooperative group chairs; this meeting could be webcast and archived so it would be available and open to the public. At that meeting, people could explore what has been successful and why, as well as actions needed for improvement.

Ms. Collyar suggested consulting patient advocates more often when determining study designs, consent forms, and other aspects of clinical trials. Unlike individual patients, patient advocates have a larger and more long-term view concerning the best ways to improve health care and research. "Patient advocates can help clinicians create and conduct better clinical trials that answer more patient-related questions faster," she said.

Ms. Collyar acknowledged that the lack of funding for clinical trials is a problem and suggested pooling money from many diverse sources, private as well as public, that could be available for publicly funded studies. "We have to be realistic about the fact that the government is not going to be able to support public clinical trials all by itself," she said. "We have to build a feasible business plan on what we need and how we are going to fund it."

Ms. Collyar concluded her talk by saying, "We should not keep tweaking an antiquated system. What we are doing is just putting band-aids on a patient or a system that is bleeding out. We have to stop imitating our mentors and start living with and dealing with the world that our kids

[27]National standards developed by the Department of Health and Human Services to protect the privacy of personal health information. See http://www.hhs.gov/ocr/hipaa.

and grandkids see." She recommended having futurists and systems-oriented experts involved in plans for improving the clinical trial system and called for building an action plan that is actually implemented. "We have to stop just talking about these issues and start taking action," she said. She concluded, "Whether we should get rid of the cooperative groups is not the appropriate question, but rather what can we do today to create a system that actually works."

Session 3: Data Collection Standards and Monitoring

In order for a new drug therapy to obtain FDA approval, clinical trials must provide evidence of safety and efficacy. In addition, the FDA and the NCI frequently audit sites and cooperative groups to ensure the quality of the data collected and the safety of the experimental treatment being given. A number of regulations and guidance documents provide guidelines for the frequency and extensiveness of audits and for the amount and type of data required to support claims of safety and efficacy. These guidelines are continually revised by the FDA and the NCI to reflect lessons learned and, when appropriate, to respond to the concerns of a variety of stakeholders, including government, industry, patients, and clinicians. However, some clinical trials investigators have suggested that the NCI and the FDA reduce the amount of audits and data required, thereby streamlining the clinical trials process and saving both time and money. At the same time, additional data and resources are needed for today's trials—such as those for targeted therapies—to identify patient candidates for new therapies, for biomarker analysis, and more. The first session of the second day of the conference explored which data are essential for demonstrating safety and efficacy and what changes could improve current auditing and data requirements.

THE NCI PERSPECTIVE

Dr. James Doroshow, director of the Division of Cancer Treatment and Diagnosis (DCTD) of the NCI, began this session by giving the NCI

perspective on data collection and monitoring. He suggested that, given the expense of complex trials and the limited budgets of government and industry, one cannot collect all the data that might potentially be needed for a future review. Instead, he suggested that the best course is collecting only the amount of data that is absolutely necessary, but he noted that it is debatable just how much data are required to ensure safety and efficacy in any given situation. For example, new investigational drugs might have novel toxicities that require the monitoring of numerous signs and symptoms. But once a novel toxicity, such as hypertension, has been documented among the first 1,000 patients tested with the experimental drug, he asked, "do we need to collect blood pressures on the next 10,000 patients?"

The amount of data needed for audits is also a debatable issue, he said. He noted that the NCI regularly audits 10 percent of the patient cases at cooperative group sites and determines major deficiencies related to a number of factors listed in Box 5. But he noted that there are no standards for these auditing data and no comparative data against which to measure them. "I personally happen to think that if there were a major deficiency in adverse-event reporting of only 2.3 percent of the cases, that's pretty good," Dr. Doroshow said. "But should we give the cooperative groups kudos or tell them that this is unacceptable? We really do not know."

Dr. Doroshow also said he has data to suggest that reviewing 10 percent of patient cases is sufficient for on-site audits and that reviewing additional cases does not improve the information gained. "Monitoring every patient at every clinical visit is not necessarily going to provide you with additional information that tells you whether or not a trial or a site is doing well or is doing badly," he said.

BOX 5
NCI Cooperative Group Program: Patient Case Review Categories

- Informed consent
- Eligibility
- Treatment
- Adverse events
- Disease outcome/response
- General data timeliness

SOURCE: Doroshow presentation (July 1, 2008).

Another debate in data collection and monitoring concerns which kinds of endpoints are valid to use and how much verification is required for those endpoints. Many clinical trials are moving away from using survival data as endpoints and instead are using time-to-progression or tumor response as endpoints. These endpoints are determined by radiologic criteria that can be subjective, because they are not easily quantified, but one study of three different trials found a close correlation between investigator assessments of radiologic endpoints and those of a radiologic review (Dodd et al., 2008). "We may think it intuitively obvious that these radiologic reviews should be done," Dr. Doroshow commented, "but where are the data that make it clear that adding a procedure is unequivocally going to be beneficial in improving the quality of the data that leads to an indication?" He added that, for technical and biostatistical reasons, an additional blinded central review may introduce as many errors as it corrects.

In a later talk, Dr. Fyfe agreed with this assessment, noting that because of the existence of different methods, different lesions selected, and measurement inconsistencies, a blinded radiologic review should not look for a concordance of findings that is then used to assess the quality of the reviewed site but should verify benefit and look for bias between the treatment arms in a study. She pointed out that there often is not a great degree of concordance in radiological assessments of small-volume disease, because such assessments can be highly subjective. "As we start to use independent review facilities, there is a real danger, because more data are not better data," Dr. Fyfe said. "They are simply confusing, whether it's an industry trial or a cooperative group trial."

Dr. Doroshow ended his presentation by saying, "It's neither appropriate nor desirable for the NCI to perform clinical trials in a manner that is identical to the model that industry has used and is continuing to use. One hundred percent source verification is neither reasonable nor necessary, nor does it necessarily get us a higher quality of data that will lead to improving treatment for our patients." In defense of industry, Dr. Canetta commented, "Sometimes our approach has been that if we believe we might need data eventually, we had better collect them. We do not relate only to the FDA, but also to a plethora of other regulatory agencies that are equally powerful in regulating the use of experimental agents in their countries."

INDUSTRY PERSPECTIVE

In the following presentation, Dr. Gwendolyn Fyfe, senior staff scientist in clinical hematology and oncology at Genentech, gave the industry perspective on data collection and monitoring. She said that much of

the data her company collects is never used. This includes data on vital signs, concomitant medications, laboratory values, medical histories, and low-grade toxicities; secondary information about adverse events; and independent reviews of efficacy endpoints. Furthermore, some data are collected excessively or in an inefficient manner.

Dr. Fyfe noted that by the time a drug enters Phase III trials, much is known about its toxicity and the time course of its toxicity. Investigators should use that information to narrow the collection of data, she said. By the time Avastin (bevacizumab) reached Phase III trials for colorectal cancer, for example, its effects on blood pressure and likely effects on bleeding were known and should have focused the collection of data on adverse effects. Dr. Fyfe suggested collecting grade 3 or 4 toxicities on a cycle-specific basis. "I know, for the most part, when I go into Phase III, whether something is going to happen at day 7 or 14. I do not learn anything by collecting that exact date, and I put a burden on the sites if I ask for a precise date," she said.

Most of the data on adverse events are "rolled up into a worst grade, so for all the data you collect, you end up with just one number," Dr. Fyfe said. "I'm not sure that all the specific stop and start dates helped us understand the safety profile of bevacizumab." Dr. Fyfe noted that much of the data collected on adverse events is superfluous, because it merely improves confidence intervals without changing clinical decisions. As Table 2 shows, increasing the number of patients analyzed for adverse events causes statistical differences that are not meaningful in the clinic. "A physician will not manage patients differently if there is a 40 percent or a 60 percent adverse event rate," she said. "When we think about collecting more data, there is this inference that it's better that we know more.

TABLE 2 Does More Safety Data Provide Greater Certainty About the Safety Profile?

Expected Rate of Adverse Event (percentage)	100 Patients Analyzed	200 Patients Analyzed	400 Patients Analyzed	800 Patients Analyzed
5	4.3	3.0	2.1	1.5
10	5.9	4.2	2.9	2.1
20	7.8	5.5	3.9	2.8
30	9.0	6.5	4.5	3.2
40	9.6	6.8	4.8	3.4
50	9.8	6.9	4.9	3.5

NOTE: Confidence intervals as a function of patient number.
SOURCE: Fyfe presentation (July 2, 2008).

It's simply not true, in terms of being helpful. It probably just slows things down at an extra cost without providing much value." Later, during discussion, Dr. Ralph deVere White suggested that many of the data points collected to show drug efficacy may also be superfluous since they, too, might merely improve confidence intervals without having any relevance to clinical decisions. Dr. Fyfe agreed that this may be so and that it should be considered when developing minimum data standards.

Not only are Genentech and other companies collecting information that they are not using, Dr. Fyfe said, but they are missing important data. In particular, she expressed dissatisfaction about the lack of placebo-controlled trials, which are needed to ensure unbiased reporting of adverse events. For example, Genentech's randomized Phase II trial of Avastin did not include an arm that received a placebo, and the rate of thrombosis—blood clots—was much higher in the Avastin arm than in the control arm receiving standard treatment (26 or 13 percent, depending on which Avastin arm, versus 9 percent in the control arm). However, differences in the rate of thrombosis in the control and treatment arms of the placebo-controlled Phase III trial of Avastin were more similar (16 percent in the placebo arm versus 19 percent in the Avastin arm) (Hurwitz et al., 2004; Kabbinavar et al., 2003). "With the best possible intentions, people under-report adverse events on the control arm," Dr. Fyfe said.

Dr. Fyfe also noted the importance of understanding why physicians or patients stop treatment, as that can provide information about the tolerability of a drug or its efficacy. Often, however, this data is not collected. "Sometimes patients stop a drug because it's toxic, but sometimes they stop the drug because they are progressing but have not reached that magical 'progressive disease' endpoint that we collect data on," she said. Collecting data on subsequent treatment is also helpful, as multiple treatment lines are often pursued, and such data can help assess optimal treatment paradigms, she added.

Dr. Fyfe suggested collecting data on the deaths, discontinuations, and SAEs in all patients at all sites, and she commented that collecting data on targeted adverse events is also appropriate in some cases. She added, however, that detailed adverse-event profiles in subpopulations are usually inadequately answered in Phase III trials and are probably better addressed in Phase II or Phase IV trials or through post-marketing registries.

She suggested that a set of data standards could ensure that the data collected are adequate to reliably assess whether an unapproved agent has a good risk-to-benefit ratio, including the issue of whether the drug significantly improves outcome when added to or in contrast to a known standard, and also what the effect on safety is when that drug is added to or substituted for a known treatment standard. Ideally, data should also

be collected that might identify subsets of patients in whom the risk/benefit ratio is different from other patients. Dr. Fyfe said that data standards should be similar for all licensure trials and that minor tweaking of current cooperative group standards may be all that is needed.

Dr. Fyfe also stressed the importance of verifying study data in licensure trials to ensure accuracy and completeness, but she noted that this need be done only in a subset of patients. She suggested that stakeholders work together to quickly determine the most appropriate and consistent standards for data collection and monitoring. "We simply need to standardize so that we can assess the risk and benefit of drugs in the medical milieu of the United States, rather than offshore, as is increasingly happening," she said. She added that there should be a funding mechanism so that cooperative groups can meet the data standards created. She suggested creating a foundation to which industry contributes when doing Phase III trials with cooperative groups, and she added that there should also be a surcharge so that the cooperative groups can do trials that help define the standard of care for patients in the United States.

COOPERATIVE GROUPS PERSPECTIVE

The next speaker, Dr. Robert Comis, president and chairman of the Coalition of Cancer Cooperative Groups and group chair of ECOG, discussed the increasing tension within cooperative groups between the need to reduce data collection in order to save money and time and the need to provide the data required for licensure of drugs. The pressure to save money is real: Dr. Comis highlighted the flat budget for the Cooperative Group Program over the past three or four years, which represents a substantial decrease when adjusted for inflation. He began his talk by describing the 1997 recommendation of the Armitage Committee, which reviewed the NCI Cooperative Group Program (NCI, 1997). The committee recommended that in designing clinical trials, data collection should be reduced and that investigators should collect only data pertinent to studying endpoints and safety. At the same time, the FDA released a guidance for industry stating that cooperative group data could be used for FDA filings (FDA, 1998). This has, in part, fueled an increase in licensure Phase III trials run by cooperative groups, Dr. Comis said.

But the NCI and the FDA differ in important ways in the data that they require and how it is reported, he said. They differ in how adverse events are reported, in eligibility and dosing checks, in how data are collected in the laboratory and audited and monitored, in what locks are placed on databases, and in what endpoints are verified. The additional data or procedures that the FDA requires for licensure add substantial

costs on to a clinical trial. Those costs are not necessarily reimbursed by industry sponsors. For example, the FDA may require:

- cardiac safety monitoring tests and procedures that are not the standard of care;
- a central review of imaging findings;
- revisions of case report forms; and
- supplemental data management efforts, such as reconciling NCI and FDA databases of adverse event reports.

"When we do a study that has registration implications," Dr. Comis said, "there are tremendous additional workloads that are imposed on the central offices and sites that are well beyond NCI funding levels." To meet those additional requirements, many cooperative groups scramble in an ad hoc manner to acquire industry or other funding to support their efforts, but this can be unreliable and difficult given that "the system is so underfunded that there is no elasticity," Dr. Comis said. "What if industry funding goes away?" he asked.

Dr. Comis suggested that cooperative groups, government agencies, and industry develop evidence-based standards for Phase III trials, including standards for data collection, data and site monitoring, and the content of case report forms. He also suggested that there be an independent and thorough analysis of the value of independent reviews of imaging findings and data, since many experts question their value and added expense. During the discussion that followed the presentation, Dr. Canetta agreed that such an analysis would be beneficial. Dr. Comis's final suggestion was that there be a cooperative group–wide support structure to provide services beyond the capacity of the central offices.

FDA PERSPECTIVE

Dr. Richard Pazdur, director of the Office of Oncology Products in the Center for Drug Evaluation and Research at the FDA, joined the speaker panel in the discussion that followed Dr. Comis's presentation, and in an impromptu presentation he agreed with many of the points and suggestions made by the previous speakers. He stressed the importance of independent reviews of the data and imaging findings for trials that are not placebo-controlled, but he added that independent review does not have to be extensive. It is not necessary, for instance, to review every patient case or solicit the opinions of three different radiologists. Dr. Pazdur suggested exploring alternative mechanisms, including requiring blinded trials, in order to ensure that there is no systematic bias in studies. The FDA does not require independent review for blinded trials, he pointed

out. He also agreed with Dr. Fyfe that it is not feasible to require that there be concurrence between reviewer and investigator in the assessment of radiologic findings.

On the subject of FDA requirements related to assessing the safety of a tested drug, Dr. Pazdur pointed out that the data needed to support a safety claim for an oncology drug are much smaller than required in other therapeutic areas. Because of this, for subsequent development of the drug in sNDAs, the FDA may require more safety information involving larger numbers of patients. That has been especially true in recent years, since the FDA has become more safety conscious in the post-Vioxx era, Dr. Pazdur said. He pointed out, however, that when oncology drugs fail to get approved it is not because investigators failed to demonstrate their safety to the FDA but rather because they failed to demonstrate their efficacy. He concluded that it would be helpful if the FDA defined more clearly what an optimal safety database is, and he suggested that a public hearing and workshop be held on this topic.

Dr. Pazdur also noted that the FDA accepts the NCI's auditing procedure but that industry often supersedes that auditing—not because of requirements of the FDA but rather in order to meet its own needs. He suggested developing uniform auditing standards that the NCI, the FDA, and industry would all follow.

In the general discussion that ensued, Dr. Bruce Hillman, professor of radiology at the University of Virginia School of Medicine, brought up the subject of innovative techniques in imaging, such as analysis software that can provide more precision and less variability in the analysis of images. "I find it really hard to understand why we are still talking about linear anatomic measurement criteria in this day and age of this extraordinary software, especially as we start talking about targeted treatments," he said. He suggested considering these innovative analyses of radiologic findings when developing data and review standards.

A few attendees raised the issue of industry funding of cooperative group trials and the effect that this might have on the data collected and reported. "The evidence necessary to sell something under a monopoly structure at a high price is very different than the evidence needed to influence the practice of medicine," Mr. Robert Erwin said. "What is the impact on the data that are collected—and even the questions that are asked—by industry stepping into the breach to fill the funding gap left by NCI?" Dr. Doroshow countered that any effects that industry might have on clinical trial data could be kept in check by having an independent auditing system. Dr. Abrams agreed that such an independent audit is critical, as conflicts of interest can arise whenever cooperative groups receive industry support. "If we do not have a robust independent review of these trials," he said, "the criticism will be raised quite quickly that

these trials are being done by industry and that public dollars should not pay for them. What will protect these trials is that they have a very robust independent review, not just a cooperative group–only review." Dr. Padzur added that most of the cooperative group trials receiving industry support are for supplemental indications of drugs whose safety and effectiveness are already well established and that clinical trials for primary indications generally are scrutinized more by the agency.

Dr. Schilsky suggested that ASCO would be more than willing to oversee the development of minimum data standards for oncology clinical trials that are acceptable to all stakeholders. He also suggested that ASCO take the lead in determining the appropriate minimal eligibility requirements among stakeholders; this is important because a lack of eligibility is a major deterrent to patient participation in clinical trials, as had been pointed out by Dr. Grubbs on the first day of the workshop. Such eligibility criteria should ensure that the patient population of the study is well defined and that the proposed treatment is likely to be safe in the population to be studied, Dr. Schilsky said. Dr. Pazdur noted that lowering the threshold of eligibility might increase the need for more safety data. If, for example, people with compromised kidney or liver function are allowed to participate in a clinical trial and it is not known how an experimental drug is excreted, safety is more of an issue, he said.

Dr. John Wagner, executive director of clinical pharmacology at Merck, suggested considering "fitness for purpose" when developing minimal data standards so that the design of an experimental protocol can adequately validate and qualify a particular use of the drug or biomarker being tested. "There can be a minimal set of data-collection standards, but for particular uses that may need to be augmented in one way or another," he said.

Dr. Canetta expanded on Dr. Fyfe's comment that new toxicities are rarely found during Phase III trials, because they are already documented in Phase II trials. Industry and investigators "have been cutting off a lot of the Phase II activities," he said, "and therefore we have lost a lot of learning opportunities." He suggested a few remedies, such as doing more randomized Phase II studies before proceeding to Phase III studies or having an independent data and safety monitoring committee that is program-wide for Phase II studies. The latter has helped his company acquire better safety information before proceeding to Phase III studies, he said.

Dr. Mendelsohn asked Dr. Comis if, in his analysis of cooperative group trials, he found any key factors that foster adequate patient accruals. "The most important characteristics of a highly successful trial are that it answers an interesting question and involves a new approach," Dr.

Comis responded. "So I think we all need to focus on those things that are the most cutting-edge."

Dr. DeVere White noted that money is often a driver of change, and he suggested changing the funding structure of cooperative groups. In particular, he suggested that instead of one-third of the money that the NCI gives to a cooperative group going towards patient reimbursements with the rest going to the infrastructure of the cooperative group, NCI funding be split more equally between patient reimbursements and cooperative group infrastructure support. If this were done, more money would be allocated to patients and to the physicians who put them in clinical trials.

Dr. Buckner noted that the NCI typically does not require data collection on attribution of adverse events, whereas the FDA does. His clinical trial findings suggest that attribution appears to be an unreliable endpoint and perhaps could be immediately removed. Dr. Canetta concurred, noting that he recently received a letter from the Japanese regulatory agency asking that such attributions not be done.

Session 4: Costs of Cooperative Group Clinical Trials

The last session of the workshop addressed the costs linked to cooperative group clinical trials, how to document those costs, and how they are covered. During this session, speakers expanded on some of the cost issues suggested by earlier speakers, such as a lack of insurance reimbursement for routine patient care costs in clinical trials, the increased costs of running registration trials or complex trials that include pharmacogenomic tests, and the decline in government funding for cooperative group trials.

COOPERATIVE GROUPS COST ANALYSIS

The first speaker in this session, Dr. Alan Benson, professor of medicine at the Northwestern University Feinberg School of Medicine and associate director for clinical investigations at the Robert H. Lurie Comprehensive Cancer Center, provided a cost analysis of cooperative groups. He reiterated that there has been a decline in NCI funding for the cooperative groups, and he noted that because of NCI funding limitations, cooperative groups usually receive 30 to 50 percent less than the total grant money asked for on their applications. Efforts to increase NCI support include a new "trial complexity" payment mechanism that CTEP is in the final stages of developing. But it is expected that the additional support for complex trials will be limited in scope and will not sufficiently relieve the cost burdens of these trials.

In the future, NCI support of cooperative group trials may decline

further, Dr. Benson said, given that preliminary data between 2005 and 2008 show that the number of new Phase III trial concepts submitted to the NCI by cooperative groups decreased by 75 percent and that the number of concepts approved for development of protocols decreased by more than 90 percent.[28] Until this trend is substantially reversed, the declining numbers of trials and accruals will mean that sites will receive lower total capitation payments than was previously the case. It may, however, be possible for cooperative groups and U10-funded sites to reallocate capitation funds to other needs, Dr. Benson added. Furthermore, he added, as trials become more complex and require more pharmacogenomic tests, there will be more fiscal pressures that are not likely to be relieved by the NCI's trial complexity payment mechanism.

Industry provides supplemental funding for cooperative group trials that can support the cooperative group's centralized activities, such as the effort involved in meeting the data reporting requirements for registration trials, or for data management and quality assurance efforts. Much of such industry support is for correlative studies. Industry also provides financial support to individual sites, such as reimbursement for patient tests and procedures beyond the standard of care, or for additional required data submissions or submissions needed for an independent post-study review of imaging findings. But the level of patient reimbursements is often insufficient, Dr. Benson said, "and there is a continuing battle between the pharmaceutical industry and the insurance providers as to who pays for the standard-of-care costs." He explained that industry support is garnered by a drug manufacturer negotiating a contract with and providing payments to the lead cooperative group, which then disburses funds directly to its sites. Industry recognizes that cooperative group trials offer a significant bargain, Dr. Benson said, and it is often willing to collaborate with the cooperative groups for that reason.

Dr. Benson pointed out, as other speakers had, that lack of reimbursement for the standard-of-care costs of patients in clinical trials leads to another major cost that cooperative groups have to bear. He noted, however, that recently Medicare has been working with the NCI and the FDA to broaden support for clinical trials, which has led to the announcement of high-priority trials that should be reimbursed (NCI, 2008a). It is too soon to determine the effects of this announcement, he said, "but certainly such interaction among our federal agencies should be encouraged to

[28]The submissions decreased from 70 in calendar year 2005 to 17 through May 1 in 2008; the approvals declined from 48 in calendar year 2005 to 4 through May 1 in 2008. However, the numbers from 2008 are not final, so these decreases may not be as dramatic. Niederhuber, J. 2008. *Presentation to the Cooperative Group Chairs.* Chicago, IL, and personal communication, S. John, National Cancer Institute, October 17, 2008.

offer levels of support." He added that payment reluctance on the part of insurers is reinforced by the high costs of newly developed drugs and biologics.

Dr. Benson noted that there is a growing need for correlative and translational studies that use biospecimen banks. The NCI provides some financial support for specimen submissions, but waiting for such supplemental support from the NCI or from industry can substantially delay activation of trials. "Many academic labs will no longer subsidize some of these efforts," he said. "We have constrained resources, both for our concurrent studies and our retroactive studies for bank specimens, and it is often hard to convince pharmaceutical companies of the importance of these studies."

Dr. Benson summed up his talk by saying, "The assault on clinical research is obvious. Clinical research is clearly undervalued in terms of the time, effort, cost, and importance by all involved, including academics, government, media, and [health care payors]. We feel that the public-sector trials are at grave risk."

In the discussion following Dr. Benson's presentation, Dr. Michaele Christian, former director of DCTD at the NCI, suggested that many of the financial pressures Dr. Benson summarized could be alleviated by having fewer cooperative group clinical trials that are done much faster. "That's actually something within our control," she said. "We need to further strengthen internal review and prioritization so that we can choose the most important studies and pay more for them."

Dr. Johnson said that greater involvement of patients receiving care from the government-funded Department of Veterans Affairs (VA) patients should be encouraged when conducting cooperative group trials. Dr. Benson agreed but noted obstacles to this approach, including a VA IRB not accepting a review of a clinical study produced by a central IRB or a local institution's IRB. "We have seen VA accrual steadily drop because it has become harder and harder to conduct research in the VA system," Dr. Benson said. "It's another example of governmental agencies working at cross purposes—no one is cooperating, and an important population of patients at the VA are being denied access to the latest research efforts," he said.

CLINICAL TRIAL COST MANAGEMENT

The next speaker, Ms. Marcy Waldinger, chief administrative officer at the University of Michigan Comprehensive Cancer Center, showed how the costs of a clinical trial can be determined and used to negotiate better

financial support from trial sponsors. She noted that many of the costs of clinical trials are overlooked or understated, such as pre- and post-award costs and the costs of specimen collection, processing, and shipping. As trials have become more complex, she noted, there can be more expenses linked to shipping specimens, especially if they have to be shipped individually and are time-sensitive. Also often overlooked or understated are the costs of pathology evaluations, multi-center coordination, and long-term follow-up. The effects of inflation should also be taken into account when performing a cost assessment.

The standard approach to determining clinical costs is to base them on the number of patients accrued—for example, to assume that one full-time employee for data management is needed for every 30 patients. "This is truly anachronistic in today's age, when trials have become so complicated," said Ms. Waldinger. "We need a new approach with multiple variables that account for the study complexity," she said, suggesting that the NCI should facilitate the development of such a complexity model. In addition to the issue of whether the trial is Phase I, II, or III, variables that should be considered include the amount of sampling, the age and degree of morbidity of the patients, how easily the patients can be accrued, and whether they will be treated as inpatients or outpatients.

To help assess clinical trial costs more accurately, the University of Michigan developed an "effort tracker" that provides real-time reporting of research support staff costs. Data managers, research nurses, regulatory staff, and staff involved in specimen processing spend about five minutes each day logging how they are spending their time for various clinical trials. For example, research nurses note how much time they spend on consenting patients, on patient education, and on screening.

"This has been very helpful to us to validate our budgets and to actually document any increased effort, as appropriate," Ms. Waldinger said. For example, the increased effort involved in acquainting new industry monitoring personnel with a clinical trial incurs a cost that is documented with the effort tracker system, and this documentation is used to petition the sponsor to increase payment. The effort tracker also provides a metric to justify staffing and workload assignments. "If staff is spending much more time on a study than had been budgeted, they can document how they spent that time, and then we can evaluate if maybe there are non-value-added steps, or if, in fact, that time was legitimately spent," Ms. Waldinger said.

In the discussion following the presentation, Ms. Linda Beekman, administrative director of clinical research at the University of Michigan Comprehensive Cancer Center, noted that an initial analysis of 67 trials whose budgets were determined using an effort tracker found that only 5 of them went over budget. But those studies had just recently opened

and had incurred significant start-up costs, so the over-budget costs were potentially overstated. If those nascent studies were taken out of the analysis, the budgets for the remaining studies were more than 95 percent accurate, she said.

In response to a question raised after her presentation, Ms. Waldinger noted that there was initial resistance from staff to having to continually document their time with the effort tracker, and some staff found the activity demeaning. But, she said, "They are our employees, so they really don't have a choice in the matter. Our vantage point is that lawyers, accountants, and very high-priced consultants do this," she said. In fact, many employees now appreciate the effort tracker, because it documents efforts on clinical trials that were previously underestimated, thereby validating employee complaints that more time is needed to do the work.

She suggested that administrators implement effort trackers or similar data systems that can assess budgeted versus actual costs and provide real cost data that can aid negotiations with sponsors. Those negotiations should be done by experienced professionals who are assertive and knowledgeable about all the costs linked to a clinical trial. Ms. Waldinger noted that most physicians are not trained in budgeting and budget negotiations, and many times their interest in conducting a trial trumps their attention to related costs, especially since most of those costs are not obvious. The University of Michigan Comprehensive Cancer Center saw an increase in its clinical trials budgets when it changed personnel three years ago to hire staff who were experienced in clinical trials finance and negotiation.

Another helpful tool that is increasingly being used to assess clinical trial costs, according to Ms. Waldinger, is "value-stream mapping," which is similar to the process map analysis Dr. Dilts presented earlier. In value-stream mapping all the steps involved in a clinical trial are mapped, including the steps of regulatory agencies, and the "value-added" and "non-value-added" steps are identified and quantified. Another useful graphic is one that depicts a "circle of influence." Used as a tool to reach consensus and prioritize where to devote energy and resources, the circle of influence graphic outlines what is within the control or influence of participating parties in a clinical trial process (Figure 3).[29]

In the remainder of her talk Ms. Waldinger discussed tools and strategies for improving the efficiency of clinical trials as well as what she called "cost-out" solutions. One tool that has greatly improved the efficiency of University of Michigan clinical trials is a homegrown electronic medical record search engine with the acronym EMERSE. This search engine is the equivalent of a Google search engine for electronic medical records,

[29]The "circles of influence" concept was adapted from Covey (1989).

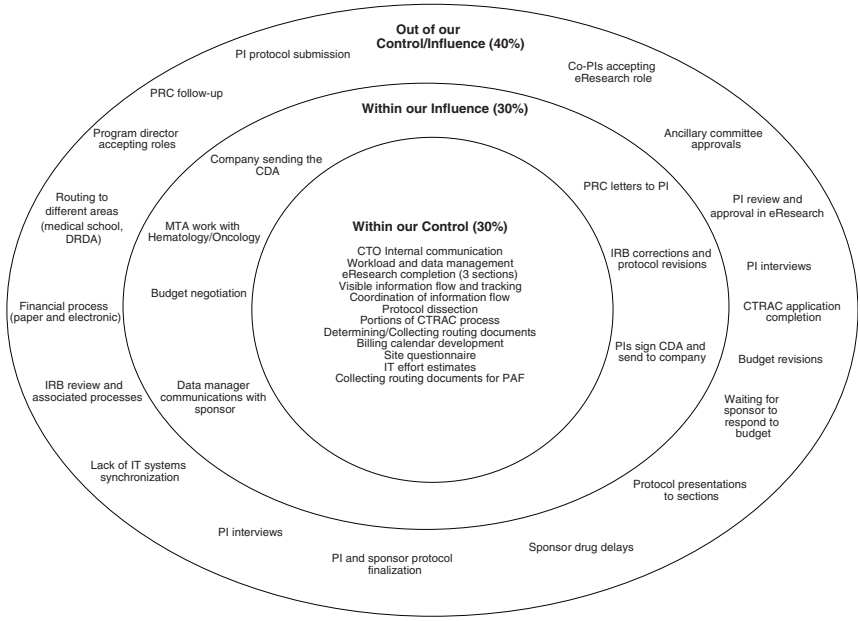

FIGURE 3 The circles of influence. The graphic demonstrates that only 30 percent of clinical trial activities are within the control of the Clinical Trials Office, while another 30 percent of activities are within the influence. Forty percent of clinical trial activities are outside the Clinical Trials Office's control or influence. App = application, CDA = confidential disclosure agreement, Co-Is = Co-investigators, CTO = Clinical Trials Office, CTRAC = Clinical/Translational Resource Allocation Committee, DRDA = Division of Research Development and Administration, Hem/Onc = Hemotology/Oncology, IRB = institutional review board, IT = information technology, Mgr = manager, MTA = materials transfer agreements, PAF = proposal approval form, PI = principal investigator, PRC = protocol review committee, syncing = synchronization.
SOURCE: Waldinger presentation (July 2, 2008) and adapted from Montague, S. 2000. *Circles of influence: an approach to structured, succinct strategy*. http://pmn.net/library/Circles_of_Influence_An_Approach.htm (accessed January 6, 2009). Reprinted, with permission, from *Circles of influence: An approach to structured, succinct strategy*. Copyright 2000 by Performance Management Network, Inc.

Ms. Waldinger said, and it can help staff to quickly determine patient eligibility for clinical trials and manage the data of those trials. "This tool has been really helpful for our data managers to rapidly access salient information," she said. "Instead of having to pore through the electronic medical record, they can just type the word 'stage' or 'disease progression'

or 'tamoxifen,' and every case where that term exists pops up." She added that data management staff at the University of Michigan Comprehensive Cancer Center reported in a recent EMERSE user satisfaction survey that the search engine saved them as much as two hours a day.

Ms. Waldinger suggested using an effort tracker or similar system to determine the hidden costs related to screening activities and screen failures. Echoing earlier suggestions, she also stressed the importance of reducing the number of open trials with no or minimal accruals so that staff time can be devoted to more productive trials. Using effort tracker data, Ms. Waldinger created a chart of the annual costs incurred by clinical trials that accrue two or fewer patients (Figure 4). But, as Dr. Comis later noted, this chart did not include the $5,000 to $8,000 of start-up costs that have been documented in other studies, and that amount should be added in to her calculations when assessing the costs of low-accruing studies.

In addition, Ms. Waldinger suggested using the lowest-cost provider to conduct the various tasks in a clinical trial. "We have quite a lot of circumstances in all of our cancer centers where physicians are doing work that nurses could do and nurses are doing work that data managers should be doing," she noted. Clinical trials could also be more efficient if the forms required by industry sponsors were simplified and standardized, she suggested.

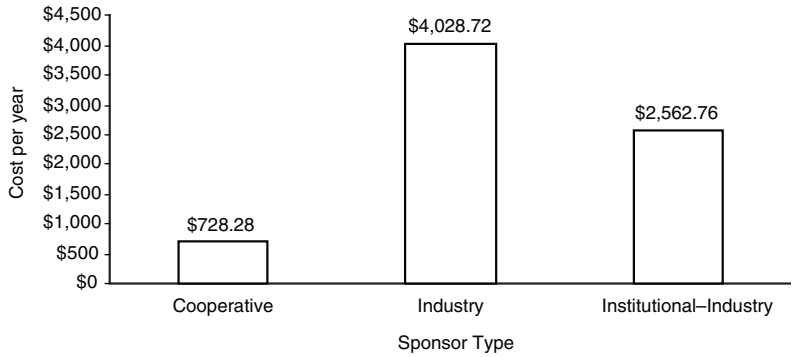

FIGURE 4 Average cost per active year for low-accruing studies. Annual costs incurred by clinical trials that accrue two or fewer patients, including data management and regulatory expenses. Figure does not include research nursing, start-up, or long-term follow-up costs.
SOURCE: Waldinger presentation (July 2, 2008).

REGULATORY COSTS

The next speaker, Dr. Maurie Markman, vice president for clinical research at the M. D. Anderson Cancer Center, addressed the impact of regulatory compliance on conducting clinical research. Much of the regulation of clinical trials is aimed at patient safety concerns, and Dr. Markman raised the issue of whether clinical trials have therapeutic intent. The supposed lack of therapeutic intent of clinical trials prevents insurance reimbursements and underlies the lengthy consent forms and IRB reviews, he said, yet most patients opt to participate in clinical trials and most physicians place them in those trials because they hope it will benefit them. "There is an extensive body of ethical literature that says that patients, through their doctors, are somehow misinformed or do not understand because there is no therapeutic intent in much of what we do, certainly in the Phase I area," he said (Glannon, 2006; Henderson et al., 2007; Joffe et al., 2001). "I would reject that argument absolutely." He suggested that this issue be explored further by the IOM. Later in discussion, a participant pointed out that FDA guidelines specify that Phase I trials merely determine the toxicity and dosing of an experimental drug and that the main difference between Phase I and II trials is the therapeutic intent of the latter.

Dr. Markman also discussed the enormous costs linked to carrying out recent regulatory decisions. The OHRP recently ruled that if, during the course of a clinical trial, substantial new toxicity comes up, it is no longer sufficient for an investigator or other provider on the research team to inform new patients verbally about this toxicity. Instead, the clinical trial has to be reviewed again by the IRB at the local institution and the written consent form modified accordingly (Abrams and Mooney, 2008; Goldberg, 2008b). "This could take months," Dr. Markman said. In addition, Medicare now requires Healthcare Common Procedure Coding System (HCPCS) modifiers to distinguish between routine care costs and those associated with an investigational clinical service when billing for patients involved in clinical trial research (CMS, 2008b). "Effective April 2008, every line item, every bill, every single test that you send on any Medicare patient has to have a modifier to say if the routine care cost is part of the trial or not part of the trial. Why are they doing this?" Dr. Markman asked. "Is this how we should really be spending our health care dollars?"

In a subsequent presentation, Dr. Fitterman answered that question by saying that changes to the HCPCS modifier requirements were instituted, in part, to enable CMS to assess the likely costs of its beneficiaries participating in clinical research so that in the future those costs might be incorporated into the prospective payment that is provided to the Medicare Advantage organizations. This would prevent beneficiaries of these

plans from having to make 20 percent copayments of the high costs that are often linked to clinical trials and, in theory, should foster more of their participation in those trials.

Dr. Markman said that research-for-hire regulations complicate research contracts and funding. Internal Revenue Service (IRS) tax laws prevent academic institutions with tax-exempt bonds from doing research for hire, he explained. To ensure that a cooperative group is not a research-for-hire institution used by industry to run its clinical trials, it must retain the intellectual property rights that result from the trials it conducts. Consequently, there can be months of negotiations between cooperative groups and industry sponsors, Dr. Markman said, so that "if someone audited those contracts at the level of the IRS, they would not conclude that you were doing research for hire. If that were the conclusion, all tax-exempt bonds would be lost."

Negotiations can also be lengthy, because both industry and cooperative groups want to retain the ownership and use of biological specimens collected during an industry-sponsored trial, because they might be useful for future studies. "This can add months and can potentially kill studies from ever being activated," Dr. Markman said. He suggested that stakeholders under the sponsorship of the NCI or the IOM should work together to craft a common agreement on the use and ownership of biological specimens and intellectual property and to resolve research-for-hire concerns. "If there can be national agreement on that, this could save an enormous amount of time and effort and cost," he said.

A final issue Dr. Markman raised is the new federal law that requires all clinical trials, including industry trials, to be registered on a publicly accessible site.[30] The law also mandates timely reporting of study results, but it is not clear how this will be implemented and who will have responsibility for reporting data from multi-center trials or from industry-sponsored trials. "The IOM could play a role in trying to help establish what the criteria will be for getting this information out to the public," he suggested. He also reiterated the concern that industry sponsors are increasingly requiring cooperative group institutions to assume the major regulatory responsibility for registration trials. This is a costly responsibility that should be recognized and reimbursed, he said.

In the discussion that followed Dr. Markman's talk, a participant suggested that to ease compliance with the new labeling mandate from Medicare, cooperative groups should provide a guide to their sites that specifies for each protocol what tests and procedures are considered part of routine care within or outside of the clinical trial. But Dr. Comis responded that cooperative groups do not have the resources to do this.

[30]See http://clinicaltrials.gov.

He added that his studies estimate that regulatory costs make up 35 percent of the total costs of a clinical trial.

CMS PERSPECTIVE

The next speaker, Dr. Leslye Fitterman, epidemiologist in the Office of Clinical Standards and Quality at CMS, explained the intricacies of the agency's coverage of clinical trial costs for its beneficiaries. Prior to 2000, she said, CMS beneficiaries were not even allowed to participate in clinical trials. Recognizing the need for this elderly population to have access to cutting-edge treatments, Medicare made a national coverage determination that took effect in 2001, which mandated that CMS cover the routine clinical care costs of its beneficiaries who participate in clinical trials, assuming that benefit categories for those costs already were established. Non-covered items and services include the specific technology being investigated, completion of case report forms, and any other services provided free of charge to other participants in the trial (CMS, 2008a).

In this coverage determination CMS defined routine clinical care costs as those falling within three categories:

- Conventional care that would be provided to the patient whether or not the patient was participating in a clinical trial;
- Care involved in administering a treatment and monitoring that treatment for adverse events; and
- Care linked to diagnosing and treating complications from adverse events.

There are still inconsistencies in coverage, Dr. Fitterman said, because each CMS contractor is allowed to determine whether or not an item or service is considered standard of care in its area and whether tests or procedures called for by the study protocol are necessary and reasonable. There is no national consensus on this issue, she said.

Another problem with the CMS clinical trial policy is that it did not account for the disincentive toward participating in clinical research that beneficiaries of Medicare Advantage Plans face. These plans reimburse providers on a fee-for-service basis and require 20 percent copayments by beneficiaries. Many beneficiaries cannot afford the copayments for the expensive drugs often used in clinical trials.[31] In addition, the masking of participants and providers in clinical trials is hampered by the obvious

[31]Although experimental drugs are often provided free of charge to participants, many trials combine these drugs with already licensed drugs, for which Medicare Advantage Plan beneficiaries must pay 20 percent.

differences in copayments for reimbursements between the investigational items and services among Medicare Advantage beneficiaries.

In 2005 Medicare made a national coverage determination that covered the off-label use of four anti-cancer drugs (NCI, 2008a). The coverage, however, was restricted to nine trials that were sponsored by the NCI. For those trials CMS began a pilot project that it is currently conducting jointly with the NCI aimed at developing tools to facilitate enrollment of Medicare beneficiaries in clinical trials. "We are trying to make things a bit easier and consistent as we can across the country," Dr. Fitterman said. For this project the two agencies developed billing instructions that could be sent to all providers that detailed how to bill for the study drug and other covered drugs and how to bill for tests and procedures. There was explicit information on what costs Medicare would cover, what costs the trial would cover, and what costs the sponsor would cover. In addition, investigators were encouraged to meet with CMS contractors to make sure that they were on the same page as to what Medicare would reimburse.

"These were guidelines to cut down on the confusion and disparity about how people were billing so that claims would get processed," Dr. Fitterman said. In addition, CMS wrote claims-processing instructions for all the contractors. Outreach to beneficiaries and their physicians was also part of the pilot project, which was done with the aid of cooperative groups and national patient advocacy groups in the gastrointestinal/colorectal areas, as the trials were focused on those diseases.

Dr. Fitterman said she was encouraged by an initial analysis that found that, for most of the trials, Medicare-eligible subjects comprised between one-fifth and one-third of the participants currently enrolled (Table 3). Later, during the discussion, Ms. Andrea Denicoff, a nurse consultant in the clinical investigations branch of CTEP in the NCI, said that traditionally only about 13 percent of people enrolled in clinical trials have been aged 65 and older. A little more than three-quarters of Medicare-eligible participants are using Medicare to cover their clinical trial costs in the pilot project, Dr. Fitterman noted. She suspects that the remaining Medicare-eligible patients are instead using some other supplemental insurance.

In 2007, the CMS clinical trial policy was modified to clearly state that if an investigational drug or other item is covered outside of the trial, it will also be covered in the trial. In addition, the policy was expanded to include Coverage with Evidence Development, which enables CMS to cover a medical intervention conditional on the agency's concurrent collection of data on the intervention while reimbursing it.[32] Beneficiaries

[32]See http://www.cms.hhs.gov/clinicaltrialpolicies.

TABLE 3 Enrollment by Age and Use of Medicare

Study ID	Total Accrual (as of 3/31/08)	Total Subjects Medicare Eligible (%)	Total Medicare Subjects Using Medicare
C80405	1,279	444 (34.7)	371
E2204	130	45 (34.6)	34
E4203	108	38 (35.2)	24
E5202	1,041	387 (37.2)	277
E5204	184	24 (13)	20
NSABP-R-04	851	246 (28.9)	175
RTOG-0522	503	109 (21.7)	98
S0502	Opened 4/15/08	—	—
7325	8	2 (25)	0

SOURCE: Fitterman presentation (July 2, 2008) and Cancer Therapy Evaluation Program Clinical Data Update System, http://ctep.cancer.gov/reporting/cdus.html.

can receive the item or service only if they are participating in a clinical research study or if they are in a specified registry.

In the discussion that followed Dr. Fitterman's presentation, a participant said that he was unable to accrue 200 Medicare patients to a clinical trial, because the patients had Medicare Advantage Plans. "A lot of these trials use a combination of an investigational agent that would be supplied by the sponsor and a licensed drug that is not being supplied by the sponsor," the participant said. "The latter becomes the deal breaker, because those are very expensive also." Dr. Fitterman said that she recognizes this is a problem and suggested a legislative movement to have Congress address the issue, along with the Office of the Actuary and the Part C program reviewing the issue internally.

PRIVATE HEALTH INSURER PERSPECTIVE

The last speaker at the workshop was Dr. Lee Newcomer, senior vice president of oncology at UnitedHealthcare. He provided the private insurance company's perspective on covering the costs linked to clinical trials. He began his talk by noting that, historically, insurance companies were reluctant to cover experimental treatments, because they were trying to prevent coverage of quackery. That reluctance evolved into a general exclusion of therapy lacking experimental evidence of effectiveness, he said. "The paradox here, of course, is how do you generate evidence without a clinical trial?"

Dr. Newcomer said that he is convinced of the value of clinical trials in providing evidence for a highly specific treatment plan. "There is an awful lot of variation in clinical practice, and a clinical trial narrows

that variation to a very discrete practice," he said, noting that a clinical trial provides a very standardized protocol—a defined treatment plan—for patients. This definition of good care that clinical trials provide aids UnitedHealthcare's coverage decisions. However, there are still looming policy concerns related to coverage of clinical trial costs, Dr. Newcomer said. These policy concerns include:

- defining experimental treatment and its scope;
- the need for cost-effective analyses in clinical trials;
- an excessive number of "me too" trials;
- payment for off-label drugs used in trials; and
- whether observational trials can substitute for randomized controlled trials.

The term "experimental" is rather vague, Dr. Newcomer said, and it is difficult to define what should be covered within the clinical trial space. Particularly problematic is scope creep, whereby an insurance company will cover an experimental drug offered within a trial and then be expected to also cover it when the same drug is used to treat patients outside of the trial before the drug is approved for the specific indication being tested. "I'm hearing an increasing number of complaints about this from practicing oncologists," Dr. Newcomer said. "It has been a major friction point and barrier to getting more coverage for clinical trials."

Clinical trials not only can indicate what treatments are effective but also can show what treatments are cost-effective. For example, Dr. Scott Ramsey utilized data from a cooperative group clinical trial to show that a recommended therapy for lung cancer was about $12,000 more expensive than an alternative therapy that the trial showed was just as effective (Ramsey and Kessler, 2002). "This is going to be very important information as we move forward, because we have to address cost," Dr. Newcomer said. "Not only should we know which therapy is more effective, but we should know what it costs to gain that extra benefit or value so that we can make decisions about what we should cover."

He was critical of what he called "me too" clinical trials that duplicate other studies excessively. He noted that at one time there were 42 open trials testing high-dose chemotherapy with bone-marrow transplantation for breast cancer, but only three of those were published—a tremendous waste of resources, time, and effort, he said. Often those "me too" studies are done by academics hoping that they will boost their tenure status more than large multi-center trials would, because little credit is given for team research, Dr. Newcomer said. "We have to figure out how to change that so that young investigators can still advance their careers without creating one of these 'me too' trials that really does not add anything to the knowledge base," he said.

Dr. Newcomer also explained why insurers are reluctant to pay for an already approved drug that is used within a clinical trial, as often happens when it is a combination of cancer drugs and not the individual drugs themselves that is being tested for effectiveness. Referring to the industrial drug sponsor in such a trial, he said "Here is a company that is already making a profit on this drug in the 20 to 25 percent range. Why should we be providing support for its next off-label indication? That's the cost of doing business, and they should be providing the drug free in the trial scenario." Industry sponsors rarely pay this cost, however, Dr. Newcomer said.

The increased cost of covering clinical trials is another issue that Dr. Newcomer discussed. Actuaries at UnitedHealthcare estimate that only about 93 cents out of its monthly $200 premium is for clinical trial coverage. But studies suggest that each premium increase of only 1 percent prompts hundreds of thousands of people to suspend their insurance coverage.[33] "Costs are getting unaffordable, and the way ERISA recipients will think about this is, 'Okay, you just added another buck a month for every employee I have,' and some people will drop out of the insurance system because of that," Dr. Newcomer said. "You have to have a very good argument to help them understand why it's worth paying for."

Dr. Newcomer expressed skepticism about clinical trials that use people with few health complications to test experimental treatment, because these people do not represent what is seen in the "real world." He also questioned what he called the "tyranny of the randomized controlled trial." The randomized, controlled trial is considered the gold standard, but given the problems with sufficient patient accrual—which are caused, in part, by patients not willing to be put into a control arm of a study—Dr. Newcomer suggested using well-run observational studies instead. These studies tend to be less expensive to run, quicker to accrue, and often provide results comparable to a randomized, controlled trial. He showed a graph from one study that supported this point (Figure 5) but added that "who you enter in those observational trials has to be carefully controlled in order to get legitimate results."

Dr. Newcomer also discussed a few operational issues, such as the difficulties his company has in identifying trial enrollees and the experimental component of trials for payment purposes as well as the difficulties in identifying who should pay for clinical trial costs when individuals have coverage determined by a mosaic of insurance carriers, state regulations, and employer plans. Insurers must also determine which types of trials qualify to be covered. UnitedHealthcare covers all clinical trials sponsored

[33]Estimates for the drop in insurance coverage range from 164,000 (Chernew et al., 2005) to 300,000 (Sheils et al., 1998) per 1 percent increase in premium.

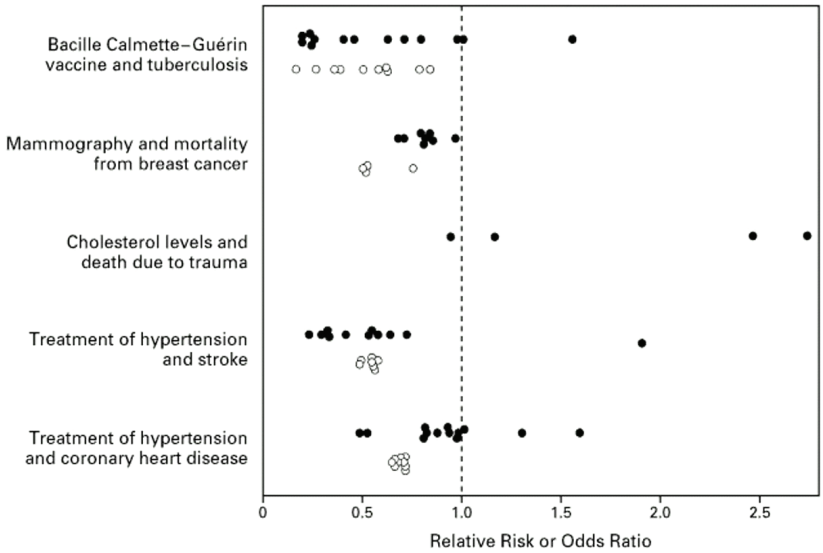

FIGURE 5 A comparison of randomized, controlled trials and observational studies. Solid circles represent randomized, controlled trials; open circles indicate observational studies.
SOURCE: Newcomer presentation (July 2, 2008) and Concato, J., N. Shah, and R. I. Horowitz. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *New England Journal of Medicine* 342(25):1887–1892. Copyright *© 2000 Massachusetts Medical Society. All rights reserved.*

by the NIH, CDC, Agency for Healthcare Research and Quality, CMS, Department of Defense, and the VA. "That's what we use for scope," Dr. Newcomer said, "but I think we could use any help possible in figuring out what would be the right kinds of studies to cover."

Dr. Newcomer concluded his talk with a number of suggestions:

- Eliminate duplication in studies and pursue novel approaches that answer important questions;
- Penalize sites for failure to accrue patients to their trials; and
- Have mandatory publication of negative trials.

Finally, he suggested excluding small "local" trials from coverage. New Jersey has a state law, for example, that mandates coverage for participation in any clinical trial that occurs within the state. "We know we are paying for a lot of one- and two-person trials that never gain any knowledge and are a waste of resources," Dr. Newcomer said.

Summary and Wrap-Up

After Dr. Newcomer's talk, the workshop finished with a general discussion and wrap-up session. Ms. Denicoff opened the discussion by asking if the IOM could work with stakeholders to determine minimum data and accrual standards as well as reporting requirements for both the NCI and industry trials, since sites often do both kinds of trials.

Dr. Mendelsohn responded by suggesting that the NCI take the lead on developing the criteria she suggested. He agreed that cooperative groups are going to be turning more and more to industry for financial support, and he noted a number of advantages that the cooperative groups offer industry, including diversity of subjects, numerous sites, and tissue banks that enable the genetic studies underlying personalized medicine. He suggested that the leaders of cooperative groups and large pharmaceutical companies come together to decide what studies are best run by cooperative groups and what studies are best run by industry. "That way we might be able to cut down the number of trials that the cooperative groups do and let them focus where they can provide the greatest value," he said.

Dr. Canetta suggested that cooperative groups conduct more Phase II trials, which are in great demand given the current era of targeted therapy, time to progression endpoints, and new toxicities linked to these novel molecules being tested.

Dr. Louis Weiner, director of the Lombardi Comprehensive Cancer Center, chair of the Department of Oncology, associate vice president of Georgetown University Medical Center, and clinical director of cancer

services at Georgetown University Hospital, brought up the clinical methods training workshops run by ASCO and the American Association for Cancer Research (AACR). In these workshops, a fellow or junior faculty member with no or limited experience writing clinical trials develops, within a week, a completed protocol after receiving feedback from biostatisticians and faculty. The protocols that emerge are generally high quality, he said, and most are ultimately executed. "For some of the high-priority Phase III types of studies that we are trying to do, a similar type of approach could be used where you actually bring together all the relevant stakeholders, including empowered representatives from the relevant sponsor, cooperative group setting, biostatistics, and regulatory agencies, and craft the protocol within a compressed timeline," he suggested. "I believe it could be done if the various stakeholders were empowered to actually make decisions on behalf of their relevant agencies within predefined parameters."

Dr. Baker responded that the idea should be examined further and is worth developing. Dr. Mendelsohn said, however, that traditionally the cooperative groups take pride in being the training ground for young investigators, and Dr. Weiner's idea "pushes them aside and pulls in the super-pros to do the job quickly. There are losses there, and we have to balance what the goals of the cooperative group are."

Dr. Canetta repeated the need for standardized case-report forms that can be used by the entire research community. "We need to sit around the table and reach an agreement," he said, adding that the FDA's participation in this process would be valuable.

Dr. Doroshow responded that there has been progress in the development of electronic case-report forms. These have been developed by the NCI with input from the FDA and industry. Currently there are 10 different modules in various stages of being vetted. "There is hope that over the next year that development, plus the electronic data-capture modules, will be helpful to everyone trying to unify what we do," Dr. Doroshow said.

Dr. Aisner brought up what he views as examples of wasted resources in clinical trials. Trials that compare an agent known to be toxic and ineffective with a treatment arm in which this relatively worthless treatment is added to another agent are one example of such wasted resources, he said. Non-inferiority trials, "where the object of the trial really is how little can we do to do as badly as we have done," are another example.

Another participant raised the concern that cooperative group trials would be limited to sites with the highest accruals, as this would eliminate a number of sites that accrue minorities or patients in rural areas.

POSSIBLE PATHS FORWARD

Throughout the workshop, whether the topic discussed was related to the cooperative groups or another infrastructure for clinical trials, or relevant to physicians, academics, or patients, the same themes arose again and again, as Dr. Mendelsohn noted in his summary remarks. In these remarks he recognized that the NCI-sponsored cooperative groups have made important contributions to improving treatment of cancer through trials that have led to new drug approvals and supplemental approvals for use of drugs off of the original label, that have established the efficacy of various combinations of agents and modalities, and that have led to various other achievements as well. On the other hand, he also observed that, during the workshop, representatives of cooperative group leadership, the NCI, academic institutions, the CCOPs, industry, and insurance payors all expressed concern that cooperative group clinical trials are often inefficient, slow, and wasteful of clinical researchers' time. Many participants also stressed the inadequacy of funding for the Cooperative Group Program. Dr. Mendelsohn noted that there was general agreement among the participants that the problems with the Cooperative Group Program had reached crisis proportions and that all stakeholders would need to participate in corrective measures. "Each of the participating sectors can make changes that will improve these deficiencies," he said. He then reviewed many of the potential action items suggested by speakers over the course of the workshop (Box 6).

In addition, he said, there were a number of areas in which the viewpoints of workshop participants clearly varied. These areas included the need to ensure adequate numbers of trials, collaboration with industry, IRB issues, and globalization of the clinical trials enterprise. While many participants saw a need to decrease the number of clinical trials in the pipeline in order to focus resources on the most important trials, others argued that decreasing the number of trials could further exacerbate problems of accrual if it meant that fewer types of cancer would be addressed, including rare cancers. There was general agreement that collaboration with industry helps stretch the modest resources of the Cooperative Group Program, but many expressed concern that such collaboration results in restrictions on the publication of data. There was little agreement on how to address problems with IRBs, especially in light of the different types of IRBs engaged in the process: locally based IRBs, the NCI-based central IRB, and private, commercial IRBs. Finally, in an era of increasing globalization, clinical research institutions face loss of industry collaboration as more clinical trials are conducted overseas, and, for cooperative groups collaborating with industry, streamlining the data

BOX 6
Potential Action Points Suggested by Speakers

The following were suggested as potential action points by speakers, as summarized by the conference planning committee chair, Dr. John Mendelsohn, and the chair of the National Cancer Policy Forum, Dr. Harold Moses. Conference participants suggested many different ideas, but the ones listed here appeared to garner significant support from participants across various stakeholder types, according to the chairs. The action points are organized according to the organizations that would undertake them.

Cooperative Groups

- Reduce the number of trials. "Just say no" to trials that are not excellent or that undergo excessive debate and revision.
- Stop "tweaking" and recycling revisions of trials.
- Seek increased industrial support of trials exploring a new agent.
- Eliminate outdated criteria for eligibility for a clinical trial (previous treatment, previous malignancy).
- Eliminate sites that enroll few patients.
- Consider increasing randomized Phase II trials and reducing Phase III trials.

National Cancer Institute

- Reduce CTEP-sponsored reviews of clinical trials, especially when they do not involve a new unapproved agent. There are too many reviewers with veto power in developing a protocol.
- Reduce overlapping audits of clinical research units.

collected is made even more difficult by the need to satisfy the regulatory requirements of multiple regulatory agencies around the world.

Dr. Moses concluded the workshop by noting that the proceedings will serve as an input to an IOM committee that will examine the role of the NCI cooperative groups in the conduct of cancer clinical trials and generate consensus conclusions and recommendations.

- Expect that recipients of payment for participation in cooperative group trials meet metrics for accruals and data reporting, and reward those who surpass the metrics with larger payments.
- Standardize data collection using an electronic format.
- Include credit for cooperative group trials in the review of Cancer Center Support Grants.

Federal Government

- Pass laws that provide reimbursement for the standard-of-care costs of clinical trials by CMS and by ERISA plans.
- For new, marginally active drugs and drugs approved based on response or time to progression, consider a policy that requires participation in a clinical trial in order to receive reimbursement for the cost of care, akin to what is done in the United Kingdom.
- Reduce requirements for collecting and reporting data on clinical trials to those essential for evaluating safety and efficacy.
- Reduce the requirements for review involving triple readings of all imaging studies used as endpoints in clinical trials.

Academic Medical Centers

- Recognize the scholarship and research accomplishments of clinical investigators in the promotion and tenure process.
- Recognize collaborative and team research in the promotion and tenure process.
- Provide clinical investigators with resources and time protected for research, in a manner parallel to that provided to laboratory researchers.

This list represents the observations of Dr. John Mendelsohn and Dr. Harold Moses; it does not represent the opinion of the IOM.

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Abbreviations and Acronyms

AACR—American Association for Cancer Research
ASCO—American Society of Clinical Oncology

CALGB—Cancer and Acute Leukemia Group B
CCOP—Community Clinical Oncology Program
CMS—Centers for Medicare and Medicaid Services
CRO—Contract Research Organization
CTEP—Cancer Therapy Evaluation Program
CTSU—Clinical Trials Support Unit

DCTD—Division of Cancer Treatment and Diagnosis at the NCI

ECOG—Eastern Cooperative Oncology Group
EMERSE—Electronic Medical Record Search Engine
ERISA—Employee Retirement Insurance Security Act

FDA—Food and Drug Administration

HCPCS—Healthcare Common Procedural Coding System
HIPAA—Health Insurance Portability and Accountability Act

IND—Investigational New Drug
IOM—Institute of Medicine
IRB—Institutional Review Board

NCCTG—North Central Cancer Treatment Group
NCI—National Cancer Institute
NCPF—National Cancer Policy Forum
NCRN—National Cancer Research Network
NDA—New Drug Application
NHS—National Health Service
NSABP—National Surgical Adjuvant Breast and Bowel Project

OHRP—Office for Human Research Protections

PAIR—Patient Advocates in Research

RTOG—Radiation Therapy Oncology Group

SAE—serious adverse event
SPORE—Specialized Programs of Research Excellence
SWOG—Southwest Oncology Group

VA—Department of Veterans Affairs

Glossary

Accrual—the enrollment of qualified patients into clinical trials.

Accrue—to enroll qualified patients into clinical trials.

Adjuvant therapy—medical treatment given in addition to a primary treatment. In the case of cancer, this can be chemotherapy, radiation, or hormone therapy given in addition to surgical removal of a tumor, for example. Adjuvant therapies are used to enhance the effect of primary treatment, and would not necessarily be expected to have therapeutic effect in the absence of the primary treatment.

Adverse event—any negative or unwanted effect from a drug, device, or medical test.

Bevacizumab (Avastin)—a monoclonal antibody drug used to treat metastatic cancer of the colon or rectum, usually in combination with 5-fluorouracil–based chemotherapy. Bevacizumab is also used in the treatment of advanced, recurrent, or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel, or other cancer drugs, and metastatic HER2-negative breast cancer, in combination with paclitaxel.

Biospecimen bank—a facility that collects, catalogs, and stores samples of biological materials (such as urine, blood, tissue, cells, DNA, RNA, and protein) used for laboratory research.

Biostatistics—the use of statistics to analyze biological or health science data.

Cetuximab (Erbitux)—a monoclonal antibody drug used to treat advanced or metastatic cancer of the colon and rectum, usually in combination with chemotherapy or irinotecan, another cancer drug. It is currently being used in research trials for treatment of head and neck cancers.

Contract research organization—an organization that offers a range of clinical trial–related services, including development of protocols, patient recruitment, collection and analysis of data, and preparation of regulatory documents.

Cooperative agreement—an administrative and funding instrument utilized by federal agencies to provide assistance to award recipients. Unlike grants, cooperative agreements are utilized when substantial governmental involvement is expected.

Cooperative group—the collection of researchers, cancer centers, academic medical centers, community hospitals, private research institutions, and community physicians who organize to design and implement clinical trials to study new cancer treatments, methods of cancer prevention and early detection, and quality of life issues. The cooperative groups are administered by the NCI, and are organized around specific diseases, treatment modalities, or geography.

Employer self-insured plan—a health plan in which the employer assumes the financial risk of providing health care benefits to its employees.

Erlotinib (Tarceva)—a drug used to treat locally advanced or metastatic non-small cell lung cancer and other cancers. Like gefitinib, it targets epidermal growth factor receptor tyrosine kinase, and specific genetic mutations correlate to patients' response to the drug.

Gefitinib (Iressa)—a drug used to treat locally advanced or non-small cell lung cancer and other cancers. Like erlotinib, it also targets epidermal growth factor receptor tyrosine kinase, and specific genetic mutations correlate to patients' response to the drug.

Grade 1 toxicities—mild adverse events.

Grade 2 toxicities—moderate adverse events.

Grade 3 toxicities—severe adverse events.

Grade 4 toxicities—life-threatening or disabling adverse events.

HCPCS—The HCPCS (Healthcare Common Procedure Coding System) is a standardized coding system that identifies products, supplies, and services in order to bill payors (such as CMS or insurance companies).

HCPCS modifier—An HCPCS code descriptor utilized to provide additional information regarding the service or item identified by the HCPCS code, including specific circumstances that may apply to the service or item.

Investigational New Drug (IND)—A new molecular, antibiotic, or biological drug that is used in a clinical investigation. It also includes a biological product used *in vitro* for diagnostic purposes.

J-Code—An HCPCS code used to bill payors (such as CMS or insurance companies) for drugs. A J-code, as opposed to another letter code (i.e., A-code or B-code), generally signifies an injectable drug that cannot be self-administered.

Lean process—a process improvement strategy designed to optimize workflow, reduce waste, and streamline business processes.

Medical informatics—an integrative discipline concerned with the acquisition, storage, and use of information in the health and biomedical domain.

New Drug Application (NDA)—FDA process to approve new pharmaceuticals for sale and marketing in the United States based on efficacy and safety.

Pathology quality assurance—a system of quality control activities that promote consistency and accuracy across collection, analysis, and classification procedures in pathology.

Phase I trial—a clinical trial in a small number of patients in which the toxicity and dosing of an intervention are assessed.

Phase II trial—a clinical trial in which the safety and preliminary efficacy of an intervention are assessed.

Phase III trial—a large-scale clinical trial in which the safety and efficacy of an intervention are assessed in a large number of patients. The Food and Drug Administration generally requires new drugs to be tested in Phase III trials before they can be put on the market.

Phase IV trial—a large-scale trial undertaken after FDA approval for safety surveillance to detect rare or long-term adverse events. Also known as a post-marketing surveillance trial.

Process map—a visual representation of a workflow comprising a stream of activities that transforms a well-defined input or set of inputs into a pre-defined set of outputs.

Protocol—a study plan on which a clinical trial is based. The plan is designed to safeguard the health of participants as well as answer specific research questions. A protocol describes what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study.

***Ras* gene—**a gene encoding for a signal transduction protein that has been found to cause cancer when the gene is altered (mutated). Agents that block its activity may stop the growth of cancer.

Serious adverse event (SAE)—an untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Special Protocol Assessment—An industry-initiated 45-day review process in which the FDA evaluates a clinical trial protocol before the trial is begun. The purpose of the special protocol assessment is to determine whether the clinical trial protocol will sufficiently address scientific and regulatory requirements for the planned new drug application (NDA) or biologic license application (BLA).

Tamoxifen—a drug used to treat certain types of breast cancer, and to prevent breast cancer in women who are at high risk of developing breast cancer. Tamoxifen is an antiestrogen, blocking the effects of the estrogen hormone.

Targeted therapy—a type of treatment that uses drugs or other substances (such as monoclonal antibodies) to identify and attack cancer cells with-

out harming normal cells. Targeted therapy may be less harmful to normal cells than other types of cancer treatments.

Translational research—the translation of novel findings obtained from scientific medical research into testable hypotheses for evaluation in clinical trials in human subjects.

Value-stream mapping—a lean process visualization technique used to analyze the flow of materials and information through a system. The goal of value-stream mapping is to understand and streamline the work processes by reducing waste, or activities that do not add value.

Appendix A

Workshop Agenda

National Cancer Policy Forum
Workshop on
Multi-Center Phase III Clinical Trials
and NCI Cooperative Groups

The Keck Center of The National Academies
Room 100
500 Fifth Street, NW
Washington, DC 20001

Agenda
July 1–2, 2008

Day 1: July 1, 2008

Welcome and Opening Remarks
8:00 am – 8:30 am

John Niederhuber, NCI

Session 1: Organization of the NCI clinical trials system and operation of Phase III clinical trials
8:30 am – 12:45 pm

- Session 1A: Organization of the NCI clinical trial system trials system
  8:30 am – 11:00 am

  Moderator: David Parkinson, Nodality, Inc.

  Jeffrey S. Abrams, NCI
  "NCI's Clinical Trials Program"

Jan C. Buckner, Mayo Clinic
"Mayo Clinic and North Central Cancer Treatment Group: An Academic-Community Partnership"
Walter J. Curran, Jr., Winship Cancer Institute, Emory University
"Organization of the Radiation Therapy Oncology Group"
David M. Dilts, Vanderbilt University
"Activating & Opening Oncology Clinical Trials: Process & Timing Analysis"
Richard L. Schilsky, University of Chicago, Cancer & Leukemia Group B
"Rising to the Challenge of Rapid Protocol Activation"

BREAK
11:00 am – 11:15 am

- Session 1B: operation of phase III clinical trials
  11:15 am – 12:45 pm

  Moderator: Richard L. Schilsky, University of Chicago

  Robert M. Califf, Duke University
  "Organization of Multi-Center Trials: Are Oncopolitics Different than Other Clinical Research Politics"
  Renzo Canetta, Bristol–Myers Squibb
  "Industry-Sponsored Multi-Center Trials"
  Alan Keller, Cancer Care Associates
  "Multi-Center Clinical Trials in the Community: Models and Methods: What Works, What Doesn't, and Why"

LUNCH BREAK
12:45 pm – 1:30 pm

SESSION 2: PATIENT RECRUITMENT AND PHYSICIAN PARTICIPATION
1:30 pm – 5:15 pm

- Session 2A: panel on academic challenges
  1:30 pm – 3:00 pm

  Moderator: John Mendelsohn, M. D. Anderson Cancer Center

Academic Panel:
Laurence H. Baker, Southwest Oncology Group and The University of Michigan
"Southwest Oncology Group View of Barriers to Cooperative Group Accrual"
Gordon R. Bernard, Vanderbilt University
"Cancer Clinical Research: The Institutional Perspective"
Michael A. Caligiuri, The Ohio State University Comprehensive Cancer Center – James Cancer Hospital
"Access to Clinical Trials: Impeding the Insured"
Allen S. Lichter, American Society of Clinical Oncology
"The Pitfalls of Career Advancement for the Clinical Trialists: A Decanal Perspective"

Panel Discussion

BREAK
3:00 pm – 3:15 pm

- Session 2B: other perspectives
  3:15 pm – 5:15 pm

Moderator: Hal Moses, Vanderbilt University

Stephen S. Grubbs, Delaware Christiana Care CCOP
"CCOP Clinical Trials Contributions and Challenges"
John E. Feldmann, Moses Cone Regional Cancer Center
"Community Cancer Centers: The Crisis in Clinical Trials"
Richard Kaplan, National Cancer Research Network, United Kingdom
"Publicly Funded Cooperative Groups Working with Industry"
Deborah Collyar, Patient Advocates in Research
"Connecting Clinical Trials to People"

ADJOURN DAY 1
5:15 pm

Day 2: July 2, 2008

Welcome and Opening Remarks
8:00 am – 8:15 am

John Mendelsohn, M. D. Anderson Cancer Center

Session 3: Data collection standards to establish safety and efficacy
8:15 am – 10:00 am

Moderator: Renzo Canetta, Bristol–Myers Squibb

James H. Doroshow, National Institutes of Health
"NIH Perspective"
Gwendolyn Fyfe, Genentech
"A Perspective on How to Quickly Define Data Standards"
Robert L. Comis, Coalition of National Cancer Cooperative Groups
"The Role of Cooperative Groups in Establishing Safety and Efficacy"

Panel Discussion: James Doroshow, Gwendolyn Fyfe, Robert Comis, and Richard Pazdur, FDA

Break
10:00 am – 10:15 am

Session 4: Costs/Payments
10:15 am – 12:45 pm

Moderator: Robert L. Comis, Coalition of National Cancer Cooperative Groups

Al B. Benson III, Robert H. Lurie Comprehensive Cancer Center
"Cooperative Groups and Cost Analysis"
Marcy Waldinger, University of Michigan Comprehensive Cancer Center
"Cost-out"
Maurie Markman, M. D. Anderson Cancer Center
"Regulatory Compliance: Impact on Patients and Academic Institutions Conducting Clinical Research"

Leslye K. Fitterman, CMS
"CMS Clinical Trial Policy"
Lee N. Newcomer, UnitedHealthcare
"An Insurer's View: Paying for Clinical Trials"

WRAP-UP
12:45 pm – 1:00 pm

John Mendelsohn and Hal Moses

ADJOURN DAY 2
1:00 pm

Appendix B

Workshop Speakers

Jeff Abrams, National Cancer Institute
Laurence Baker, Southwest Oncology Group and the University of Michigan
Al Benson, Robert H. Lurie Comprehensive Cancer Center
Gordon Bernard, Vanderbilt University
Jan Buckner, Mayo Clinic
Robert Califf, Duke University
Michael Caligiuri, Ohio State University Comprehensive Cancer Center
Renzo Canetta, Bristol–Myers Squibb
Deborah Collyar, Patient Advocates in Research
Robert Comis, Coalition of National Cancer Cooperative Groups
Walter Curran, Winship Cancer Institute
David Dilts, Vanderbilt University
James Doroshow, National Institutes of Health
John Feldmann, Moses Cone Regional Cancer Center
Leslye Fitterman, Centers for Medicare and Medicaid Services
Gwendolyn Fyfe, Genentech
Stephen Grubbs, Christiana Care Community Clinical Oncology Program
Richard Kaplan, National Cancer Research Network in the United Kingdom
Alan Keller, US Oncology, Cancer Care Associates
Allen Lichter, American Society of Clinical Oncology
Maurie Markman, M. D. Anderson Comprehensive Cancer Center

Lee Newcomer, UnitedHealthcare
John Niederhuber, National Cancer Institute
Richard Pazdur, Food and Drug Administration
Richard Schilsky, University of Chicago
Marcy Waldinger, University of Michigan Comprehensive Cancer Center

Appendix C

Letter from John Niederhuber, Director of the National Cancer Institute, to Members of the National Cancer Policy Forum

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

JUN 23 2008

Dear Forum Members:

I am pleased to welcome everyone to the National Cancer Policy Forum's Meeting on Multi-Center Phase III Clinical Trials and NCI Cooperative Groups. As we convene today, I know each of us is committed to making every effort to develop the latest scientific advances coming from our laboratories into clearly definable improvements in outcomes of cancer treatment. Over many years, our clinical trials system has served us admirably in that regard—in large part advanced and supported by various cooperative groups.

Today, the very nature of biomedical science is rapidly changing, and as we move from non-specific, broadly toxic chemotherapies to combinations of highly targeted therapies, it has become imperative that our clinical trials enterprise be nimble enough to change, as well. We, as stewards of the nation's health, must look beyond the horizon, in planning how future trials will need to be designed, managed and funded. The clinical trials system must be structured today to meet the challenges and requirements of tomorrow.

I believe that we are faced with two major issues, in terms of designing a future structure for the most effective conduct of clinical research. First, the current system has, over time, become inefficient. It is duplicative, under-funded, and time consuming. Second, the system was designed during an era of non-specific mono-therapeutic and combination chemotherapeutic interventions. We do not have the capacity within the current structure to highly characterize each patient and carefully match that patient profile to the therapeutic combinations designed to target the specifically defined variation(s) that he or she may carry. To address these problems, we will need to design a trials structure that can obtain drug approval and demonstrate safety and benefit, just as the current system does; but it must also be a structure that will have the ability to incorporate multiple, specifically targeted agents optimally matched to the patient.

Current, early phase trials for non-small cell lung cancer (NSCLC) provide a glimpse into the future of translational research: a notion of what we should strive to create as we, at the forum, undertake the redesign of the clinical trials system. The investigation into the various EGFR mutations that affect therapeutic efficacy of the EGFR tyrosine kinase inhibitors has allowed us to specifically target the agents to the mutations known to respond to this therapy. It has led to investigations into mechanisms of resistance; it has allowed the design of agents that may overcome such resistance. My hope is that, by the end of this meeting, we will have identified the building blocks of a system appropriate to this new era of drug discovery, efficacy demonstration, and FDA approval: a new structure that will at least begin to remove the barriers that have been identified.

Page 2 – Forum Members

I am very much looking forward to discussing these ideas with you, and hope that together we are able to address this issue for the benefit of those fighting the battle with cancer, now and in the years ahead.

Sincerely,

John E. Niederhuber, M.D.
Director
National Cancer Institute