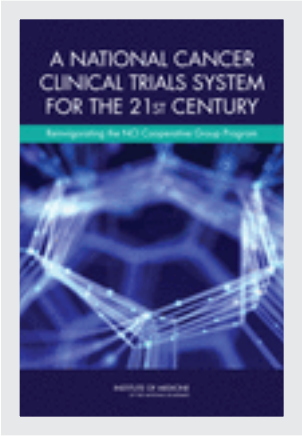

A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program

DETAILS

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A NATIONAL CANCER CLINICAL TRIALS SYSTEM FOR THE 21ST CENTURY

Reinvigorating the NCI Cooperative Group Program

Committee on Cancer Clinical Trials and the
NCI Cooperative Group Program
Board on Health Care Services

Sharyl J. Nass, Harold L. Moses, and John Mendelsohn, *Editors*

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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 thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Harold J. Fallon, Dean Emeritus, School of Medicine, University of Alabama at Birmingham.** 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 authoring committee and the institution.

Preface

Clinical trials that test the safety and therapeutic benefit of drugs and other treatments are essential for developing new and improved therapies for patients with cancer. However, the system for conducting cancer clinical trials in the United States is approaching a state of crisis. Changes are urgently needed if we are to continue to make progress against the second leading cause of death in this country. If the clinical trials system does not improve its efficiency and effectiveness, the introduction of new treatments for cancer will be delayed and patient lives will be lost unnecessarily.

For the past 50 years, the Clinical Trials Cooperative Group Program supported by the National Cancer Institute (NCI) has played a critical role in testing new cancer therapies. The Program comprises a network of cancer centers and community oncology practices across the country that develops cancer clinical trials and enrolls patients in those studies. More than 25,000 patients and thousands of clinical investigators participate in these clinical trials annually. The knowledge gained from the large-scale, multicenter trials conducted by the Cooperative Groups has been instrumental in establishing the therapies that are now routinely used to treat patients with cancer.

Cooperative Group trials have diminished the impact of cancer on many fronts. Most obviously, they have identified superior treatment strategies that have led to longer lives. Findings from pediatric cancer trials, largely carried out by Cooperative Groups over the past four decades, have boosted childhood cancer cure rates from less than 10 percent in the 1950s to nearly 80 percent today. Cooperative Groups have performed the definitive studies of many of the standard treatments for adult cancers as

well and have played a major role in evaluating innovative therapies, such as those targeted to tumors with specific genetic characteristics and those designed to halt tumor growth by blocking the blood vessels that support the tumor rather than by directly killing cancer cells.

In addition to identifying treatments that prolong life, the Cooperative Groups have also given attention to the important issue of quality of life. Many important studies have focused on minimizing the adverse consequences of cancer treatments. A landmark example was the trial demonstrating that breast-conserving surgery plus radiation was as effective at eradicating early-stage breast cancer as radical mastectomy. Other Cooperative Group trials have shown that some less intensive regimens for pediatric cancers could control cancer while reducing the risks of long-term harms from the highly toxic therapies typically used to treat those cancers. Finally, the Cooperative Groups have also addressed cancer prevention. One important trial showed that by taking a drug such as tamoxifen, breast cancer incidence could be reduced by 50 percent for women at high risk for breast cancer over a 5-year period.

Publicly sponsored trials fill an important information void by conducting head-to-head comparisons of different treatment regimens, combining treatments, and investigating whether drugs approved for the treatment of one type of cancer can be used to effectively treat other types of cancer, all of which are far less likely to be pursued by pharmaceutical companies. However, the NCI Cooperative Group Program is falling short of its full potential to improve the quality of care that cancer patients receive. An accumulation of problems is hampering progress, just at a time when new knowledge about the genetic and molecular underpinnings of cancer has created opportunities for designing trials with new, targeted anticancer agents. Increasingly, biomarkers (predictors of a response to a particular therapeutic intervention) can be used to select which treatment strategy is most likely to benefit individual patients.

One major problem is the complex system of designing, reviewing, and initiating Cooperative Group clinical trials, which has become a lengthy and redundant process typically requiring years to complete. In attempting to optimize the effectiveness and safety of trials, proposals often are redrafted and recycled by multiple stakeholders from academic institutions, federal agencies, institutional review boards, and industry. This results in frustration and a perception that stakeholders are working at cross-purposes. In addition, the system lacks an adequate process for prioritizing trials and selecting those most likely to be successful. Finally, when there are long delays in designing and initiating clinical trials, the slow accrual of patients is often the result. Only about 60 percent of NCI-sponsored trials are actually completed and published, which is a terrible waste of human and financial resources.

Another major problem is the inadequacy of NCI funding for Cooperative Group clinical trials. As much as half of the cost of clinical trials today are borne by the clinical investigators and clinical care providers who design and carry out these important studies. Almost universally, investigators are compelled to seek supplemental support from outside sources, such as pharmaceutical companies. The problem is further compounded by the increased costs of trials because of the opportunity to measure biomarkers in a patient's cancer and use them to predict and monitor appropriate therapy. Added to these challenges is the relatively low value placed on Cooperative Group trials by academic institutions in evaluating faculty accomplishments and by the NCI in evaluating Cancer Center achievements; this discourages physician participation. Moreover, the nonexperimental costs of care in clinical trials are not borne by some insurance plans, which significantly hinders patient participation.

In this report, developed at the request of the director of the NCI, an Institute of Medicine committee makes recommendations to address these challenges. Stepping back to gain a comprehensive perspective, the committee took a broad look at the needs and goals of all stakeholders in the current cancer clinical trials system and has made recommendations for changes across the board that will improve the efficiency and effectiveness of the system. Our goal was to preserve the historical strengths of the Cooperative Group Program while recommending improvements to components that are not working well.

Some functions will need to be better integrated, and others must be carried out in parallel rather than in series to reduce the amount of time lost to repetitive steps. The report stresses the need to consolidate functions and processes within the clinical trials network, streamline oversight, enhance collaboration, select and prioritize trials more stringently, fully fund the most innovative and promising studies, and open and complete trials with greater speed. There must also be agreement on strict deadlines that should be met at each step along the way. The committee further recommends (with regret) that the number of trials be reduced if adequate funding to pay for the highest-priority studies is not available.

Changing any particular component of the system will not suffice. All participants and stakeholders, including physicians, patients, and health care insurers, as well as the NCI and regulatory agencies, must reevaluate their combined roles and their contributions to a successful, streamlined process for carrying out Cooperative Group clinical trials that will improve the care of patients with cancer. Collectively, implementation of the recommendations presented in this report will lead to the faster approval and adoption of new therapies, new discoveries upon which to base future studies, and the accelerated translation of new knowledge into beneficial therapies for patients with cancer. The committee also endorses recom-

mendations recently made by NCI's Operational Efficiency Working Group, which aim at achieving similar goals and which are incorporated as an appendix to this report.

The members of the committee wish to express their gratitude to the staff of the Institute of Medicine, with whom we have worked so closely for more than a year. Special thanks are due to Sharyl Nass, whose skills in assimilating information and formulating our proposals into systematic recommendations are unparalleled in our collective experience, and to Erin Balogh, who was instrumental in helping the committee draft the chapters of the report. We hope that our report will stimulate and guide the Cooperative Group Clinical Trials Program to enhance its critical role in advancing treatments for patients with cancer.

John Mendelsohn, *Chair*
Committee on Cancer Clinical Trials and
the NCI Cooperative Group Program

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Contents

Executive Summary

Advances in biomedical research are yielding significant opportunities to improve cancer prevention, detection, and treatment. However, the ability to translate biomedical discoveries into meaningful advances in cancer care depends on an effective clinical trials system. Publicly funded clinical trials play a vital role by addressing questions that are important to patients but are less likely to be top priorities of industry, which has an important primary focus on new drug development and Food and Drug Administration (FDA) registration. For example, companies may have less incentive to

- conduct clinical trials to compare the effectiveness of different treatment options that are already approved for clinical use,
- combine novel therapies developed by different sponsors,
- develop therapies for rare diseases,
- determine optimal duration and dose of treatment with drugs in clinical use,
- test multimodality therapies, such as radiation therapy, surgery, or devices in combination with drugs,
- study screening and prevention strategies, or
- focus on rehabilitation and quality of life following therapy.

The National Cancer Institute (NCI) supports the largest U.S. network for clinical trials of any type. The largest component of that network is the Clinical Trials Cooperative Group Program, which comprises 10 Groups that involve more than 3,100 institutions and 14,000 investigators who

enroll more than 25,000 patients in clinical trials each year. The results of Cooperative Group trials have steadily improved the care of patients with cancer in the United States and worldwide for more than 50 years.

One of the Program's strengths is the extensive involvement of physicians and patients from the community setting. Participation by the diverse patient populations treated in the community setting helps to ensure that the results of clinical trials are meaningful to a broad segment of the U.S. population and provides these patients with access to promising, innovative therapies as they are developed and tested. The clinical trials conducted by the Cooperative Groups also provide a valuable mechanism for the training of clinical investigators.

However, despite these important contributions and a long record of accomplishments, the Cooperative Group Program is at a critical juncture. Numerous challenges threaten its ability to conduct the timely, large-scale, innovative clinical trials needed to improve patient care. With many iterative layers of oversight, the complex trials system has become inefficient and cumbersome. The average time required to design, approve, and activate a trial is 2 years and many of the trials undertaken are not completed. Furthermore, since 2002 funding for the Cooperative Group Program has decreased by 20 percent, whereas new knowledge of the molecular changes underpinning cancer and the use of predictive biomarkers in cancer therapy not only increase the potential impact of trials but also add to their complexity and cost.

The director of NCI asked the Institute of Medicine (IOM) to conduct a consensus study of cancer clinical trials and the Cooperative Group Program and to develop recommendations on how to improve the system. To address the charge, the IOM appointed a 17-member committee with a broad range of expertise and experience.

The committee concluded that a robust, standing cancer clinical trials network is essential to effectively translate discoveries into clinical benefits for patients. There are hundreds of cancer therapies in development and a continuous need for design and implementation of new clinical trials, so it would be highly inefficient to fund and develop infrastructures and research teams separately for each new trial. Thus, it is imperative to preserve and strengthen the unique capabilities of the Cooperative Group Program as a vital component in NCI's translational continuum.

However, the current structure and processes of the entire clinical trials system need to be redesigned to improve value by reducing redundancy and improving the effectiveness and efficiency of trials. Numerous changes are needed, including an evaluation and justification of the unique contribution of each Cooperative Group and a shift in the primary focus of NCI from oversight to the facilitation of Cooperative Group trials. The Program

needs to move beyond cooperation to integration, which can be achieved by reorganizing clinical trial structures and operations in a truly national trials network. The revised system must also be sufficiently funded to enable the rapid completion of well-designed, high-priority trials. In addition, government agencies need to streamline and coordinate the oversight process, with parallel, concurrent, or ideally, joint reviews to the extent possible. In sum, the academic, government, and commercial sectors must join with the public to develop a 21st-century multidisciplinary clinical trials system to more effectively leverage scientific advancements and translate them into public health benefits by improving the science; technology; efficiency; and timely creation, launch, and completion of the highest-priority cancer clinical trials. With adequate funds and support, a more effective and efficient clinical trials system will speed the pace of advances in cancer patient care.

On the basis of a review of the available published literature, along with input from experts in the field and interested individuals, the committee's recommendations (Box ES-1) focused on four broad goals to enhance the value of national Cooperative Group clinical trials in cancer:

Consolidation and Efficiency. Improve the efficiency and reduce the average time for the design and launch of innovative clinical trials by consolidating functions, committees, and Cooperative Groups; streamlining oversight processes; facilitating collaboration; and streamlining and standardizing data collection and analysis.

Science. Incorporate innovation in science and trial design, for example, in studies identifying biomarkers that can predict therapeutic response.

Funding and Support. Adequately support those clinical trials that have the greatest possibility of improving survival and the quality of life for cancer patients, and increase the rate of clinical trial completion and publication.

Participation. Incentivize the participation of patients and physicians in clinical trials by providing adequate funds to cover the costs of research and by reimbursing the costs of standard patient care during the trial.

BOX ES-1
Summary of the Committee's Goals and Recommendations

Goal I. Improve the speed and efficiency of the design, launch, and conduct of clinical trials

1. Review and consolidate some front office operations[a] of the Cooperative Groups on the basis of peer review
2. Consolidate back office operations of the Cooperative Groups and improve processes[b]
3. Streamline and harmonize government oversight
4. Improve collaboration among stakeholders

Goal II. Incorporate innovative science and trial design into cancer clinical trials

5. Support and use biorepositories
6. Develop and evaluate novel trial designs
7. Develop standards for new technologies

Goal III. Improve the means of prioritization, selection, support, and completion of cancer clinical trials

8. Reevaluate the role of NCI in the clinical trials system
9. Increase the accrual volume, diversity, and speed of clinical trials
10. Increase funding for the Cooperative Group Program

Goal IV. Incentivize the participation of patients and physicians in clinical trials

11. Support clinical investigators
12. Cover the cost of patient care in clinical trials

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[a]Front office operations refer primarily to the Cooperative Group scientific committees and statistical offices, which are responsible for activities such as trial design, prioritization, and data analysis.

[b]Back office operations refer to administrative structures and activities that include such things as data collection and management, data queries and reviews, patient registration, audit functions, case report form processing, image storage and retrieval, drug distribution, credentialing of sites, and funding and reimbursement for patient accrual.

Overview of Conclusions and Recommendations

Advances in biomedical research have produced significant opportunities to improve cancer prevention, detection, and treatment. Insights about the genomic and molecular mechanisms of disease have enabled basic scientists to identify new therapeutic targets and develop new agents that are changing the paradigm of cancer research from nonspecific, broadly toxic chemotherapies to highly targeted combinations of therapies. However, the ability to translate biomedical discoveries into advances in care for patients with cancer remains dependent on the clinical trials system. Clinical trials provide an essential link between scientific discovery and clinical practice. These trials are crucial to the translation of new knowledge into tangible benefits for patients, and the knowledge gained in a clinical trial can also inform and guide further research into the biology of the disease.

Many clinical trials are undertaken by the pharmaceutical and biotechnology industries, whose primary objectives are to develop novel therapeutic agents and gain Food and Drug Administration (FDA) approval for clinical use. These research and development efforts entail enormous costs (hundreds of millions of dollars) and are critical to progress in cancer treatment. Publicly funded clinical trials also play a vital role and are complimentary to industry trials in advancing science and patient care, particularly by addressing questions that are important to patients but are less likely to be top priorities of industry. For example, companies may have less incentive to

- conduct clinical trials to compare the effectiveness of different treatment options that are already approved for clinical use,

- combine novel therapies developed by different sponsors,
- develop therapies for rare diseases,
- determine optimal duration and dose of treatment with drugs in clinical use,
- test multimodality therapies, such as radiation therapy, surgery, or devices in combination with drugs,
- study screening and prevention strategies, or
- focus on rehabilitation and quality of life following therapy.

Publication of negative research findings about the therapies used in practice, which are underreported in the literature but which are essential in setting the standard of care, is also an important aspect of publicly funded research.

To address these needs, the National Cancer Institute (NCI) supports the largest U.S. network of clinical trials of any type through several different funding mechanisms. The largest component of that network is the Clinical Trials Cooperative Group Program (informally known as the Cooperative Group Program), which comprises 10 Groups that involve more than 3,100 institutions and 14,000 investigators who enroll more than 25,000 patients in clinical trials each year. Most Cooperative Group trials are either moderate-scale Phase II or large-scale Phase III clinical trials that may have practice-changing implications directly relevant to patient care. In contrast, many single-institution, investigator-sponsored trials are relatively small, nonrandomized Phase II trials that are less likely to have a major impact on the standard of care.

Since its inception in the 1950s, the Clinical Trials Cooperative Group Program has been instrumental in establishing the standards for cancer patient care and clinical research methods. The research undertaken by the Cooperative Groups has contributed to significant advances in cancer treatment and prevention, including the introduction of new treatments or new drug indications that have led to improved survival and increased cure rates, particularly for pediatric cancers and some early-stage cancers in adults. Furthermore, the role of the Cooperative Group Program is growing in importance as industry trials are increasingly being conducted outside of the United States. The Cooperative Group Program provides a primary mechanism by which the value of therapeutic agents can be assessed within the medical milieu of the U.S. health care system.

One of the Program's strengths is the extensive involvement of physicians and patients from the community setting. Participation by the diverse patient populations treated in the community setting helps to ensure that the results of clinical trials are meaningful to a broad segment of the U.S. population and provides these patients with access to promising, innovative therapies as they are developed and tested. In addition, Cooperative

Group trials have contributed high-quality, annotated biospecimens that have aided preclinical and translational research activities, providing critical prognostic and predictive markers of response to therapy. The Cooperative Groups also provide data that support initial or expanded FDA labeling on the basis of clinical trial results supporting new indications for cancer therapeutics. The Cooperative Groups also provide a valuable training ground for clinical investigators, offering opportunities for mentorship, collaboration, and career advancement.

However, despite these important contributions and a long record of accomplishments, the public clinical trials system in the United States is at a critical juncture. The Cooperative Group Program in particular is facing numerous challenges that threaten its ability to continue to undertake large-scale, innovative clinical trials that benefit patient care. Funding for the Program has never covered the full cost of the trials that the Groups undertake. Stagnant and declining funding, inefficient processes, extensive and complex government oversight, and a lack of resources to accommodate the new targeted and personalized approach to the development and evaluation of cancer therapy contribute to the Cooperative Group Program's current difficulties in efficiently and effectively translating research discoveries into timely clinical applications.

Recognizing the importance of maintaining an effective publicly funded clinical trials system, the director of NCI, John Niederhuber, requested that the Institute of Medicine (IOM) conduct a consensus study of cancer clinical trials and the Clinical Trials Cooperative Group Program and develop recommendations for how to improve the current system. To address the charge, the IOM appointed a 17-member committee with a broad range of expertise and experience, including experts in biomedical and clinical investigations in academia and community practice, statistics, radiology, research and development in the biotechnology and pharmaceutical industries, management research, systems engineering, the health insurance industry, and patient advocacy.

Because the environment in which clinical trials are conducted influences the pace of clinical advances, the committee took a broad view of the clinical trials process rather than simply focusing on NCI's role. The committee concluded that the academic, government, and commercial sectors must join with the public to develop a 21st-century clinical trials system to more effectively leverage scientific advancements and translate them into public health benefits by improving the science; technology; efficiency; and timely creation, launch, and completion of the very best cancer clinical trials. The committee began by describing the needs of an ideal cancer clinical trials system of the near future (Box O-1). Then, on the basis of a review of the available published literature along with input from experts in the field and interested individuals, the committee developed a set of goals and

BOX O-1
Needs for Cancer Clinical Trials in 2015

Rapid translation of scientific discoveries into public health benefits
- Trials that address questions with significant implications for patient care
- Collaboration among stakeholders, with effective and timely communication, in developing the most promising treatments
- Streamlined procedures for the rapid planning, approval, and launch of trials, with accountability for meeting timelines and the provision of rewards for productivity
- Efficient incorporation of new technologies and scientific questions, such as the identification and application of biomarkers and molecular imaging, into clinical trials

A strong publicly supported clinical trials system in the United States that complements industry trials to develop drugs and devices
- A highly efficient and flexible system for innovative, rigorously prioritized clinical trials
- Adequate funding for well-designed, high-quality trials
- Patient access to promising therapies as they develop
- Addresses questions and collects data that are relevant and meaningful to the diverse U.S. patient population

A robust, standardized, and accessible clinical trials infrastructure
- A complete database of active and planned trials
- Standardized electronic data capture
- Publicly accessible tissue repositories with high-quality, fully annotated, and inventoried samples collected and stored in a standardized fashion

strategies that aim to enhance the value of national Cooperative Group clinical trials in cancer.

The committee concluded that a robust, standing cancer clinical trials network is essential to effectively translate discoveries into clinical benefits for patients. Multi-institutional collaborations are necessary to conduct large Phase III trials for indications such as adjuvant therapy, first-line therapy of metastatic disease, and prevention; single institutions are not capable of undertaking such large-scale trials. For research on some other diseases, the National Institutes of Health (NIH) supports large trials on a case-by-case basis, aggregating appropriate institutions for a particular study and then disbanding the group on completion of the study. However, cancer encompasses more than 100 different diseases, the treatment regimens are complex and diverse (and becoming more so), and hundreds of experimental therapies for cancer are in development. Thus, there is a

- Broad use of those samples in retrospective studies as new hypotheses evolve
- A consistent and dynamic process for rapidly setting national standards and unified procedures for new technologies, such as diagnostics, with reproducibility and effective incorporation into clinical trials

Harmonized and synchronized rules and guidelines across federal regulatory agencies

- Guidance grounded in an understanding of contemporary science as new paradigms in therapeutic approaches as well as in clinical trials methodology develop

Support for clinical investigators

- Training and retention of professionals to efficiently and swiftly carry out important clinical research
- Adequate paid protected research time for active clinical investigators
- Recognition and appropriate rewards for collaborative clinical research by providing advancement in academia and community practice careers
- Adequate reimbursement of costs for actively participating institutions and physicians

Broad patient involvement in clinical trials

- Third-party payor coverage of the nonexperimental costs of care to ensure that patients do not forgo participation in trials because of financial hardship
- Participation in the design, implementation, and conduct of trials and in the communication and dissemination of trial results

continuous need for the design and implementation of new trials, and it would be highly inefficient to fund and develop infrastructures and research teams separately for each new clinical trial.

If NCI is to achieve the goal of improving outcomes for patients with cancer, it is imperative to preserve and strengthen the unique capabilities of the NCI Clinical Trials Cooperative Group Program as a critical component of NCI's translational continuum. Given its long and impressive history of accomplishment, the Cooperative Group Program should ideally provide an established infrastructure for the rapid and efficient translation of scientific knowledge into practical therapeutic solutions that incorporate targeted agents matched to the characteristics of the patient and tumor and routinely achieve change in clinical practice, as well as FDA approval, where appropriate.

However, although a strong and adequately funded clinical trials coop-

erative network is essential for addressing questions of national importance, the current structure and operating processes of the entire trials system need to be reevaluated to improve value by reducing redundancy and improving effectiveness and efficiency. Numerous changes, as further delineated throughout this report, are needed to fully achieve that ideal, including an evaluation and justification of the unique role of each Cooperative Group, as well as an evaluation of the key roles that NCI has in administering and overseeing the Cooperative Group Program. Novel, multidisciplinary solutions are needed for currently intractable problems in cancer clinical trials. Redesigning a more effective and efficient clinical trials system would likely speed the pace of advances in cancer patient care.

The committee's recommendations are organized under four broad goals: Goal I, improve the speed and efficiency of the design, launch, and conduct of clinical trials; Goal II, incorporate innovative science and trial design into cancer clinical trials; Goal III, improve the prioritization, support, and completion of cancer clinical trials; and Goal IV, incentivize the participation of patients and physicians in clinical trials (Box O-2). Taken together, these recommendations would alter the entire clinical trials system, including the functions of NCI as well as those of the Cooperative Groups.

GOAL I. IMPROVE THE SPEED AND EFFICIENCY OF THE DESIGN, LAUNCH, AND CONDUCT OF CLINICAL TRIALS

Background

A clinical trial is a highly complex endeavor. It comprises hundreds of steps that must be taken, numerous decision points, and multilayered and iterative review processes because multiple oversight bodies with different objectives and responsibilities have jurisdiction over clinical trials. Inefficiencies in the processes used to develop, launch, and complete cancer clinical trials lead to lengthy delays in each step. Recent studies indicate that the time needed to transit from concept approval to activation of a Phase III Cooperative Group trial often exceeds 2 years. Given the rapid pace at which new scientific findings from basic or preclinical studies accumulate, a trial concept may lose relevance or become outdated in that 2-year time period. Moreover, evidence indicates that trials with lengthy activation times are statistically less likely to accrue the targeted number of patients required to draw valid scientific conclusions. Thus, process improvements are essential to achieve the rapid translation of scientific discoveries into public health benefits.

The current structure and organization of the Cooperative Groups did not result from any kind of strategic planning with regard to what might be optimal with respect to trial design and execution. Each Group

BOX O-2
Summary of the Committee's Goals and Recommendations

Goal I. Improve the speed and efficiency of the design, launch, and conduct of clinical trials

1. Review and consolidate some front office operations of the Cooperative Groups on the basis of peer review
2. Consolidate back office operations of the Cooperative Groups and improve processes
3. Streamline and harmonize government oversight
4. Improve collaboration among stakeholders

Goal II. Incorporate innovative science and trial design into cancer clinical trials

5. Support and use biorepositories
6. Develop and evaluate novel trial designs
7. Develop standards for new technologies

Goal III. Improve prioritization, selection, support, and completion of cancer clinical trials

8. Reevaluate the role of NCI in the clinical trials system
9. Increase the accrual volume, diversity, and speed of clinical trials
10. Increase funding for the Cooperative Group Program

Goal IV. Incentivize the participation of patients and physicians in clinical trials

11. Support clinical investigators
12. Cover the cost of patient care in clinical trials

operates independently, with its own administrative structures and operating procedures, committees, and statistical and data management centers. Although the Groups were originally organized by geographic area or, in some cases, by type of disease or therapeutic modality, today there is considerable overlap in the interests of the existing Groups, most of which conduct clinical trials in medical oncology, radiation, and surgery and thus compete for similar trial strategies and funding. Although some overlap generates competition for trial ideas, and some replication is necessary to serve as validation, too much redundancy in the Groups and in individual activities can lead to an unnecessary duplication of efforts, which wastes limited resources. The recent voluntary consolidation of the pediatric oncology Groups, which was done to pool and conserve limited resources, serves as an informative precedent for how the system could change. Some consolidation of the Cooperative Groups and common activities, along

with a focus on best practices, could increase operational efficiencies and conserve resources, ease the workload of the Cooperative Groups, and lead to more consistency for providers who would like to enroll patients in trials launched by different Cooperative Groups. At the same time, maintaining a robust competition for innovative trial concepts is essential.

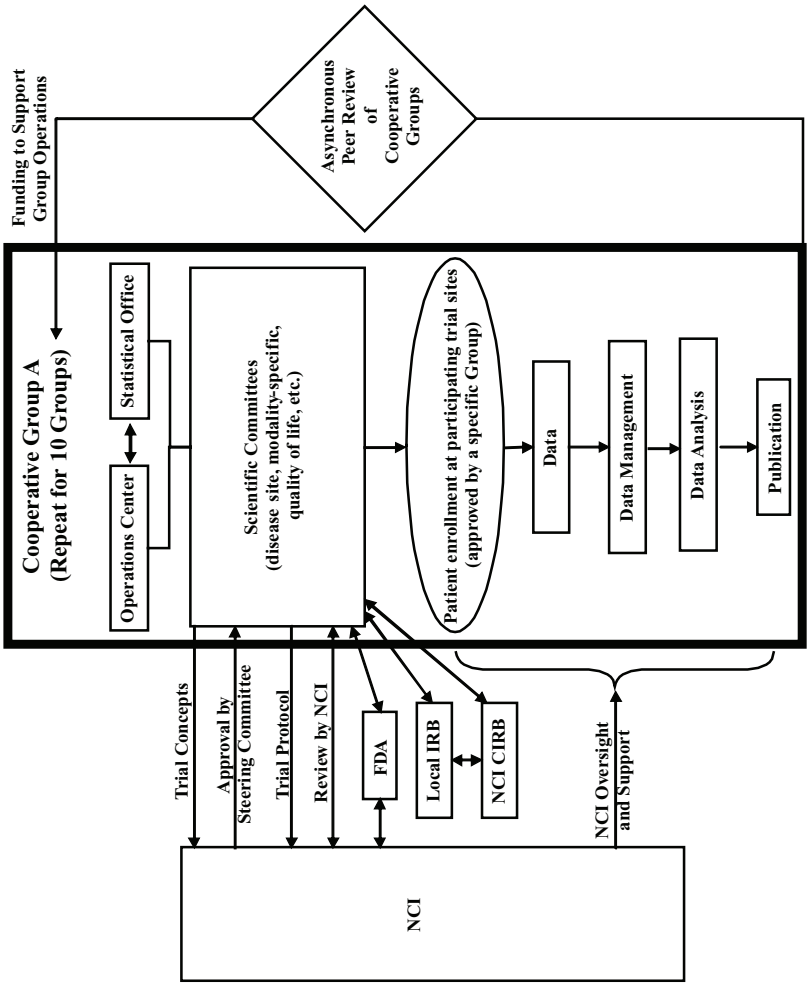
Large-scale clinical trials also necessitate interactions among numerous stakeholders, including governmental agencies, academic medical centers, community practices, patients, and industry. However, effective communication and collaboration among stakeholders has been challenging. Thus, meaningful change to the cancer clinical trials system will require actions by the numerous stakeholders. Although NCI should play a leading role in instituting the necessary changes, other agencies within the U.S. Department of Health and Human Services (HHS), such as FDA, as well as academic centers, community practices, and others, will need to be actively involved in improving the system. Because of the complexity of the system and the interconnected roles that these stakeholders play, changing only one or a few steps is unlikely to achieve the desired improvements.

Recommendations 1 to 4 provide strategies to achieve the goal of improving the efficiency and the average time for the design and launch of innovative clinical trials by consolidating Groups, committees, and functions, by enhancing collaboration, and by streamlining and standardizing data collection and analysis. The first two recommendations, in particular, would significantly alter the definition, structure, and operations of Cooperative Groups (Figure O-1). The current system entails 10 independent Groups that generate ideas for clinical trials and then conduct trials using their own infrastructures for trial operations and data management. Cooperation primarily occurs among the members within each Group. The revised system that would result from implementation of the committee's recommendations would go beyond cooperation to integration for many functions. Each Cooperative Group would consist of multidisciplinary committees focused on particular disease sites (referred to as disease site committees) and statistical offices that generate trial concepts and provide leadership for the conduct of trials selected as high priorities. The number of Groups and committees should be reduced on the basis of peer review. Most of the infrastructures used to support clinical trial operations and management would be consolidated to achieve greater consistency and efficiency under the new system. The committee's recommendations also aim to streamline and coordinate the many iterative oversight processes to achieve further gains in the speed and efficiency of trial launch and conduct. NCI's role would shift from a primary focus on oversight to a greater focus on supporting high-priority trials conducted through the national cancer trials network. Trial sites would be certified to participate in a national trials network and could enroll patients in any high-priority

FIGURE O-1 (**a**) Overview of the current structure and function of the Cancer Clinical Trials Cooperative Group Program. The components within the bold box are unique to each Cooperative Group. Each of the 10 Cooperative Groups has an operations center and a statistical center, scientific committees, and data management infrastructure. NCI is involved at multiple points throughout the process of trial concept design, protocol development, and trial implementation and conduct. Patient enrollment occurs at sites affiliated with and approved by specific Cooperative Groups to carry out clinical trials. The basis of peer review includes the scientific accomplishments and future plans of the Group, the organization of Group resources, the organization of data management and statistical centers, overall leadership, the Group's publication record, and the effectiveness of disease- and modality-specific committees (collectively and, to some extent, individually). All of these factors are reviewed against a general standard for Cooperative Groups. FDA oversight is not required for all trials; FDA is involved any time a trial is conducted under an investigational new drug (IND) application. In general, any trial designed to provide information that may be used to change the drug label is conducted under an IND application, but this is not always the case. Double-sided arrows indicate repetitive interactions between organizations; changes in response to one review can trigger a re-review by another body.

(**b**) Overview of the proposed structure and function of the Cancer Clinical Trials Cooperative Group Program, as described in the committee's recommendations. The components within the bold box would be unique to each Cooperative Group, while the other components would be consolidated and shared across the Groups. The Cooperative Groups would primarily consist of multidisciplinary disease site committees and statistical offices that generate concepts for clinical trials. These concepts would be prioritized through external peer review, with only high-priority trials being selected for implementation. Patient enrollment would be at sites certified to participate in a National Trials Network that comprises cancer centers, Community Clinical Oncology Programs, and community practices. Most of the infrastructure used to support trial operations and management would be consolidated to facilitate greater consistency and efficiency, but leadership for each trial would still be provided by the originating cooperative Group and principal investigators. The basis of front office peer review would include the success of the multidisciplinary disease site committee in innovation, winning study approvals, completing high-impact studies, mentorship of younger clinical investigators, and the publication of findings. Each multidisciplinary disease site committee will be reviewed against others in its peer group (i.e., committees focused on the same disease site will be reviewed against each other at the same time). Back office operations will also be evaluated through the use of new performance metrics and will be funded accordingly. In cases in which NCI is the IND holder in a clinical trial, the type of NCI oversight would be similar to that used for the current Cooperative Group Program. For other studies, NCI's role would be limited to facilitating the launch and completion of the trial.

NOTE: CIRB = central institutional review board; FDA = Food and Drug Administration; IRB = institutional review board; NCI = National Cancer Institute.



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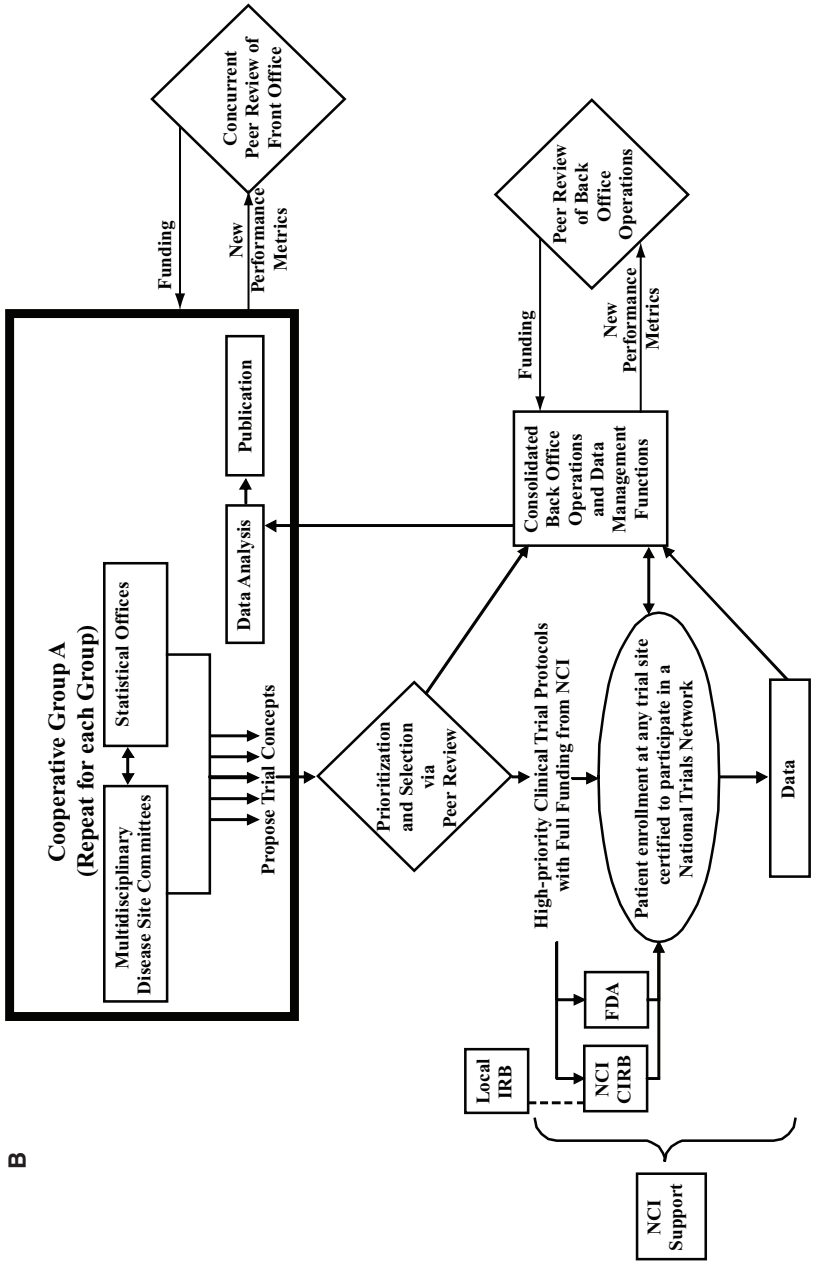

trial launched under the new system, regardless of the origin of the trial concept.

Recommendation 1: NCI should facilitate some consolidation of Cooperative Group front office operations by reviewing and ranking the Groups with defined metrics on a similar timetable and by linking funding to review scores.

- **Key planning and scientific evaluations should be at the disease site committee level. The focus should be on the quality and success of the clinical trial concepts developed and the committee's record of development of new investigators.**
- **Committees that do well in review should be funded, and committees with low review scores should be eliminated.**
- **Committees should be organized with a multidisciplinary focus on disease sites, and Group leaders should consolidate disease site committees from different Groups to strengthen their productivity and review scores.**

Rationale

Some consolidation of the current Cooperative Group front offices,[1] which entail the Groups' disease site committees and statistical offices that generate and vet potential concepts and statistical designs for trials, would reduce redundancy in the Program, enable the pooling of resources, and reduce competition for enrollment in trials on the basis of Group-specific priorities. At present, the Groups are evaluated separately, on different schedules, and the score derived from that evaluation has no real impact on the amount of funding awarded to a particular group. Changing the timeline and focus of the review process to facilitate direct comparisons of the front office operations would ensure that only the most innovative and successful disease site committees would thrive, expand their membership, and maintain a sense of community.

The logical extension of the proposed consolidations will be a reduction in the number of Cooperative Groups. Cooperative Group leaders would have an incentive to work together to merge disease site committees

[1] Front office operations, which are called front-end processes in information systems, are those operations that interface directly with the customer (in this case, patients and physicians). Back office operations, also called back-end processes, are those operations that rarely directly interface with a customer. For example, for a website, the webpage would be considered the front office and the database used to populate the website would be considered the back office. For clinical trials, statistical operations span both front and back office operations and, for this report, are considered front office.

across the existing Groups to enhance productivity and review scores. For example, Groups focused on a single disease site or modality would likely need to merge with multidisciplinary Groups under this system. Such a system would ideally maintain strong competition for trial concepts among a smaller number of Cooperative Groups and their disease site committees and thus help to ensure that only the highest-priority trials are undertaken. A reduction in the number of trials competing for patient enrollment would help to align patient and clinician incentives, as providers would focus on finding the best possible trial for each patient and his/her particular disease, regardless of where the trial originated.

A similar rationale was behind the recent consolidation of the four Cooperative Groups focused on pediatric cancers into a single new Children's Oncology Group (COG). Because of the relatively small number of children with cancer, greater collaboration was deemed essential to achieving adequate enrollment in trials and further progress in the cure rate for this disease. Operations of the consolidated Group are now streamlined, and pediatric patients are assured that they will be offered the best possible trial of the Program rather than the trial preferred by a particular Group. Other types of cancer that are rare or that have consistently had suboptimal accrual in trials (e.g., lymphoma) would also likely benefit from such a consolidation.

Recommendation 2: NCI should require and facilitate the consolidation of administration and data management operations across all of the Cooperative Groups (the back office operations) and, working with the extramural community, make process improvement in the operational and organizational management of clinical trials a priority. For example, NCI should

- **facilitate the consolidation of offices and personnel for such activities as data collection and management, data queries and reviews to ensure that the data collected are complete and accurate, patient registration, audit functions, submission of case report forms, training of clinical research associates, image storage and retrieval, drug distribution, credentialing of sites, and funding and reimbursement for patient accrual;**
- **work with governmental and nongovernmental agencies with relevant expertise to facilitate the identification of best practices in the management of clinical research logistics and develop, publish, and use performance, process, and timing standards and metrics to assess the efficiency and operational quality of clinical trials;**
- **coordinate and streamline the protocol development process, as recommended by the Operational Efficiency Working Group;**

- **devote more funds to drug distribution;**
- **provide resources and technical assistance to facilitate the rapid adoption of a common patient registration system as well as a common remote data capture system;**
- **facilitate more efficient and timely methods for ensuring that trial data are complete and accurate; and**
- **develop standardized case report forms that meet regulatory requirements.**

Rationale

Each Cooperative Group devotes significant resources to support similar administrative structures and activities in what is defined in the operations management literature as back office operations. Although the ways in which the Groups accomplish these administrative and data management functions vary, there is little technical rationale for why they must be unique to the scientific focus of each Group. Consolidated back office operations work very successfully in other industries. The consolidation of offices and personnel to conduct these information-based activities across all the Cooperative Groups would streamline the operations, reduce redundancy, conserve resources, and offer greater consistency to providers enrolling patients in trials launched by different Cooperative Groups. The consolidation of COG again provides a model for such a transition, but NCI should work with the Cooperative Group leaders to develop a mechanism by which this transition can be accomplished efficiently and smoothly. It will be imperative to ensure high service quality and responsiveness to the principal investigators and Cooperative Groups leading the trials, through periodic peer review of formal metrics of performance.

In addition, the operational processes used to conduct clinical trials are idiosyncratic to individual institutions or Cooperative Groups, with little sharing of best practices or lessons learned. Although good clinical practice guidelines provide an international ethical and scientific quality standard for the design, conduct, recording, and reporting of the findings of clinical trials that involve the participation of human subjects, at present there is no mechanism for the systematic collection of best management and administrative practices that can be used as benchmarks by a clinical trials office in a cancer center or a Cooperative Group. Furthermore, few standard processes or metrics of what constitutes operational "quality" in the development or management of clinical trials exist. Thus, the operational performance metrics used to evaluate cancer centers and Cooperative Groups need to be enhanced and redefined to include quality, outcome, and timing metrics for clinical trials.

Because these operational issues can significantly delay clinical trials

and the evaluation of innovative therapies for all types of cancer, there is a need for NCI to work with other agencies and to make novel research on these topics a priority. In addition, a transparent process that could be used to measure and reward Cooperative Groups, cancer centers, and individual investigators not only for doing meaningful clinical research (as determined by an assessment of the essential scientific elements of the trial) but also for how rapidly and efficiently they conduct such research and for the impact of that research would greatly facilitate the adoption and use of best practices and metrics.

One of the most time-consuming and complex activities in the clinical trials process is the development of a scientific concept into a viable and approvable clinical trial protocol. NCI's Operational Efficiency Working Group, which was charged with identifying ways to reduce the study activation time for Cooperative Group and cancer center trials by 50 percent, has recently put forth specific, measurable goals that the IOM committee endorses. These include reducing the time from protocol submission to final protocol approval to 300 workdays for Phase III trials and 210 work days for Phase II trials and eliminating trials that do not open and accrue patients within 18 calendar months for Phase II trials or 2 years for Phase III trials. To achieve those goals, the working group recommended staffing changes, more coordinated, parallel reviews, improved project management, and better tracking of the trial protocol.

More active and consistent support from NCI to facilitate trial operations would also be beneficial. For example, more resources for the rapid implementation and adoption of a common electronic registration and data capture system would increase consistency across trials, conserve resources by reducing the workload associated with patient enrollment and follow-up, allow for the more timely review of the data from a trial, and enhance the knowledge gained from a trial. Standardized case report forms would ease the burden of regulatory oversight and lead to better compliance.

However, all these activities will require additional NCI staff and resources to support the Cooperative Group Program, as noted in the discussion of Goal III.

Recommendation 3: The U.S. Department of Health and Human Services should lead a transagency effort to streamline and harmonize government oversight and regulation of cancer clinical trials. For example,

- **All review bodies should distinguish between major review concerns (regarding patient safety and critical scientific flaws, which must be addressed) and minor concerns (which should be considered, but are not obligatory).**

- **NCI should coordinate with FDA for the review and oversight of trials involving an investigational new drug or investigational device exemption to eliminate iterative review steps.**
- **FDA should establish a coordinated Cancer Program across its centers that regulate oncology products.**
- **FDA should update its regulatory guidelines for the minimum data required to establish the safety and efficacy of experimental therapies (including combinations of products) and eliminate requirements for nonessential data, particularly for supplemental new drug and biologic license applications.**
- **The Office for Human Research Protections should develop guidance that clearly establishes the accountability of the NCI central institutional review board, to encourage its wider use and acceptance by local institutions.**
- **Federal oversight should be more flexible in allowing minor amendments to the protocol or consent form to fast-track the chain of reapprovals.**
- **Patient consent forms should include a shortened and simplified summary to enhance the provision of informed consent.**

Rationale

Compliance with regulatory requirements for the conduct of clinical trials is a major challenge for investigators in all fields of medicine. Multiple agencies and institutional bodies of HHS review and provide oversight for cancer clinical trials, including NCI, FDA, the Office for Human Research Protections (OHRP), the Office for Civil Rights (OCR), and institutional review boards (IRBs). The many oversight bodies have different objectives and responsibilities and thus seek similar, overlapping, but not identical information and action for compliance. Moreover, the review processes are serial and iterative. A change made in response to one review or in response to new findings can trigger a loop or re-review among the other review bodies as well. This delays the trial process and increases the burdens on investigators. Parallel, concurrent, or ideally, joint reviews and a clear distinction between major and minor reviewer concerns would help to reduce iterative reviews.

A departmental effort by HHS, with strong leadership from the HHS secretary and agency heads, to strengthen the scientific underpinnings of regulations, as well as to harmonize, coordinate, and streamline the oversight and review processes, could significantly improve the speed and efficiency of clinical trials, ease the burden on investigators, and better protect patients. For example, the HHS Secretary's Advisory Committee on Human Research Protections and the IOM have recommended harmonization of

the regulatory language as well as the guidance and policies associated with the Common Rule[2] and the Health Insurance Portability and Accountability Act Privacy Rule[3] because of the difficulties that investigators and IRBs encounter in trying to reconcile the discrepancies between the two. Improved communication and coordination of reviews would also improve the process. For instance, NCI coordination with FDA for oversight of NCI-funded trials involving an investigational new drug application (IND) or investigational device exemption would ensure appropriate protocol design early in the process and thus reduce the number of revisions and re-reviews that may be required.

Changes within individual agencies would also be beneficial. For example, FDA may have multiple centers with jurisdiction over trials testing combination products, such as drug-biologic combinations or therapeutic-diagnostic combinations. A coordinated Cancer Program across the centers that regulate oncology products could avoid the conflicting expectations that may arise when sponsors seek approval through multiple centers. FDA committed in principle to the formation of such a Cancer Program in 2004 to "facilitate cross agency expert consultation," but it has yet to follow through on that commitment. In addition, for trials intended to support product registration, FDA has extensive data collection requirements that could likely be reduced, especially for agents currently on the market that are being tested for new indications, as significant amounts of data on the safety of such agents often exist. Defining a core set of data elements, along with guidance on how those elements could be modified under certain circumstances, would speed the FDA review process and lead to greater uniformity in data requirements. Eliminating unnecessary and onerous data requirements would also conserve resources and result in the testing of more combination therapies in particular.

A major challenge unique to large multi-institutional studies is the involvement of many local IRBs. Regulatory language is often complex and subject to interpretation, so decisions by IRBs can be highly variable, which can cause delays and lead to protocol variations at different sites. Local IRBs can defer to a central IRB (CIRB), but in practice, many institutions are reluctant to rely on decisions made by the NCI CIRB, in large part because of concerns about being held accountable for the decisions that the CIRB makes. Guidance and policies from OHRP that address that concern would encourage the wider use of CIRBs and would thus increase

[2]The Common Rule is the term used by 18 federal agencies that have adopted the same regulation governing the protection of human subjects of research (Subpart A of 45 Code of Federal Regulations [C.F.R.] part 46).

[3]The HIPAA Privacy Rule ("Standards for Privacy of Individually Identifiable Health Information: Final Rule") can be found at 45 C.F.R. parts 160 and 164.

the efficiency and reduce the costs of clinical trials, as well as increase consistency in patient protections across sites. Guidance from OHRP and OCR to allow the use of simplified summaries of consent forms, which have become very lengthy and complex, would also improve patient communication and decision making.

Recommendation 4: NCI should take steps to facilitate more collaboration among the various stakeholders in cancer clinical trials. For example, NCI should

- **develop standard licensing language and contract templates for material and data transfer and for intellectual property ownership in biospecimen-based studies and trials that combine intellectual property from multiple sources;**
- **facilitate the creation of more public-private partnerships and precompetitive consortia, guided in part by successful models;**
- **facilitate the development of appropriate hybrid funding models, in which NCI and industry support clearly defined components of trials that are of mutual interest;**
- **facilitate a process by which stakeholders (NCI, NIH, FDA, industry, investigators, and patients) can define an effective mechanism for the development of targeted cancer therapies, with particular emphasis on combinations of products; and**
- **implement a highly visible grand challenge competition to engage experts in cancer and noncancer fields (e.g., engineering, social science, management, and marketing) and to reward significant innovation leading to increased efficiency in clinical trials processes.**

Rationale

Cancer clinical trials often necessitate effective collaboration among diverse stakeholders, but there are numerous challenges to achieving such collaborations. For example, negotiations to reach contract and licensing agreements to transfer or share materials, data, and intellectual property (IP) are complex and can cause lengthy and costly delays in the launch of clinical trials. Pharmaceutical companies in particular may be reluctant to share IP or data and patient samples with academic collaborators and may require IP rights that are unacceptable to collaborators. However, valuable insights and discoveries may be lost and progress toward clinical advances may be slowed if important data or samples are withheld from collaborating institutions that could explore novel, additional hypotheses with those resources. Standard IP licensing language and contract templates, similar to the standardized trial contract language that was developed in conjunction

with the CEO Roundtable on Cancer, could reduce the delays due to these negotiations and facilitate important new research.

Given the limited funding capacity of NCI, it would also be beneficial to leverage the resources of industry to support the work of the Cooperative Groups in a transparent way to benefit patients, for example, in comparison trials or for secondary indications. Two recent reports from the President's Council of Advisors on Science and Technology acknowledge the importance and value of strengthening public-private collaborations to enhance innovation, particularly for discovery and translational research in personalized medicine. However, industry funding for Cooperative Group trials has been limited for a variety of reasons, including concern about the inherent inefficiencies in the Program, the Groups' concern about maintaining independence in study design and execution, and concerns about conflicts of interest. These concerns may contribute to the increasing tendency of pharmaceutical and biotechnology companies to conduct trials in other countries.

Commercial firms might be more interested in collaborations with the Cooperative Groups if the review and operational procedures of the Program were streamlined, as recommended in this report. However, novel hybrid funding mechanisms, as well as new efforts to establish public-private partnerships and precompetitive consortia would further aid progress toward effective collaboration, to the benefit of patients, who desire access to new and promising cancer therapies. Maintaining a critical mass of clinical trials in the United States via appropriate collaborations is important to ensure that patients in this country gain access to promising therapies as they develop, that trials address questions and generate data that are relevant and meaningful to patients in the United States, and that the nation retains a sufficient number of properly trained clinical trial specialists.

Effective collaboration among stakeholders will be particularly important for combination therapies, which may hold the key to successful personalized medicine. Traditionally, most cancer drugs have been broadly cytotoxic and nonselective in their mechanisms of action, resulting in significant toxicity to healthy tissues. In recent years, research has elucidated many of the molecular changes underpinning the initiation and progression of cancer (e.g., molecular changes affecting signaling pathways; cell death mechanisms; cancer spread; and DNA synthesis, repair, and modification). Because most cancers have multiple abnormalities, combination therapies that target multiple key cellular pathways and activities should benefit patients by increasing the efficacy of cancer treatments and reducing the likelihood that resistance will develop. Preclinical models of cancer support that hypothesis, and clinical studies also indicate that some targeted therapeutics that work effectively in concert with other agents may not induce significant responses when they are used as a single agent. This circum-

stance creates a significant challenge for the design of clinical trials and for FDA oversight. For example, traditional FDA standards require sponsors to "isolate the contribution of each agent." Companies may also be reluctant to work with competitors to test promising combinations at an early and risky stage of development. To date, most combinations tested in Phase III trials have involved at least one agent currently approved by FDA.

The progress of clinical oncology research is also impeded by numerous obstacles that are well known but have eluded solution, despite decades of discussion and multiple reports by review panels. The low proportion (~3 to 5 percent) of adult cancer patients who enroll in clinical trials is a prime example. In recent years, NCI used the traditional request for application mechanism to solicit proposals that aimed to increase patient accrual, but that effort achieved little meaningful gains in accrual.

Well-run R&D organizations devote a portion of their resources to improve how they do research, not just doing research. A new and novel approach is required to solve these well-known intractable problems, with application of the best minds in multiple disciplines (engineering, social science, management, marketing, etc.). The potential for impact can often be a stronger motivator to good science than money per se, and competition can foster rapid and innovative solutions, much like what occurred with the sequencing of the human genome. Thus, one promising novel approach would be to develop a major, influential grand challenge for those well-known problems in oncology research.

Models for the development of such grand challenges exist and have shown some successes. A widely known example of such an approach is the X PRIZE, a multimillion-dollar award given to the first team to achieve a specific goal that has the potential to benefit humanity. A recent report on such incentive prizes, which spur innovation by tapping into competitive and entrepreneurial spirits rather than directly funding research, concluded that they are unique and powerful tools that can produce change not only by identifying new levels of excellence and by encouraging specific innovations but also by changing wider perceptions, improving the performance of communities of problem solvers, building the skills of individuals, and mobilizing new talent or capital.

GOAL II. INCORPORATE INNOVATIVE SCIENCE AND TRIAL DESIGN INTO CANCER CLINICAL TRIALS

Background

Progress in the treatment of cancer patients depends on the effective incorporation of scientific advances into clinical trials. For example, to achieve the goals of targeted cancer therapy, the use of validated biomark-

ers will be essential. Cooperative Group clinical trials provide a unique opportunity to enable the emerging science of molecular markers through retrospective analyses of archived samples and prospective evaluations of biomarkers. High-quality annotated biorepositories are needed to gain useful knowledge about the biology of cancer and biomarkers from the analysis of patient samples archived from past trials, but the maintenance of tissue banks and the analysis of stored samples are costly activities that are not fully covered by the core funding that NCI provides to the Cooperative Groups. Access to stored samples can also be problematic. The increasing complexity of cancer clinical trials, along with the great expense and high failure rate of late-stage clinical trials, has spurred innovation in trial design as well, with the aim of conducting clinical trials more efficiently and with a greater likelihood of success. However, when new methods or technologies are incorporated into clinical trials, standards to ensure that the results collected at the various trial sites are consistent enough to attain accurate and meaningful conclusions from a study are often lacking.

Recommendations 5 to 7 aim to facilitate the incorporation of innovation in cancer clinical trial design and conduct.

Recommendation 5: NCI should mandate the submission of annotated biospecimens to high-quality, standardized central biorepositories when samples are collected from patients in the course of Cooperative Group trials and should implement new funding mechanisms and policies to support the management and use of those resources for retrospective correlative science. For example,

- **All data, including biomarker data from serum, tissue, and imaging analyses should be considered precompetitive, unencumbered by intellectual property restrictions, and made widely available.**
- **The accompanying clinical data should be reported on standardized forms.**
- **NCI should establish a national inventory of samples held in the central repositories and have a defined process for access by researchers that includes a single scientific peer review linked to funding.**

Rationale

The Cooperative Groups have a history of collecting biospecimens from the diverse populations of patients who participate in their clinical trials and maintaining them in repositories with detailed information about patient characteristics, treatment, and outcome. These resources have proven immensely valuable in the development of molecular-based classifi-

cation schemes and diagnostic tests that now guide decisions on the most appropriate therapy for numerous types of cancer. However, high levels of evidence are needed to validate and qualify biomarkers for specific uses, and current funding is inadequate to support the research needed to generate that evidence. Although current NCI policies and funding do support a portion of the costs involved in the collection and storage of samples, the Groups must routinely seek supplemental funding to manage and maintain the repositories. Moreover, little funding is available to conduct retrospective studies of samples that have been collected in previous trials.

Furthermore, current NCI policies require research studies that propose to use specimens collected from intergroup protocols to undergo scientific review by a scientific steering committee before specimens are made available. However, such a review is not linked to funding, so investigators must often seek funding through other mechanisms. This process creates many review loops, time delays, and significant double jeopardy, in that each proposal requires at least two scientific reviews (one to receive specimens and one to receive funding) that are conducted at different times by different review groups. The availability of a consistent and adequate funding source devoted to correlative studies with stored samples and with appropriate peer review that includes direct input from the Group that collected the samples is imperative. The broader use of high-quality, standardized repositories would speed the pace of scientific and clinical advances at a much lower expense than would be required if new clinical samples had to be collected to study each new concept.

In addition, access to biospecimens for research is inconsistent and can entail complex negotiations with the various custodians of the samples. Policies regarding ownership and access vary across different institutions, and this impedes progress. Furthermore, many hospitals discard samples after a period of time, so valuable resources are lost to research. Because the Cooperative Groups have a long history of responsible stewardship of repositories, they are a logical choice to play a central role in the ongoing efforts of NCI to establish consistent policies on ownership and access. The creation of a national inventory of samples held by the Cooperative Groups would also greatly facilitate important research in correlative science.

Recommendation 6: Cooperative Groups should lead the development and assessment of innovative designs for clinical trials that evaluate cancer therapeutics and biomarkers (including combinations of therapies).

Rationale

Cooperative Groups are in a unique position to develop innovative designs for clinical trials and to demonstrate the feasibility and utility of

using innovative, efficient designs in their clinical trials. The development and use of innovative trial designs could speed progress in clinical trials in numerous ways. For example, prospective clinical trial designs that randomize patients on the basis of biomarkers or treatments, or both, should be explored and evaluated. For targeted therapies, a predictive hypothesis for a biomarker should be put forward in the preclinical phase and tested in early-phase clinical trials (Phase I and II trials). Better Phase II trial designs are needed to more accurately assess which patients benefit from a particular therapy, and thus guide the decisions about whether to move into Phase III trials. Improved designs for Phase III trials, which are the most costly and lengthy trials and entail the majority of Cooperative Group trials, could lead to faster, more accurate conclusions about new therapeutics and in the process reduce costs and conserve resources. For example, recent innovations, such as the use of adaptive designs for Phase II trials that assess response endpoints during trial accrual in real time, suggest that relevant clinical questions might be addressed more efficiently, with fewer patients required, with less time needed to show differences between Groups, and with enhanced confidence in the clinically (and statistically) meaningful differences that are observed between Groups. These or related designs may be particularly amenable for the comparison of treatment effects in patients with different biomarker profiles and could hasten the identification of the most promising predictive biomarkers that could be validated in a Phase III trial setting.

Recommendation 7: NCI, in cooperation with other agencies, should establish a consistent, dynamic process to oversee the development of national unified standards as needed for oncology research. This process should

- **be used by NCI when standards are required for any important new technology, tool, or breakthrough method (e.g., biomedical imaging and other biomarkers and biospecimens);**
- **replicate successful aspects of standards development by other standard-setting bodies, both governmental and nongovernmental (e.g., the American Society for Testing and Materials, the National Standards Foundation, the National Institute for Standards and Technology, the International Organization for Standardization, and professional societies);**
- **utilize the input of experts in both subject matter and standards design in developing standards;**
- **include consistent operating procedures for developing standards (e.g., representation of stakeholders in committee composition, decision making, and voting rules); and**

- **publish and update the standards in a timely manner such that they are useful to those performing clinical trials.**

Rationale

As new scientific methods and technologies develop and mature, standards are needed to ensure appropriate and consistent use. The current approach to standards development is often ad hoc, with the processes and rules for such things as committee composition and voting rules being reinvented on a case-by-case basis. This can lead to heterogeneous and delayed results. A more systematic, multidisciplinary, and dynamic approach to standards development fostered by NIH and NCI would be advantageous for the rapid and consistent setting of unified national standards as the need arises. NCI could further assist by facilitating the creation of systems and software to aid the process of standards implementation.

This need for standards will become increasingly important as the science of cancer research becomes more complex and more dependent on technologies such as imaging and on molecular tools such as biomarkers. In the case of biomedical imaging, many technologies and imaging reagents, both those in current use and those under development, have the potential to provide information that can aid drug development and clinical decision making by providing improved means of diagnosis and monitoring. However, the lack of standards for image acquisition and quantification of results compromises the validity of the results and the interpretation of those results. In addition, the lack of harmonization of methods among the different vendors of imaging equipment compromises the quality and consistency of results. The consistent development of standard methodologies for established tumor-imaging modalities (e.g., computed tomography, fluorodeoxyglucose positron emission tomography, and conventional magnetic resonance imaging) by expert panels, along with a requirement that manufacturers meet those standards, could significantly improve the accuracy and value of those tests. Validation standards are also needed to continuously evaluate novel imaging methods and modalities to determine their merit and appropriate use.

Similarly, expert panels are needed to establish validation and qualification standards for the development and use of in vitro biomarker tests, to ensure that the results of those tests are consistent and accurate, and for the appropriate interpretation and use of those results. Such standards could also inform FDA guidance for the codevelopment of diagnostic-therapeutic combinations or for the inclusion of a biomarker test on the label for a drug or biologic that is already FDA approved.

GOAL III. IMPROVE PRIORITIZATION, SELECTION, SUPPORT, AND COMPLETION OF CANCER CLINICAL TRIALS

Background

Clinical oncology research has changed a great deal since the early days of the Cooperative Group Program in the 1950s. The process of conducting large-scale trials has become highly complex, with the incorporation of new technologies and trial designs, the increasing number of therapeutic agents to be tested, the increase in the number of Cooperative Groups, and the evolving regulatory environment. Many of these issues are addressed in the recommendations in the preceding sections, but it is also necessary to examine the contributions of and interactions between NCI and the Cooperative Groups in developing and implementing large-scale cancer clinical trials. NCI's coordination role within the current environment is quite challenging, and inefficient interactions between NCI and the Groups contribute to delays in the system. To improve the speed of advances in oncology care, streamlined processes are needed for the prioritization, selection, and support of trials and for the enrollment (accrual) of patients quickly after a trial is launched.

A major challenge that the Cooperative Group Program faces is the prioritization and selection of trial concepts before a trial is launched. The effective prioritization and selection of trial concepts is critical to ensure that limited public funds are used in ways that are likely to have the greatest impact on patient care. A previous report by the Clinical Trials Working Group (CTWG) recommended that NCI establish scientific steering committees that leverage intergroup, Cooperative Group, SPORE (Specialized Programs of Research Excellence), and cancer center structures to work with NCI in the design, evaluation, and prioritization of Phase III trials. The goal is to better allocate resources, increase scientific quality, and reduce duplication in trials proposed by Cooperative Group committees focused on a particular disease site, SPOREs, and other sources. However, the disease-specific steering committees set up in response to that recommendation do not appear to have fully achieved that goal.

Moreover, prioritization alone is not sufficient. At present, only about 60 percent of cancer clinical trials supported by NCI are completed and published. Inefficiencies in the system, including the time needed to respond to iterative reviews (as described in section I), can delay the launch of trials, and the longer it takes to open a trial, the less likely it is that a trial will meet its accrual goals. This represents a tremendous waste of very limited resources, including time, effort, and money. Once a priority trial has been selected, resources and effective procedures are needed to ensure rapid launch, patient accrual, and completion of the study.

The NCI Clinical Trials Cooperative Group Program has been chronically underfunded for the work that it performs, as noted in a 1997 review of the Program commissioned by the NCI director, and current funding does not cover the cost of the clinical trials undertaken. For the past 3 years, the annual budget for the Program has been held at about $145 million, but in real dollars it has declined to less than the 1999 funding level of $119 million, when the funding is adjusted for inflation. Despite this decrease in funding, the Cooperative Group Program has maintained patient accrual, with several hundred clinical trials ongoing at any given point. This level of funding, which represents approximately 3 percent of the total NCI budget, is simply not sufficient to support the number of trials that the Groups undertake. As a result, the Cooperative Group Program is highly dependent on the voluntary efforts of participating investigators and on supplemental funding from other sources, such as foundations, the pharmaceutical industry, and the institutional contributions of Cooperative Group members. Especially in light of the new focus on targeted therapy and personalized medicine, which raises the complexity and cost of clinical trials, the Cooperative Group funding process is becoming increasingly unsustainable.

Recommendations 8 to 10 aim to improve prioritization, selection, and support for clinical trials that have the greatest possibility of improving survival and quality of life for cancer patients and, along with Recommendations 11 and 12, aim to substantially increase the proportion of initiated clinical trials that are completed and published.

Recommendation 8: NCI should reevaluate its role in the clinical trials system. For example,

- **NCI should file more investigational new drug applications for agents to be tested in high-priority trials and provide a leadership role to ensure the success of those studies.**
- **In cases in which NCI does not hold the investigational new drug application, the primary focus of NCI should be on supporting high-priority trials, with less emphasis on oversight of the selection and implementation process and greater focus on facilitating the launch and execution of the trial.**
- **The process of peer review for trial concepts should be strengthened and streamlined and should entail the evaluation of concise proposals (including the intended statistical design) that are ranked against each other. The emphasis should be on scientific strength and opportunity, innovation, feasibility, and the importance to improving patient outcomes.**
- **Steering committees administered by NCI should operate independently of NCI staff and should focus on the prioritization of**

clinical needs and scientific opportunities, selection of trial concepts proposed by the Cooperative Group disease site committees, and facilitation of communication and cooperation among the Groups.

Since the funding mechanism for the Cooperative Group Program was changed from grants to cooperative agreements in 1980, NCI has exercised oversight of every aspect of the clinical trials process, including trial selection, protocol development, and trial operations. NCI has crucial responsibilities in the clinical trials system, for example, by providing a framework for both cooperatively and competitively organized interactions between Groups and their committees and in the management of IND sponsorship. As already noted in Recommendation 2, there are numerous steps that NCI could take to further improve the support and facilitation of high-priority trials. Helping Group investigators gain access to more experimental therapeutic agents for high-priority trials by filing an IND application would reduce the time that the Groups spend in negotiations with industry to acquire agents before a trial is launched and also ensure the availability of the agent during the trial.

At the same time, it is necessary to reassess NCI's role and interaction with the Groups, which has evolved over the past 50 years and has become quite complex. NCI has leadership and legal obligations associated with holding an IND, but in cases in which NCI does not hold the IND, NCI should shift its limited resources from oversight to support of the trials process. A Cooperative Group whose trial concept has scored well in peer review should be able to request assistance from NCI as needed to develop and implement the protocol, but it should have the necessary expertise to develop and run the trial without extensive oversight by NCI, which can delay the process. Specific research projects funded through other grant mechanisms on the basis of peer review (the bulk of NCI extramural funding) are not subjected to such oversight.

The role of the steering committees should also be reevaluated. The historical CTEP approval rate for trial concepts before implementation of the steering committees was about 65 percent. As of January 1, 2010, the approval rate under the new system was not substantially different, with 62 percent of the concepts reviewed by these committees being approved. The length of concept proposals has also increased substantially (now about 20 to 25 pages compared with 10 to 12 pages in the past), making the review process more arduous. Moreover, multiple layers of review still slow the process, and trial concepts are still not ranked against each other with consistent criteria, as is usually done in peer review. Steering committees review and vote up or down on trial concepts as they are submitted and NCI staff actively participate in the review process, unlike other NCI

peer review groups. In addition, there is little interaction among the disease-specific steering committees to determine trial priorities across disease categories, nor do they consider how to balance the inclusion of Phase II or Phase III trials in the trial portfolio, although the steering committees are charged with "guiding the development of strategic priorities." A possible alternative approach might be for the steering committees to identify research priorities and then issue requests for proposals to address them. If the steering committees continue to function as peer-review bodies, then NCI should have a more traditional role of facilitating the review process rather than actively participating in it.

In any case, it is imperative to strengthen the process for selecting high-priority trials. Launching only the highest-ranked trials would improve quality, speed advances, and ensure that patients are enrolling in the most meaningful and potentially beneficial trials.

Recommendation 9: NCI, Cooperative Groups, and physicians should take steps to increase the speed, volume, and diversity of patient accrual and to ensure high-quality performance at all sites participating in Cooperative Group trials. For example, they should

- **develop electronic tools that cue physicians practicing oncology via electronic medical record systems about trials for which a particular patient is eligible;**
- **encourage patient eligibility criteria that allow the broadest participation possible;**
- **encourage greater enrollment in high-priority trials, regardless of where the trial originates;**
- **establish a centralized credentialing system for participating sites;**
- **eliminate investigators and sites with low rates of accrual or inadequate data management skills or quality;**
- **strive to make participation in clinical trials a key component of clinical practice and to achieve the exemplary attributes of the American Society of Clinical Oncology for academic and community clinical trial sites, including high accrual rates[4] of 10 percent or more; and**
- **encourage greater participation of patient advocates in trial concept development and accrual planning, and partnerships with patient advocacy organizations to support accrual efforts.**

[4]The American Society of Clinical Oncology defines "accrual rate" as the number of patients enrolled in trials annually/number of new patients seen annually.

Rationale

Surveys indicate that the most important factor affecting patient accrual in clinical trials is whether a care provider offers participation in a trial to his or her patients. The majority of patients who participate in clinical trials are enrolled by a small percentage of participating sites, while many sites enroll only a few patients in trials to maintain their status as investigators. These circumstances can contribute to the underrepresentation in clinical trials of minority and medically underserved populations. Given the importance of trials in generating the evidence needed to make the best treatment decisions, more physicians should be encouraged to include trial participation in their clinical practice.

As noted in Recommendation 10, providing adequate case reimbursement would help to align physician and patient incentives and facilitate higher accruals at participating sites. However, another obstacle to increasing patient enrollment is that physicians may lack timely and easy-to-access information about clinical trials that would be appropriate for their patients. Some public databases with information about clinical trials exist, but in their current form, they may not adequately serve the information needs of physicians and patients as they are not part of the normal work flow of a busy clinical practice. User-friendly electronic tools, available with the right features for a physician's work flow, would increase awareness of trials and make it easier for physicians and patients to enroll in the most appropriate studies.

Eligibility criteria present another challenge to increasing enrollment. Historically, stringent eligibility criteria have excluded many patients, including, for example, those with prior cancers or certain prior treatments. However, it has been argued that the adoption of less restrictive eligibility criteria for most studies would permit more rapid accrual and would also allow broader generalizations to be made, would better mimic the situation as it occurs in medical practice, and reduce the complexity and costs of clinical trials without compromising patient safety or requiring major increases in sample size. Greater involvement by patient advocates could help facilitate this change. Patient advocates also provide valuable input to study design and procedures, safety and confidentiality issues, feasibility, informed-consent processes, and other factors important to potential research participants to help facilitate the development, implementation, and recruitment processes.

Ensuring consistent quality at participating trial sites is also important. Site credentialing requirements vary among the Cooperative Groups, making the credentialing process onerous for sites that wish to engage with multiple Groups. A centralized credentialing system, perhaps outsourced to an independent entity, would increase consistency and quality across

sites and eliminate the burden of recredentialing. Such a system would also facilitate higher levels of enrollment in high-priority trials, regardless of where the trial originates, because sites would be credentialed to participate in any Cooperative Group trial. Moreover, elimination of sites with low rates of accrual would reduce costs and improve the efficiency of the clinical trial system.

Recommendation 10: NCI should allocate a larger portion of its research portfolio to the Clinical Trial Cooperative Group Program to ensure that the Program has sufficient resources to achieve its unique mission.

- **NCI should increase the per case reimbursement rate and adequately fund highly ranked trials to cover the costs of the trial, including the costs of biomedical imaging and other biomarker tests that are integral to the trial design.**
- **To ensure sufficient funding for high-priority trials, the total number of NCI-funded trials undertaken by the Cooperative Groups should be reduced to a quantity that can be adequately supported.**
- **External advisory boards, such as the National Cancer Advisory Board and the Board of Scientific Advisors, should have a greater roles in advising NCI on how it allocates its funds to support a national clinical trials program.**

Rationale

High-priority trials must be adequately funded to efficiently and effectively attain results that can move the field forward. Compromising the science to launch more trials than the available funding can support is detrimental to progress. Innovative approaches to leveraging funding from sources other than NCI, as described in Recommendation 4, could also strengthen the Program, but NCI has an obligation to adequately fund trials identified as being of high priority. NCI should increase the total funding allocation for the Cooperative Group Program to ensure the effective translation of discoveries made with public funding to improved clinical care.

A first important step will be to raise the per case reimbursement, which has been set at $2,000 since 1999, although the median costs are estimated to be from $3,500 to $6,000 per patient. The many duties required of physicians and other key research staff, such as research nurses and clinical research associates, to participate in clinical trials are costly in terms of both time and resources. For example, before a trial can be opened at a particular site, much work must be done to ensure compliance with federal regulations

governing human subjects research. Once a trial is opened, a significant amount of time is spent discussing potential trial options with patients. If a patient enrolls, the data collection and documentation requirements are substantially more onerous than they are for patients receiving standard therapy outside of a trial. These voluntary contributions of clinicians who participate in the Cooperative Group Program constitute a substantial value and strength of the Program. However, when the discrepancy between the per case reimbursement and the actual cost of participation is excessive, as it is now, it becomes a major disincentive to participation. A substantial increase in the NCI per case reimbursement rate would constitute a major step toward aligning the incentives of physicians with those of their patients who wish to participate in clinical trials. Even in the absence of a substantial increase in the overall funding of the Program, the funds saved by launching fewer but higher-priority trials could be allocated for increased per case reimbursements to trial sites.

The existing system also often does not provide the resources required to thoroughly characterize each patient's tumor and carefully match that profile to targeted therapeutics. Biomedical imaging and other biomarker tests are commonly becoming integral components of modern cancer clinical trials, but supplemental funding for these tests must be obtained by the Cooperative Groups through other support mechanisms.

The allocation of NCI funds among the competing needs of its various programs is a major challenge for the NCI director, who must take many factors into consideration. Greater input from the broad expertise and experience of external advisory boards, such as the National Cancer Advisory Board and Board of Scientific Advisors, would be helpful to ensure the most rational distribution of funds across the major NCI programs, in light of such factors as scientific opportunity and clinical need. These high-level boards should not be involved in the oversight of individual trials or in concept review, which would further slow the process, but rather, they should have a greater influence on how much funding is allocated to the overall Cooperative Group Program.

GOAL IV. INCENTIVIZE THE PARTICIPATION OF PATIENTS AND PHYSICIANS IN CLINICAL TRIALS

Background

A robust clinical trials infrastructure is largely dependent on a critical mass of patients and physicians willing to participate in clinical trials. However, current indications suggest that participation in clinical trials is the exception rather than the rule, both for patients and for physicians. For clinical investigators, concerns about reimbursement, extensive regulatory

burdens, and academic procedures regarding tenure, promotion, and career development can all deter participation in trials. Investigator participation in trials requires substantial resources and staff. Given the limits in funding and capacity of the system, it is unrealistic to expect all or most clinicians to participate in trials, but those who are motivated to do so should be supported and encouraged.

Patient access to clinical trials is also an import issue to consider. Even if patients are eligible for trials and are informed about the option by their physicians (as discussed in the section describing Goal III), they may decline because of financial concerns, as coverage of patient care costs in clinical trials by health insurers is not consistent.

Recommendations 11 and 12 provide strategies to achieve the goals of increased participation by physicians and patients in Cooperative Group clinical trials.

Recommendation 11: All stakeholders, including academic medical centers, community practices, professional societies, and NCI, should work to ensure that clinical investigators have adequate training and mentoring, paid protected research time, the necessary resources, and recognition. For example,

- **NCI should recognize and reward Cooperative Group efforts in Cancer Center Support Grant (CCSG; P30) site visits, and allow the CCSG research base to include the federal per case funding received by cancer centers that participate in Cooperative Group trials.**
- **NCI should provide funding to site and trial principal investigators to cover the time that they need to develop and oversee approved trials.**
- **Academic medical centers should develop policies and evaluation metrics that recognize and reward clinical and team research in promotion and tenure decisions.**
- **NCI should work with a nonprofit foundation to develop a certification program and registry, as recommended by the Clinical Trials Working Group.**

Rationale

Multiple stakeholders need to take steps to support the recruitment and retention of clinical investigators both in community practice and in academia. The large-scale, multi-institutional trials that are the hallmark of the Cooperative Group Program require a team approach to research. However, career advancement in the field has traditionally focused on individual accomplishment. The current system does not adequately recognize,

reward, or support collaborative work. Furthermore, clinical investigation is often accorded less value than either basic research or patient care. This must change if the goal is to have talented individuals embark on a career that entails active participation in clinical trials for cancer as well as other diseases. Clinical research is a complex endeavor that requires training, mentoring, and paid time set aside for research to master and apply the skills needed to undertake innovative trials.

For example, the provision of funds for principal investigators to cover the time that they need to develop and oversee approved trials could improve the speed and quality of those trials. Recognizing the per case reimbursements for Cooperative Group trials in the CCSG assessment of a cancer center's funding base would acknowledge the importance of patient accrual in these trials and encourage broader participation at those centers. A certification program for all research staff (including physicians, nurses, clinical research associates, pharmacists, etc.) would recognize the valuable contributions that these professionals make to the improvement of patient care and treatment.

Ultimately, the inability to recruit, train, and retain a sufficient number of talented clinical investigators will compromise the ability to conduct clinical trials in the United States, to the detriment of the U.S. biomedical research enterprise and to patients, those who participate in clinical trials as well as those who do not. Clinical trials help to raise the standard of care in the community by setting examples, and they have educational and training value for the oncologists involved, as physicians gain early knowledge of new drugs and gain experience with delivering complex therapies.

Recommendation 12: Health care payment policies should value the care provided to patients in clinical trials and adequately compensate that care. For example, the Centers for Medicare & Medicaid Services (via a national coverage decision), federal and state health benefits plans, and private health insurers should

- **establish consistent payment policies to cover all patient care costs (except for study-related costs, such as study drugs, devices, and tests, which should be paid for by the manufacturer) in clinical trials approved through the NCI prioritization mechanism, without having to pay for experimental therapies administered to patients outside of a clinical trial (any such limitation in coverage should not affect off-label use that is backed by evidence from clinical trials published in the scientific literature, as evidence-based off-label use constitutes the standard of care for many cancer therapies and is therefore not experimental) and**

- **work with health care providers to educate patients more effectively about the availability, payment coverage, and value of clinical trials.**

In addition,

- **The American Medical Association should establish new *Current Procedural Terminology* codes, reimbursed by the Centers for Medicare & Medicaid Services, private insurers, and other third-party payors, to pay an enhanced reimbursement for offering, enrolling, managing, and following a patient in a clinical trial.**
- **The U.S. Congress should amend the Employee Retirement Income Security Act of 1974 to prohibit health plans from denying (or from limiting or imposing additional conditions on) coverage for the routine care associated with clinical trial participation.[5]**

Rationale

Inadequate health care coverage is a major deterrent to participation in clinical trials for patients as well as physicians. Health care insurers traditionally have not paid for experimental therapies. However, much of the care provided to cancer patients is similar regardless of whether the patient is receiving a standard of care or an experimental drug. Some insurers and states acknowledge this and provide reimbursement for the routine clinical care of patients enrolled in trials, whereas others do not. The policies of the Centers for Medicare & Medicaid Services (CMS) regarding coverage of care in clinical trials have recently been in flux and, absent national coverage

[5] After the committee had completed its report, the Patient Protection and Affordable Care Act (H.R. 3590) was signed into law by President Barack Obama on March 23, 2010, which provides coverage of routine care costs for individuals participating in approved clinical trials. According to this Act, a group health plan or a health insurance issuer "may not deny (or limit or impose additional conditions on) the coverage of routine patient costs for items and services furnished in connection with participation in the trial." As stipulated by the legislation, routine patient care costs include all items and services consistent with the coverage provided in the plan (or coverage) that is typically covered for a qualified individual who is not enrolled in a clinical trial. Approved clinical trials include Phase I–IV studies relating to the prevention, detection, or treatment of cancer or other life-threatening diseases or conditions that are either (a) federally funded; (b) a study or investigation conducted under an investigational new drug application reviewed by FDA; or (c) a drug trial that is exempt from having such an investigational new drug application. This provision will go into effect in 2014 and is intended to apply to both types of ERISA plans as well as plans offered by the Federal Employees Health Benefits Program. The Patient Protection and Affordable Care Act, H.R. 3590, 111th Cong., 2nd sess., Coverage for Individuals Participating in Approved Clinical Trials, § 2709 (March 23, 2010).

decisions, may not be nationally uniform because fiscal intermediaries and carriers have some discretion on coverage, which can cause variations and inconsistencies by geographical region. Furthermore, the provisions of the Employee Retirement Income Security Act of 1974 (ERISA), which places the regulation of employee benefit plans (including health plans) primarily under federal jurisdiction for about 131 million people, preempts state laws governing such things as access to care and mandated coverage.

Thus, coverage of care in clinical trials is variable and may be uncertain, and patients who are interested and willing to enroll in a trial may decline because of an inability to pay for care that is not or may not be covered. Others might still enroll but may then experience significant financial hardship as a result. If such patients drop out of the trial, the scientific integrity of the trial can be compromised because of inferential problems that result from missing data. If cancer care is to be evidence based and relevant to the diverse population of patients with cancer, it is important for coverage policies to encourage rather than deter patient enrollment in trials. However, as a quid pro quo for improved coverage of care in clinical trials, insurers should be able to eliminate coverage of experimental therapies delivered outside of the clinical trial setting. Currently, many patients who are not enrolled in trials receive experimental therapy and expect coverage for it. The committee's recommended approach is analogous to the "coverage with evidence development" mechanism that CMS has occasionally used, in which coverage is provided only within the context of a clinical trial. However, any such limitation in coverage should not affect off-label indications backed by evidence from clinical trials published in the scientific literature, as off-label use constitutes the standard of care for many cancer therapies and is therefore not experimental.

For physicians, even in cases in which routine patient care in a clinical trial is covered by health insurers, the current payment policies do not reflect the additional time needed to enroll and follow patients in a trial. For example, if a patient receiving off-protocol chemotherapy reports an adverse event or unanticipated problem, the physician can respond however he or she thinks is clinically the most appropriate. However, if a patient on a protocol who receives the same therapy reports the same adverse event, the physician must grade the severity, assess the attribution, document the event, consult the protocol, and make treatment modifications as required by the protocol. New codes in the *Current Procedural Terminology*, with higher reimbursement rates that acknowledge the additional time and resources needed to counsel and care for a patient in a clinical trial would address an important deterrent to physician participation in clinical trials. With a proper definition of eligible trials, use of such a code could easily be audited.

However, taking steps to align the incentives of patients and providers to participate in clinical trials may not be effective unless more is done to

educate patients about the availability and value of clinical trials. Educational efforts should focus on making the general population more aware of clinical trials. One reason is that it can be difficult for patients to sort through a large volume of new information and make complex decisions just after they have received a diagnosis of a life-threatening illness. Patients often lack comprehensive and reliable information about clinical trials and may not be able to identify the trials for which they might be eligible. Patients value reliable information from trusted sources, including family members, so appropriate education efforts could provide useful information that would allow patients to make informed choices about participation in a clinical trial. In addition, as noted in more detail in Recommendation 9, user-friendly electronic tools would increase awareness of clinical trials and make it easier for physicians and patients to enroll in the most appropriate studies.

SUMMARY

Collectively, the implementation of these recommendations would reinvigorate the Clinical Trials Cooperative Group Program for the 21st century and strengthen its position as a critical component of the translational pathway from scientific discovery to improved treatment outcomes for patients with cancer. Modifying any particular element of the Program or the clinical trials process will not suffice; changes across the board are urgently needed. All participants and stakeholders, including physicians, patients, and health care insurers, as well as NCI, other federal agencies, academia, foundations, and industry, must reevaluate their current roles and responsibilities in cancer clinical trials and work together to develop a more effective and efficient multidisciplinary trials system.

The Cooperative Group Program is beset by serious problems, but they are not intractable. The committee envisions a system that retains the current strengths, but moves beyond collaboration to integration, with reorganized structures and operations in a truly national clinical trials network and with sufficient funding and support to enable the rapid completion of well-designed, high-priority cancer clinical trials that advance patient care.

1

Introduction

Advances in biomedical research have produced significant opportunities to improve cancer prevention, detection, and treatment. Insights about the genomic and molecular mechanisms of disease have enabled basic scientists to identify new therapeutic targets and develop new agents that are changing the paradigm of cancer research from the development of nonspecific, broadly toxic chemotherapies to the development of highly targeted combinations of therapies. However, the ability to translate biomedical discoveries into advances in cancer care remains dependent on the clinical trials system. Clinical trials provide an essential link between scientific discovery and clinical practice. These trials are crucial to the translation of new knowledge into tangible benefits for patients, and the knowledge gained in a clinical trial can also inform and guide further research into the biology of the disease.

Since its inception in the 1950s, the Clinical Trials Cooperative Group Program has been instrumental in establishing the standards for the care of patients with cancer and for clinical research methods. Research undertaken by the Cooperative Groups has contributed to significant advances in cancer treatment and prevention, including the introduction of new treatments and the use of established treatments for new indications that have led to improved survival and increased cure rates, particularly for pediatric cancers and some early-stage cancers in adults. Furthermore, the importance of the Cooperative Group Program is growing as industry trials are increasingly being conducted outside of the United States. The Cooperative Group Program provides a primary mechanism by which the value of therapeutic agents can be assessed within the medical milieu of the U.S. health care system. However, despite these important contributions and a long record

of accomplishments, the Cooperative Group Program is facing numerous challenges that threaten its ability to continue to undertake large-scale, innovative trials that benefit patient care. Confronting these challenges is essential. A national cancer clinical trials enterprise is necessary "to ensure that the advances in understanding the biological basis of cancer, generated by the past 40 years of research, are harnessed effectively to bring measurable, meaningful benefits to patients" (NCI, 2005).

IMPORTANCE OF CANCER CLINICAL TRIALS

Clinical trials are essential for establishing the evidence base that the oncology community uses to make treatment decisions and to determine the direction of future clinical research. By evaluating the safety and efficacy of new therapies, comparing the effectiveness of existing therapies, and assessing different prevention, screening, and detection strategies, clinical trials are responsible for setting the standard of patient care. In fact, today's most effective therapies began as hypotheses tested within the clinical trials environment (C-Change and Coalition of Cancer Cooperative Groups, 2006). Clinical trials also provide fundamental information about the biology of cancer, which investigators leverage to advance preclinical research and drug development.

Numerous stakeholders conduct clinical trials with various goals across the spectrum of research. While industry trials primarily focus on drug discovery and development activities with the potential for a substantial return on investment, publicly sponsored trials have a more diverse portfolio, from small, proof-of-concept Phase I and II studies that typically enroll patients with metastatic disease who have already had one or more lines of therapy to large Phase III studies that may focus on adjuvant or neoadjuvant therapy, first-line therapy for metastatic disease, or prevention strategies. Publicly sponsored trials are also more likely to study less common cancers that are not often a focus of industry research and development.

The National Cancer Institute (NCI) supports the largest U.S. network for clinical trials of any type through the use of several different funding mechanisms. NCI supports individual trials through grant mechanisms and research contracts, funds programs that use clinical trial data to advance preclinical research, and also partially funds cancer centers that conduct clinical trials as a component of their overall research and patient care activities. In addition, NCI supports trials through cooperative agreements, such as the Clinical Trials Cooperative Group Program. The various recipients of the funds provided by the use of these different funding mechanisms bring different strengths to the research portfolio.

The largest component of the NCI-supported clinical trials portfolio is the Clinical Trials Cooperative Group Program. The Cooperative Group

Program is the major mechanism through which large-scale cancer clinical trials are conducted in the public interest. The expansive, multi-institutional clinical trials infrastructure maintained by the Cooperative Group Program is recognized for its fundamental importance in reaching a large, diverse community-based patient population, acquiring high-quality data and biospecimens that advance preclinical research, and incorporating a broad range of expertise into trial design, implementation, and statistical analyses. Within the portfolio of NCI-supported clinical trials, the Cooperative Group Program primarily focuses on late-stage translation activities, such as large Phase II and Phase III clinical trials that may have implications for changing treatment practices directly relevant to patient care. Individual institutions can rarely undertake such trials because it would take too long to accrue a sufficient number of patients to achieve timely results.

THE CLINICAL TRIALS COOPERATIVE GROUP PROGRAM

The Clinical Trials Cooperative Group Program began in 1955. At that time, the U.S. Congress was interested in developing a more systematic and planned program for the study of chemotherapy in cancer treatment because studies had shown that the treatment of leukemia and lymphoma with alkylating agents, steroids, antifolate, and mercaptopurine could occasionally result in complete remission of these cancers. Congress appropriated $5 million to establish the Cancer Chemotherapy National Service Center, and NCI initiated the Cooperative Group model to test chemotherapeutic agents in clinical trials. By 1958, 17 Cooperative Groups had been organized and operated under research grants from NCI. Federal funding for chemotherapy research continued to climb: in 1958 alone, Congress appropriated $25 million (Zubrod, 1984).

In the beginning, the primary objective of the Clinical Trials Cooperative Group Program was to test new anticancer agents from NCI's drug development program. However, between 1955 and 1966, NCI underwent an internal reorganization. In recognition of the importance of clinical trials as an independent research activity, the Cooperative Group Program was separated administratively from the drug screening program and transferred to the Cancer Therapy and Evaluation Branch of the Chemotherapy Program (Keating and Cambrosio, 2002).

During the following decades, NCI implemented some organizational changes to the Program. In 1980–1981, the mechanism of support for the Cooperative Group Program was converted from a grant to a cooperative agreement, which had a profound effect on the Cooperative Group Program. A cooperative agreement enabled NCI to have a considerable role in Cooperative Group activities, including trial concept selection, protocol development, and trial operations (CTEP, 2006) (these are described fur-

BOX 1-1
NCI Cooperative Group Program 2010

The NCI Cooperative Group Program is composed of 10 Groups:

- American College of Radiology Imaging Network (ACRIN)
- American College of Surgeons Oncology Group (ACOSOG)
- Cancer and Leukemia Group B (CALGB)
- Children's Oncology Group (COG)
- Eastern Cooperative Oncology Group (ECOG)
- Gynecologic Oncology Group (GOG)
- National Surgical Adjuvant Breast and Bowel Project (NSABP)
- North Central Cancer Treatment Group (NCCTG)
- Radiation Therapy Oncology Group (RTOG)
- Southwest Oncology Group (SWOG)

ther in Chapter 3). In 1983, the Community Clinical Oncology Program (CCOP) was established to ensure that community physicians and cancer patients not treated in academic medical centers had access to cancer clinical trials and to boost the rates of accrual to clinical trial protocols. NCI established the Minority-Based CCOP in 1990 to increase the involvement of racial and ethnic minority patients in clinical trials research and to improve access to the latest advances in cancer treatment, prevention, and control (NCI, 2003).

Cooperative Group membership has evolved over time (Hoogstraten, 1980), and the Program currently includes 10 Cooperative Groups (the names of the 10 Groups and the abbreviations for the groups used throughout the remainder of this chapter are presented in Box 1-1). The focus of each Group varies, but there are four main types of groups: (1) disease-oriented Groups (e.g., GOG); (2) Groups that focus on high-technology, single-modality studies (e.g., RTOG); (3) Groups in which investigators focus on a particular patient population (e.g., COG); and (4) multimodality Groups. Over time the Cooperative Groups have expanded their research mission beyond testing new anticancer agents from NCI's drug development program to include cancer treatment, prevention, early detection, quality of life issues, rehabilitation, and comparative effectiveness. Each year more than 25,000 patients participate in multi-institutional clinical trials involving more than 3,100 institutions and 14,000 investigators within the 10 Cooperative Groups.[1]

[1] Some funds from the Cooperative Group Program also support the European Organisation for Research and Treatment of Cancer and the NCI of Canada—Clinical Trials Group.

ACHIEVEMENTS OF THE COOPERATIVE GROUP PROGRAM

The Cooperative Groups have been responsible for numerous advances in cancer research, treatment, and prevention and in the training of investigators. Over the five decades since its inception in the 1950s, the high-quality research conducted by the Cooperative Groups has been instrumental in establishing the standards of cancer patient care and clinical research methods (Mauer et al., 2007), and research undertaken by the Cooperative Groups leads to more than 200 peer-reviewed publications annually. Cooperative Group accomplishments can be organized by influential trials that have, over the 50 years of the Groups' existence, incrementally provided practitioners with evidence to guide the treatment of patients with cancer (see Box 1-2 for a list of some of these accomplishments). Likewise, Cooperative Group accomplishments can be organized thematically by clinical objective and type of disease. Cooperative Group research has led to the

- development of new standards for the management of patients with cancer;
- development of sophisticated investigative techniques;
- collection of data to obtain regulatory approval for new drugs or new drug indications;
- refinement in diagnosis and treatment of cancer based on the identification of histologic subtypes of tumors and the recognition of prognostic variables;
- development of adjuvant and neoadjuvant chemotherapy and concurrent chemoradiotherapy for solid tumors through studies that combine modalities;
- refinement of the use of chemotherapy through the study of new agents and different dosing schedules;
- comparison of new cancer treatments against the best available treatments; and
- development of novel therapeutic agents in Phase I and II trials (Mauer et al., 2007).

Significant advances derived from Cooperative Group research include improvements in the treatment of childhood cancer, the treatment of solid tumors and hematologic malignancies in adults, adjuvant therapy, and combined-modality treatment. Additionally, trials of cancer prevention and the publication of negative findings from Cooperative Group research greatly contribute to ensuring the use of evidence-based treatment and prevention strategies.

BOX 1-2
A Sampling of Cooperative Group Accomplishments

Pediatric cancers

- Development of effective treatments for childhood cancers, including Wilms' tumor, leukemia, and rhabdomyosarcoma, which have improved the cure rates for childhood cancers from less than 10 percent when the Cooperative Groups were first founded to nearly 80 percent today. The outcome of acute lymphoblastic leukemia (ALL) has progressed from a 6-month median survival to an 80 percent overall cure rate. There has also been substantial improvement in the 5-year cancer survival rates; between 1960 and 2000, the 5-year rate of survival for children with solid tumors increased from 27 to 80 percent.
- The high rate of participation of children in Cooperative Group trials; if a clinical trial is available, 50 to 60 percent of children eligible are enrolled and 90 percent of children under age 5 years are enrolled. With high participation rates, the results of clinical trials performed by COG define the standard of care for children with cancer in the United States and elsewhere.
- Definition of new risk-based classification schemes that use clinical and expanded biological factors for ALL, acute myeloid leukemia (AML), and neuroblastoma (NBL). These classification schemes are used at the time of diagnosis to determine therapy on the basis of risk.
- Incorporation of minimal residual disease (MRD) assessments at distinct points in therapy into trial design to ascertain the impact of an earlier intervention on the basis of this surrogate marker, given the degree of correlation between the early outcome, the response to therapy, and the presence of MRD in patients with ALL, AML, and NBL.
- Identification of candidate genes and patterns of gene expression as predictors of outcomes in ALL, NBL, and meduloblastoma.
- Clinical translation of targeted agents in pediatric cancers. For example, antibody-based immunotherapy (chimeric anti-glycoprotein D2 antibody ch 14.18) in NBL improved the rate of event-free survival by 20 percent after stem cell transplantation for these high-risk patients.
- For Philadelphia chromosome-positive (Ph+) ALL, the integration of imatinib into an aggressive chemotherapy backbone resulted in a significant improvement in the rate of overall survival for children with Ph+ ALL. The rate of event-free survival after treatment with imatinib and aggressive chemotherapy appears to be superior to that obtained historically by the use of stem cell transplantation. Whereas stem cell transplantation provided the best curative option for children with Ph+ ALL, prolonged follow-up has demonstrated that superior outcomes are achieved with imatinib treatment plus chemotherapy. This also has significant ramifications for the treatment of adults, given the high incidence of Ph+ ALL in adults with ALL.

Hematologic malignancies

- Development of the framework for the current therapy of patients with AML. Trials also defined the standard of care for patients with AML, refining classification of leukemia to include cytogenetic and molecular genetic characteristics (CALGB).

- First demonstration of the significant progression-free survival benefit of using fludarabine during first-line therapy in patients with chronic lymphocytic leukemia (CLL), leading to fludarabine becoming a standard of care for the initial therapy of CLL (CALGB).
- Clinical development and Food and Drug Administration (FDA) approval of 5-azacytidine for the treatment of myelodysplastic syndrome (CALGB).
- Definition of the role of all-trans retinoic acid in the induction and maintenance of acute promyelocytic leukemia (ECOG).
- Trials to establish thalidomide plus dexamethasone as standard of care for patients with newly diagnosed myeloma. Trial E1A00 was the basis for the approval of thalidomide for the treatment of myeloma by the FDA in 2006 (ECOG).
- Demonstration of three cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) plus involved field radiotherapy as the standard therapy for early-stage, nonbulky, aggressive non-Hodgkin's lymphoma (SWOG).

Breast cancer

- Landmark trials supporting the use of more conservative, less disfiguring treatment of breast cancer, altering the standard of care toward breast-conserving therapy. These trials demonstrated equivalent survival between patients undergoing radical mastectomy and patients undergoing total mastectomy and then equivalent rates of survival and in-breast recurrence between patients undergoing lumpectomy and patients undergoing total mastectomy when lumpectomy and mastectomy were followed by radiation therapy (NSABP).
- Demonstration of a significant survival benefit of adjuvant treatment with trastuzumab, a monoclonal antibody, in women with human epidermal growth factor receptor 2 (HER-2)-positive breast cancer (NCCTG, NSABP).
- Development of Oncotype DX, a 21-gene assay that predicts the benefit of chemotherapy and the 10-year risk of a recurrence of breast cancer, using clinically annotated Cooperative Group tumor blocks. Oncotype DX testing enables some women to safely forgo chemotherapy treatment and its associated side effects (NSABP).
- Demonstration by the Breast Cancer Prevention Trial that tamoxifen treatment reduced the incidence of breast cancer by nearly 50 percent in women with an increased risk of developing breast cancer (NSABP).
- Demonstration that tamoxifen and raloxifene are equally effective in reducing the risk of invasive breast cancer (NSABP).
- Development and demonstration of clinical effectiveness of dose-dense adjuvant therapy for breast cancer (CALGB).
- Definition of the role of adjuvant paclitaxel as part of adjuvant therapy for breast cancer leading to FDA approval of the use of paclitaxel for this indication. Correlative science studies found that the benefit of adding paclitaxel was limited primarily to women with estrogen receptor-negative and HER-2-positive tumors (CALGB).

continued

BOX 1-2 Continued

- Demonstration that patients receiving adjuvant tamoxifen for breast cancer with reduced cytochrome P-450 2D6 (CYP2D6) activity or those receiving CYP2D6 inhibitors have shorter lengths of disease-free survival compared to those with highly active CYP2D6 (NCCTG).
- Assessment of the beneficial role of hormonal therapy plus chemotherapy in premenopausal women with hormone receptor-positive, node-positive breast cancer. Before the trial, the combination of hormonal therapy and adjuvant chemotherapy was of uncertain benefit in this patient group (ECOG).
- Demonstration that breast cancer patients with positive axillary nodes benefit more (significantly superior rates of disease-free and overall survival) from 1 year of combination chemotherapy (cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, and prednisone) compared with the benefit achieved from 2 years of therapy with a single agent (melphalan). Additional trials built on this combination chemotherapy (SWOG).
- Comparison of the effectiveness of different imaging strategies has refined imaging usage. For example, a trial demonstrated that digital mammography is superior to film-screen mammography for a subset of women (e.g., women with dense breasts, such as those who are younger and pre- or perimenopausal) (ACRIN).

Lung cancer

- Development of combined-modality treatment for Stage III non-small-cell lung cancer (NSCLC) as a standard of care (CALGB).
- Demonstration that both radiation therapy and chemotherapy are effective in elderly patients with lung cancer but that the risk of toxicity is substantially greater in older patients (NCCTG).
- Demonstration that bevacizumab can improve the response rate, the length of progression-free survival, and the overall survival rate when it is combined with chemotherapy for the first-line treatment of NSCLC (ECOG).
- First randomized comparison of new agent-platinum chemotherapy regimens (vinorelbine-cisplatin versus paclitaxel-carboplatin) for advanced NSCLC, which found improved tolerability of the paclitaxel-carboplatin combination (SWOG).
- Demonstration that healthier patients with inoperable NSCLC had better results if they received chemotherapy during their course of radiotherapy rather than before radiotherapy (RTOG).

Gastrointestinal cancer

- Demonstration that adjuvant chemotherapy improves the rate of survival in patients with Stage III colon cancer (NCCTG).
- Demonstration that bevacizumab (a vascular endothelial growth factor [VEGF] inhibitor) significantly improved the rate of overall survival when it was used in combination with a regimen of oxaliplatin, fluorouracil (5-FU), and leucovorin (FOLFOX4) in patients with advanced colorectal cancer, expanding the FDA-approved indication for bevacizumab (ECOG).
- Demonstration that oxaliplatin added to infusional 5-FU as first-line therapy improves the rate of survival in patients with metastatic colorectal cancer (NCCTG).

- Demonstration that the 3-year disease-free survival rate is a valid surrogate of the 5-year overall survival rate in patients receiving adjuvant 5-FU-based chemotherapy for resected colon cancer (NCCTG).
- Demonstration that laparoscopic resection of colon cancer is as effective as open colectomy for the treatment of localized colon cancer (NCCTG).
- Change of the standard of care for adjuvant therapy for Stage II and III colon cancer. Over time, trials evaluating different adjuvant approaches found significant survival advantages for first 5-FU plus levamisole, then for 5-FU plus leucovorin, and finally 5-FU plus leucovorin plus oxaliplatin, improving patient outcomes (NSABP).
- Validation of the utility of combined-modality therapy for localized esophageal cancer. Investigators observed a 4.5-year median survival rate and a 39 percent 5-year survival rate for patients randomized to induction chemoradiotherapy followed by surgery but a 1.8-year median survival rate and a 16 percent 5-year survival rate for those randomized to surgery alone. Although this trial had limited accrual, it is unlikely that a more robust trial will be undertaken as a result of these findings and the direction of the field (CALGB).
- Prevention trials, such as one demonstrating that aspirin reduced the risk of development of colon adenoma in patients with colon cancer treated by complete resection of the colon (CALGB).
- Demonstration that adjuvant chemotherapy plus radiation improves survival in patients with Stage II and III rectal cancer (NCCTG).
- Significantly improved survival for patients with advanced pancreatic adenocarcinoma when they received the drug gemcitabine, in addition to standard therapy, after surgery (RTOG).

Genitourinary cancer

- Demonstration that finasteride can significantly alter the risk of prostate cancer in men over 55 years of age (SWOG).
- Determination that radiotherapy combined with long-term hormone suppression significantly improves the survival rate for men with high-grade prostate cancer (Gleason Score 8 to 10). However, men with locally advanced prostate cancer (Gleason Score 2 to 6) benefit most from hormonal suppression before radiotherapy (RTOG).
- Identification of several prognostic biomarkers from specimens of patients with androgen-independent prostate cancer (AIPC) obtained in a CALGB trial. These biomarkers, including plasma and urine VEGF levels, were inversely related to the rate of survival and were independent prognostic factors. This research provided a rationale for the trial of bevacizumab in combination with docetaxel chemotherapy in patients with AIPC (CALGB).
- Demonstration of the utility of bacillus Calmette-Guérin (BCG) for the treatment of superficial bladder cancer. Immunotherapy with BCG reduces the risk of recurrence of superficial bladder cancer, establishing BCG as standard therapy and leading to a new drug approval for the use of BCG for this indication (SWOG).

continued

BOX 1-2 Continued

Brain cancer

- Demonstration that lower-dose radiation therapy is as effective as and less toxic than higher-dose radiation therapy for patients with low-grade glioma (NCCTG).
- Establishment of proof of principle that chemotherapy is effective for the treatment of patients with low-grade oligodendroglioma (NCCTG).
- Determination that chromosome arm 1p and 19q deletions in gliomas are associated with a longer period of survival in patients (NCCTG, RTOG).
- First U.S. research organization to coordinate an international brain tumor trial. This landmark study used high-dose temozolomide after radiotherapy for patients with newly diagnosed glioblastoma and is a joint effort between RTOG and the European Organisation for Research and Treatment of Cancer.
- Improvement in survival by more than 33 percent for patients with a single brain metastasis obtained by the use of whole-brain radiotherapy followed by stereotactic radiosurgery instead of whole-brain treatment alone (RTOG).

Gynecologic cancer

- Determination of the standards for multiagent chemotherapy for all gynecologic sites. For example, the trial evaluating treatment with paclitaxel-cisplatin in ovarian cancer demonstrated that paclitaxel adds further treatment benefits, including a significantly better response rate, progression-free survival, and overall survival, leading to a new standard of care (GOG).
- Confirmation of the value of cytoreductive surgery in patients with ovarian cancer (GOG).
- Demonstration that the combination of cisplatin and cyclophosphamide was not superior to carboplatin and cyclophosphamide in patients with suboptimal Stage III and IV ovarian cancer and that the combination of carboplatin and cyclophosphamide was significantly less toxic. These findings led to a new drug approval for carboplatin in 1989 (SWOG).

Childhood Cancer

One of the major accomplishments in research on and the treatment of pediatric cancer is the high rate of participation of children in Cooperative Group clinical trials. In the United States, 90 to 95 percent of all children with a newly diagnosed malignancy are seen at an institution that participates in COG (O'Leary et al., 2008). If a clinical trial is available, more than half of these children participate; for young children (less than 5 years of age), the rates of participation in a clinical trial are closer to 90 percent. The collective achievements of Cooperative Group research over the past four decades have led to effective treatments for childhood cancers and improved cure rates (Mauer et al., 2007). The age-adjusted mortality rate for

- Definition of the value of chemoradiation for the treatment of cervical cancer. Five Cooperative Group trials found that radiation therapy combined with platinum-based chemotherapy conferred mortality rate reductions of 30 to 50 percent compared with the mortality rate after radiation therapy alone for women with locally or regionally advanced cervical cancer or localized cervical cancer with poor prognostic indicators (GOG, RTOG, and SWOG).
- Definition of the pattern of spread of endometrial carcinoma and defined risk groups (GOG).
- Identification of the limited value of reassessment laparotomy (GOG).
- Confirmation of the value of intraperitoneal therapy. Intraperitoneal cisplatin and paclitaxel were associated with significantly better progression-free survival and overall survival, but they were also more toxic and had more complications (GOG).

Head and neck cancer

- Definition of the role of taxanes in the treatment of head and neck cancers (ECOG).
- Discovery that patients who received chemotherapy together with radiotherapy after surgery were far less likely to have a recurrence of cancer for patients with high-risk head and neck cancer (RTOG).

Skin cancer

- Establishment of the role of high-dose interferon alpha-2b as the first FDA-approved adjuvant therapy for high-risk malignant melanoma (ECOG).

SOURCES: Coltman, 2008; Dignam, 2004; Giantonio et al., 2008; Green et al., 2008; Grothey et al., 2008; Hillman and Gatsonis, 2008; Mauer et al., 2007; O'Leary et al., 2008; Omura, 2008; RTOG, 2009; and Wickerham et al., 2008. For further information on additional Cooperative Group achievements, see CTEP, 2002.

children with cancer has decreased since 1950 (Figure 1-1), and cure rates have increased from less than 10 percent when the Cooperative Groups were founded to nearly 80 percent at present (O'Leary et al., 2008).

Adult Solid Tumors and Hematologic Malignancies

Cooperative Group research has been instrumental in providing data on the treatment of specific tumors and hematologic malignancies. For example, landmark trials from NSABP first demonstrated equivalent rates of survival between patients undergoing a radical mastectomy and patients undergoing a total mastectomy and then between patients undergoing a

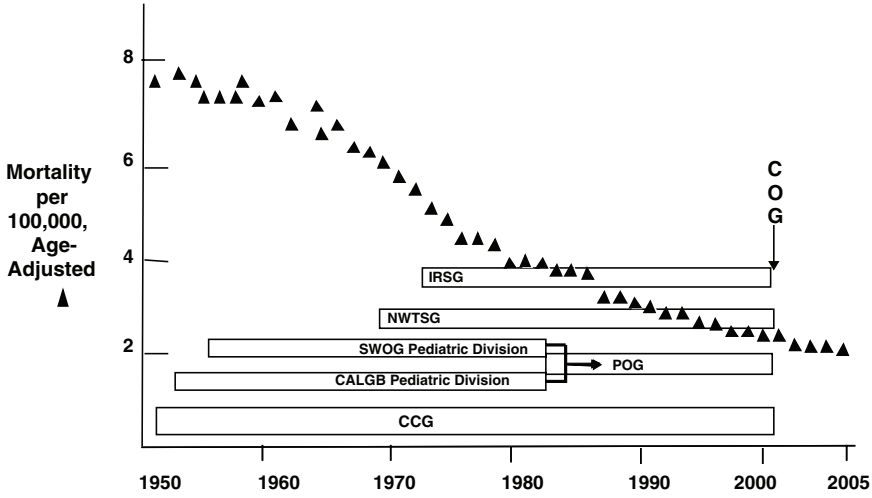

FIGURE 1-1 National rate of mortality from cancer among children younger than 15 years of age and the pediatric Cooperative Groups.
NOTE: CALGB = Cancer and Leukemia Group B, CCG = Children's Cancer Group, COG = Children's Oncology Group, IRSG = Intergroup Rhabdomysosarcoma Study Group, NWTSG = National Wilms' Tumor Study Group, POG = Pediatric Oncology Group, SWOG = Southwest Oncology Group. SWOG and CALGB previously had pediatric divisions within their cooperative group structures. In 2001, the four pediatric groups (IRSG, NWTSG, POG, and CCG) merged to form COG.
SOURCE: Reprinted, with permission, from Reaman, 2009. Copyright 2009 by Children's Oncology Group.

mastectomy and patients undergoing a lumpectomy followed by radiation therapy, ushering in an era of breast-conserving therapy (Fisher et al., 1977, 1985, 2002a,b). NCCTG demonstrated that lower-dose radiation therapy is as effective as and less toxic than higher-dose radiation therapy for patients with low-grade glioma (Shaw et al., 2002). An ECOG trial demonstrated that bevacizumab (a vascular endothelial growth factor [VEGF] inhibitor) significantly improved the overall rate of survival when it was used in combination with a regimen of oxaliplatin, 5-FU, and leucovorin in patients with advanced colorectal cancer, expanding the FDA-approved indication for the use of bevacizumab (Giantonio et al., 2007, 2008). GOG set the standards for multiagent chemotherapy at all gynecologic sites; for example, the GOG paclitaxel-cisplatin trial demonstrated that paclitaxel adds further benefits when it is used for the treatment of ovarian cancer (reviewed by Omura, 2008).

In terms of hematologic malignancies, CALGB developed the framework for the current therapy of adult patients with AML, refining classifica-

tion of leukemia to include cytogenetic and molecular genetic characteristics (reviewed by Green et al., 2008). In addition, ECOG's Multiple Myeloma Committee developed trials that established treatment with thalidomide plus dexamethasone as a standard of care for newly diagnosed myeloma (Rajkumar et al., 2006).

Adjuvant Therapy for Solid Tumors

The Cooperative Groups are uniquely positioned to undertake trials of adjuvant therapies because such trials require large numbers of patients, significant data management and statistical support, and the collaboration of multiple oncology specialists (Mauer et al., 2007). Cooperative Group research has demonstrated the benefit of adjuvant therapy for breast, lung, colon, and gastric cancer, as well as melanoma (Haller et al., 2005; Kirkwood et al., 2004; MacDonald et al., 2001; Mamounas et al., 1999; Moertel et al., 1995; Strauss et al., 2004; Winton et al., 2005). For example, CALGB defined the role of adjuvant paclitaxel as part of adjuvant therapy for breast cancer, leading to FDA approval of the use of paclitaxel for this indication (Green et al., 2008; Henderson et al., 2003). NSABP/NCCTG trials demonstrated a significant survival benefit for adjuvant treatment with trastuzumab, a monoclonal antibody, in women with HER-2-positive breast cancer (Romond et al., 2005). NCCTG first demonstrated the value of adjuvant chemotherapy in early-stage colon cancer almost 20 years ago, when patients treated with 5-FU and levamisole after curative surgery were found to have significantly improved outcomes compared with the outcomes for patients treated with surgery alone (Moertel et al., 1990).

Combined-Modality Therapy

Advances in combined-modality therapy are attributable to the multidisciplinary organization and expertise of the Cooperative Groups (Mauer et al., 2007). Five Cooperative Group trials conducted by GOG, RTOG, and SWOG defined the value of chemoradiation for the treatment of cervical cancer. Radiation therapy combined with platinum-based chemotherapy conferred reductions in mortality rates of 30 to 50 percent compared with the mortality rate after treatment with radiation alone for women with locally or regionally advanced cervical cancer or localized cervical cancer with poor prognostic indicators (Keys et al., 1990; Morris et al., 1999; Peters et al., 2000; Rose et al., 1999; Whitney et al., 1999). The results of a CALGB trial (Trial 8433) established the use of induction chemotherapy before definitive radiation as the new benchmark for the management of fit patients with locally advanced non-small-cell lung cancer (Dillman et al., 1996). RTOG found that patients with high-risk head and neck cancer

who received chemotherapy together with radiotherapy after surgery were far less likely to have a recurrence of cancer (RTOG, 2009).

Cancer Prevention and Detection

Prevention efforts have also been a focus of Cooperative Group research. The NSABP Breast Cancer Prevention Trial demonstrated that tamoxifen treatment reduced the incidence of breast cancer by nearly 50 percent in women with an increased risk of developing breast cancer (Fisher et al., 1998). Additionally, the Study of Tamoxifen and Raloxifene demonstrated that tamoxifen and raloxifene are equally effective in reducing the risk of invasive breast cancer (Vogel et al., 2006). A CALGB chemoprevention study demonstrated that aspirin can reduce the risk of colorectal adenoma in patients with a history of colon cancer (Sandler et al., 2003). SWOG's Prostate Cancer Prevention Trial demonstrated that finasteride treatment resulted in a 24 percent reduction in the prevalence of prostate cancer at 7 years compared with the prevalence in those treated with a placebo (Thompson et al., 2003).

ACRIN focuses on the evaluation of imaging techniques for the screening, diagnosis, and treatment of cancer. One trial, ACRIN Trial 6652, found that digital mammography is superior to film-screen mammography for a subset of women (i.e., women with dense breasts, such as those who are younger and pre- or perimenopausal) (Pisano et al., 2005). These findings have refined the use of digital mammography for women who can benefit from its application (Hillman and Gatsonis, 2008). Also noteworthy are ACRIN trials that are unlikely to be conducted in industry settings but that may provide practice-changing information in the future. Examples include trials that are evaluating colorectal cancer screening using computed tomography (CT) colonography, breast cancer screening using ultrasound and magnetic resonance imaging, and lung cancer screening using CT.

Negative Findings and Previously Unobserved Treatment Risks

Negative research findings are underreported in the published medical literature but are essential in setting the standard of care. A recent study evaluated the proportion of trials listed in a public trials registry that have been published in the peer-reviewed literature. Between 1999 and 2007, the results of less than 6 percent of all industry-sponsored studies had been published, and 75 percent of those had reached a positive conclusion. In contrast, 59 percent of the clinical trials performed by NCI-supported clinical trials networks had been published over the same period of time, and half of those trials reported a positive result (Ramsey and Scoggins, 2008). The latter figure is consistent with an ongoing evaluation of the publication rate

of the findings of more than 1,500 Phase II and III clinical trials performed from 2000 to 2005 by the Cooperative Groups (Doroshow, 2008).

Published Cooperative Group research has demonstrated, for example, that there is no clear benefit of high-dose chemotherapy with stem cell support (a more aggressive therapy with high rates of morbidity and mortality) for the treatment of breast cancer, as well as results from the Selenium and Vitamin E Cancer Prevention Trial, which found that treatment with 200 micrograms of selenium and 400 international units of vitamin E daily does not prevent prostate cancer (reviewed by Coltman [2008] and Dignam [2004]). Large Cooperative Group trials have also revealed important secondary effects of therapy, including both adverse events and previously unobserved treatment risks. For example, an increased incidence of leukemia was observed after treatment with chemotherapy, as was an increase in the incidence of endometrial cancer following tamoxifen treatment (reviewed by Dignam, 2004).

STRENGTHS OF THE COOPERATIVE GROUP PROGRAM

The pharmaceutical and biotechnology industries play a critical role in developing new therapeutic agents for the treatment of cancer. Oncology has become one of the most active areas of drug development by industry, with more new cancer drugs entering the market in recent years than for any other disease category (Woodcock, 2009). Between July 2005 and December 2007, FDA approved 53 new indications in oncology, with 18 new molecular entity approvals and 35 supplemental applications. In comparison, FDA currently approves around 18 new molecular entities annually for all disease areas, which means that oncology has been taking the lion's share (Woodcock, 2009). The research and development efforts undertaken by industry entail enormous costs and are critical to the progress in cancer treatment.

Publicly funded clinical trials also play a vital, complementary role in advancing science and patient care, particularly by addressing questions that are important to patients but are less likely to be top priorities of industry. With many new therapies already in clinical use, and more than 800 cancer therapeutics in development (PhRMA, 2009), it can be difficult for physicians to assess which treatment is best for an individual patient, especially considering that some drugs may confer only weeks or months of extra benefit, on average.[2] Publicly sponsored trials fill an important information void by conducting head-to-head comparisons of different therapeutics from different companies that are already approved for clinical use. The

[2]Because only a minority of patients respond to a given drug, the average benefit of many cancer therapeutics can be small.

pharmaceutical industry has less incentive to undertake these comparative effectiveness trials because doing so may negatively affect a company's bottom line if that company's drug is found to be inferior. Companies may also have less incentive to combine novel therapies developed by different sponsors, but this may more readily occur in a publicly funded clinical trials environment. Clinical trials evaluating therapies in rare diseases may not be top priorities for industry, since the research and development costs may not be recouped by the small number of patients who receive the therapy. Likewise, trials that assess multimodality therapies, such as radiation therapy, surgery, or devices in combinations with drugs provide data that inform clinical practice, but are usually not high priorities of industry. Clinical trials that determine the optimal duration and dose of treatment with drugs in clinical use may also be lower priorities for industry. In addition, screening and prevention strategies and rehabilitation and quality of life studies are less likely to be top priorities of industry. In these cases, the Cooperative Group Program provides an important setting to conduct clinical trials. Some current examples of Cooperative Group trials that probably would not have been conducted by industry alone include:

- C80405, a head-to-head trial in first-line treatment for metastatic colorectal cancer that directly compares chemotherapy plus bevacizumab to chemotherapy plus cetuximab. Bevacizumab and cetuximab are both monoclonal antibodies with different specificities. Both have been approved for the treatment of metastatic colorectal cancer, but it is unclear which strategy of combining chemotherapy with a monoclonal antibody is superior, i.e., whether targeting the epidermal growth factor receptor (EGFR) pathway (cetuximab) or VEGF pathway (bevacizumab) increases overall survival. The results of this clinical trial will likely influence treatment decisions, but the companies who developed bevacizumab and cetuximab (Genentech and Bristol-Myers Squibb/ImClone Systems, respectively) are not incentivized to conduct this trial. In addition to the expense of the trial, it is possible that the results of the trial may demonstrate one drug is inferior to the other, impacting one company's revenue negatively.
- S0307, a trial that compares adjuvant zoledronate, clodronate, and ibandronate in women with primary breast cancer. One of the agents under evaluation, ibandronate, is off-patent, making it is less likely that this study would be undertaken by industry, although it may have important benefits for the selected patient population.
- S0521, a trial assessing maintenance therapy versus observation for patients with previously untreated low and intermediate risk

acute promyleocytic leukemia. This study involves a very rare disease with already approved agents. The research question, whether favorable outcomes can be achieved with more limited therapy, is also unlikely to be addressed by industry because it may constrict the use of drugs already approved.

- RTOG 0525, a trial that compares conventional adjuvant temozolomide with dose-intensive temozolomide for newly diagnosed glioblastoma. Pharmaceutical companies may have less incentive to study dose scheduling questions, especially for drugs already approved.
- GOG 0238, a trial that evaluates radiation therapy versus radiation therapy and chemotherapy with cisplatin in women with pelvic only recurrence of endometrial cancer. Cisplatin is an already approved therapy, and industry is unlikely to investigate this multimodal research question.

Table 1-1 provides additional examples of Cooperative Group trials that the pharmaceutical and biotechnology industries have less incentive to conduct, but have implications that will likely affect clinical practice. It is important to note that industry does help support some of these trials (typically by supplying a drug) but it is unlikely that these trials would have been initiated with industry-only support.

The Cooperative Group Program provides a unique environment for investigators to conduct clinical trials. The public and academic nature of the Groups enables the pooling of public resources to conduct studies in the public interest. The Cooperative Group Program supports trials that explore new methods of cancer treatment and prevention, including studies of combination therapies and proof-of-concept studies, as well as trials that focus on early detection, quality of life, rehabilitation, and comparative effectiveness. In doing so, the Groups often engage the patient advocacy community in the selection and design of their trials (Collyar, 2008). For example, after patient advocates successfully pushed for testing of a lower dose of a standard therapy for multiple myeloma in a Cooperative Group study, the trial results demonstrated improved survival and fewer side effects in the low-dose arm, altering the standard of care (International Myeloma Foundation, 2007). Cooperative Group trial databases and clinically annotated biospecimen repositories have also enabled researchers to conduct correlative science and analyses of cancer prognosis and survivorship that have delineated specific subpopulations, defined cancer staging, and aided in validating prognosis indicators (see also Chapter 2). Cooperative Group trials also extend participation beyond research-oriented facilities—such as academic medical centers and cancer centers—to community hospitals and individual physician practices, some of which participate through

TABLE 1-1 Current Examples of Cooperative Group Phase II and III Trials That Probably Would Not Have Been Conducted by Industry Alone

Trial	Title
Brain and Central Nervous System Cancers	
N0577	Intergroup Study of Radiotherapy vs. Temozolomide Alone vs. Radiotherapy with Concomitant and Adjuvant Temozolomide for Patients with 1p/19q Codeleted Anaplastic Glioma
RTOG-0525	Trial Comparing Conventional Adjuvant Temozolomide with Dose-Intensive Temozolomide in Patients with Newly Diagnosed Glioblastoma
Breast Cancer	
ACOSOG-Z1031	Randomized Trial Comparing 16 to 18 Weeks of Neoadjuvant Exemestane (25 mg daily), Letrozole (2.5 mg), or Anastrozole (1 mg) in Postmenopausal Women with Clinical Stage II and III Estrogen Receptor Positive Breast Cancer
ACOSOG-Z1041	Randomized Trial Comparing a Neoadjuvant Regimen of FEC-75 Followed by Paclitaxel + Trastuzumab with a Neoadjuvant Regimen of Paclitaxel + Trastuzumab Followed by FEC-75 Plus Trastuzumab in Patients with HER-2 Positive Operable Breast Cancer
E5103	Double-Blind Trial of Doxorubicin + Cyclophosphamide Followed by Paclitaxel + Bevacizumab or Placebo in Patients with Lymph Node Positive and High-Risk Lymph Node Negative Breast Cancer
PACCT-1	Program for the Assessment of Clinical Cancer Tests (PACCT-1): Trial Assigning IndividuaLized Options for Treatment: The TAILORx Trial
S0307	Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer
Gastrointestinal and Neuroendocrine Cancers	
C80405	Trial of Irinotecan/5-FU/Leucovorin or Oxaliplatin/5-FU/Leucovorin with Bevacizumab, or Cetuximab (C225), or with the Combination of Bevacizumab and Cetuximab for Patients with Untreated Metastatic Adenocarcinoma of the Colon or Rectum
CALGB-80702	Trial of 6 vs. 12 Treatments of Adjuvant FOLFOX Plus Celecoxib or Placebo for Patients with Resected Stage III Colon Cancer
RTOG-1010	Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2 Overexpressing Esophageal Adenocarcinoma
RTOG-0436	Trial Evaluating the Addition of Cetuximab to Paclitaxel, Cisplatin, and Radiation for Patients with Esophageal Cancer Who Are Treated Without Surgery

Brief Rationale for Selection	Phase
Study of radiation and temozolomide in patients with 1p/19q co-deleted anaplastic gliomas in a rare disease with unique biology.	Phase III
Study of 2 doses of temozolomide (conventional dose vs. dose-intensive dose) in patients with glioblastoma multiforme.	Phase III
Neoadjuvant hormonal study in breast cancer.	Phase III
Neoadjuvant study in breast cancer.	Phase III
Study includes 3 arms in order to test a duration question relative to bevacizumab-based therapy.	Phase III
Evaluates the potential benefit of chemotherapy in a patient population selected by a diagnostic test.	Phase III
Evaluates an agent (ibandronate) that is off-patent but may have important benefits for the selected patient population.	Phase III
Involves a direct head-to-head comparison of 2 types of monoclonal antibody-based therapy combined with chemotherapy with overall survival as the primary endpoint.	Phase III
Uses a 2 × 2 factorial design. The duration question regarding adjuvant chemotherapy has clear public health implications and is part of the International Duration Evaluation of Adjuvant Chemotherapy meta-analysis, which leverages other international trials with compatible endpoints.	Phase III
Study in a very rare subset of a rare disease, in a clinical setting using a specific therapeutic approach (trimodality therapy).	Phase III
Evaluates an agent in combination with radiation therapy in a rare disease and for a very select therapeutic approach in a specific patient population (nonoperative therapy).	Phase III

continued

TABLE 1-1 Continued

S0518	Prospective Randomized Comparison of Depot Octreotide Plus Interferon Alpha vs. Depot Octreotide Plus Bevacizumab (NSC #704865) in Advanced, Poor Prognosis Carcinoid Patients
Genitourinary Cancers	
E2805	ASSURE: Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma
Gynecologic Cancers	
GOG-0218	Trial of Carboplatin and Paclitaxel + Placebo vs. Carboplatin and Paclitaxel + Concurrent Bevacizumab (NSC #704865, IND #7921) Followed by Placebo, vs. Carboplatin and Paclitaxel + Concurrent and Extended Bevacizumab, in Women with Newly Diagnosed, Previously Untreated, Stage III or IV Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer
GOG-0249	Trial of Pelvic Radiation Therapy vs. Vaginal Cuff Brachytherapy Followed By Paclitaxel/Carboplatin Chemotherapy in Patients with High-Risk, Early-Stage Endometrial Carcinoma
GOG-0250	Randomized Trial of Docetaxel (NSC #628503) and Gemcitabine (NSC #613327) + G-CSF with Bevacizumab (NSC #704865, IND #7921) vs. Docetaxel (NSC #628503) and Gemcitabine (NSC #613327) + G-CSF with Placebo in the Treatment of Recurrent or Advanced Leiomyosarcoma of the Uterus
GOG-0252	Trial of Bevacizumab with IV vs. IP Chemotherapy in Ovarian, Fallopian Tube, and Primary Peritoneal Carcinoma NCI-Supplied Agent(s): Bevacizumab (NSC #704865, IND #7921)
GOG-0255	Randomized, Double-Blind Trial of a Polyvalent Vaccine-KLH Conjugate (NSC 748933) + OPT-821 vs. OPT-821 in Patients with Epithelial Ovarian, Fallopian Tube, or Peritoneal Cancer Who Are in Second or Third Complete Remission
GOG-0258	Randomized Trial of Cisplatin and Tumor Volume Directed Irradiation Followed by Carboplatin and Paclitaxel vs. Carboplatin and Paclitaxel for Optimally Debulked, Advanced Endometrial Carcinoma
GOG-0261	Randomized Trial of Paclitaxel Plus Carboplatin vs. Ifosfamide Plus Paclitaxel in Chemotherapy-Naive Patients with Newly Diagnosed Stage I-IV, Persistent or Recurrent Carcinosarcoma (Mixed Mesodermal Tumors) of the Uterus
RTOG-0724	Randomized Study of Concurrent Chemotherapy and Pelvic Radiation Therapy with or without Adjuvant Chemotherapy in High-Risk Patients with Early-Stage Cervical Carcinoma Following Radical Hysterectomy
GOG-0238	Randomized Trial of Pelvic Irradiation with or without Concurrent Weekly Cisplatin in Patients with Pelvic-Only Recurrence of Carcinoma of the Uterine Corpus
GOG-0248	Randomized Trial of Temsirolimus (NCI-Supplied Agent, NSC #683864, IND #61010) or the Combination of Hormonal Therapy Plus Temsirolimus in Women with Advanced, Persistent, or Recurrent Endometrial Carcinoma

Study evaluates a new agent in a very rare tumor directly against a very different therapy (not against placebo or a combination involving the new agent).	Phase III
Adjuvant study comparing 2 drugs from different companies to observation.	Phase III
Included 3 arms in order to test a duration question relative to bevacizumab-based therapy.	Phase III
A relatively rare clinical scenario in which chemotherapy is being tested with standard agents.	Phase III
A study in a very rare tumor type—leiomyosarcoma of the uterus.	Phase III
Study of intravenous (IV) vs. intra-peritoneal (IP) chemotherapy.	Phase III
Evaluates polyvalent vaccine + adjuvant therapy vs. adjuvant therapy alone in women in 3rd remission ovarian cancer. Involves an academic vaccine without any company support.	Phase III
A study in a relatively rare clinical scenario evaluating standard agents.	Phase III
A study in a rare tumor type evaluating standard agents.	Phase III
Evaluating chemoradiation with or without adjuvant chemotherapy in women with high-risk early-stage cervical cancer after hysterectomy with involving standard agents.	Phase III
A study of radiation therapy vs. chemoradiation in women with pelvic only recurrence of endometrial cancer and the agents being evaluated are standard.	Phase II
A study of temsirolimus with or without hormonal therapy in women with recurrent endometrial cancer in a very rare clinical scenario.	Phase II

continued

TABLE 1-1 Continued

Hematologic Cancers	
CALGB-10603	Randomized, Double-Blind Study of Induction (Daunorubicin/Cytarabine) and Consolidation (High-Dose Cytarabine) Chemotherapy + Midostaurin (PKC412) (IND # 101261) or Placebo in Newly Diagnosed Patients < 60 Years of Age with FLT3 Mutated Acute Myeloid Leukemia
CALGB-50303	Randomized Study of R-CHOP vs. Dose-Adjusted Epoch-R with Molecular Profiling in Untreated De Novo Diffuse Large B-Cell Lymphomas
S0521	Randomized Trial of Maintenance vs. Observation for Patients with Previously Untreated Low and Intermediate Risk Acute Promyelocytic Leukemia
S0777	Randomized Trial of CC-5013 (Lenalidomide, NSC-703813) and Low Dose Dexamethasone vs. Bortezomib (PS-341, NSC-681239), Lenalidomide and Low Dose Dexamethasone for Induction, in Patients with Previously Untreated Multiple Myeloma without an Intent for Immediate Autologous Stem Cell Transplant
S0816	Trial of Response-Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) Imaging
Lung Cancers	
CALGB-30506	Randomized Trial of Adjuvant Therapy in Early-Stage Non-Small Cell Lung Cancer Evaluating the Potential Utility of a Genomic Prognostic Model to Identify Patients as Candidates for Adjuvant Chemotherapy
S0819	Randomized Study Comparing Carboplatin/Paclitaxel or Carboplatin/Paclitaxel/Bevacizumab with or without Concurrent Cetuximab in Patients with Advanced Non-Small Cell Lung Cancer
E1508	Randomized Study of Cisplatin and Etoposide in Combination with Either Hedgehog Inhibitor GDC-0449 or IGF-1R MOAB IMC-A12 for Patients with Extensive Stage Small Cell Lung Cancer
Pediatric Cancers	
AALL0232	High-Risk B-Precursor Acute Lymphoblastic Leukemia
AALL0331	Standard-Risk B-Precursor Acute Lymphoblastic Leukemia
AALL0434	Intensified Methotrexate, Nelarabine (Compound 506U78; IND# 52611) and Augmented BFM Therapy for Children and Young Adults with Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia
AEWS0331	European Ewing Tumor Working Initiative of National Groups Ewing Tumour Studies 1999 (EURO-E.W.I.N.G. 99)

A rare disease subset that required significant collaboration.	Phase III
Evaluation of standard agents that involves molecular profiling.	Phase III
Evaluating whether favorable outcomes can be achieved in a very rare disease with more limited therapy with approved agents.	Phase III
Evaluating competing therapies involving agents from 2 different companies.	Phase III
Evaluating the utility of FDG-PET as a biomarker for use in risk stratification and treatment determination for approved therapies in Hodgkin lymphoma.	Phase II
Evaluating a risk model for relapse in the adjuvant setting for patients with Stage 1 NSCLC and involves comparing standard chemotherapy to observation.	Phase III
A complex study with 4-drug combinations using 2 targeted therapies to evaluate outcomes and to validate epidermal growth factor receptor (EGFR) markers for EGFR-targeted therapy.	Phase III
A study in small cell lung cancer with 2 new investigational agent-based therapies from different companies.	Phase II
Evaluating both induction and maintenance therapy in patients who are less than 10 years of age.	Phase III
Evaluating the benefit of augmented intensity consolidation as a therapeutic approach.	Phase III
Involves multiple research questions in a 2×2 randomization design evaluating nelarabine therapy and interim maintenance therapy with Capizzi methotrexate or high-dose methotrexate.	Phase III
Evaluating the schedule/timing of therapy in Ewing sarcoma (every 3 weeks vs. every 2 weeks).	Phase III

continued

TABLE 1-1 Continued

ANBL0032	Randomized Study of Chimeric Antibody 14.18 (Ch14.18) in High-Risk Neuroblastoma Following Myeloablative Therapy and Autologous Stem Cell Rescue

SOURCE: Personal communication, Jeffery Abrams, National Cancer Institute, March 2, 2010.

the CCOPs.[3] This allows the evaluation of therapies in settings more representative of current medical practice, because the majority of cancer treatment in the United States occurs in the community (Dignam, 2004), and ensures patient access to innovative therapies in settings other than academic medical centers or cancer centers. Additionally, the Cooperative Group Program enables international collaboration, fostering multiple joint protocols involving the Cooperative Groups, the European Organisation for Research and Treatment of Cancer, and other international trial sites (Corn et al., 2008; EORTC, 2009). The Cooperative Groups also provide a training ground for investigators, offering opportunities for mentorship, collaboration, and career advancement through participation in scientific steering committees.

CHALLENGES CONFRONTING THE COOPERATIVE GROUP PROGRAM

Despite the unique mission and history of accomplishments of the Cooperative Groups, the Program is facing numerous challenges that threaten its ability to undertake large-scale, innovative clinical trials that benefit patient care (these challenges are described briefly below; Chapters 2, 3, and 4 explore these challenges in greater detail). Many of these challenges stem from systems problems rather than scientific difficulties. Fundamental to these challenges is a clinical trials infrastructure that has not evolved to accommodate the rapid pace of biomedical discovery. Stagnant funding, inefficient processes, extensive and complex government oversight, and a growing trend toward the conduct of industry trials overseas have contributed to inadequate physician and patient participation in clinical trials, threatening the Cooperative Group Program's ability to efficiently translate discoveries into clinical applications.

Problems with the current cancer clinical trials system are readily acknowledged by a number of stakeholders: clinical investigators, patient

[3] CCOP enables community physicians to participate in and enroll patients in Cooperative Group Program clinical trials. See http://prevention.cancer.gov/programs-resources/programs/ccop.

Evaluating maintenance therapy in high-risk neuroblastoma; no pharmaceutical company was involved in the development or production of the agent (ch14.18).	Phase III

advocates, Cooperative Group leadership, industry participants, as well as NCI. Multiple expert committees have been convened to study these issues and recommend paths forward. Evaluations of the Cooperative Group Program over the past decade, including the Armitage report and implementation committee (NCI, 1997), the Clinical Trials Working Group report (NCI, 2005), and the Translational Research Working Group report (NCI, 2007), acknowledge the many challenges that limit the ability of the Cooperative Groups to rapidly translate biomedical discoveries into clinical applications and have recommended changes to the Program (see Appendix A). However, for the most part, these reports have not yet resulted in transformative program changes. Current NCI activities include the implementation of several recommendations from the Clinical Trials Working Group and Translational Research Working Group reports that have the potential to address some of the recognized challenges.

Clinical Trial Costs Outstrip Program Funding

In recent years, NCI funding for the Cooperative Group Program has been flat and has been declining when the funding is adjusted for inflation. Proponents argue that the $145 million that NCI provides annually to the Program is far below the amount needed to sustain the clinical trials research infrastructure and to support the enrollment and follow-up of patients at clinical trial sites (IOM, 2009). In addition, clinical trials are becoming increasingly expensive as researchers design trials reflective of biomedical innovations, including imaging studies and correlative studies that require the collection, annotation, and storage of biospecimens, as well as biomarker analyses. With growing financial pressures, there are concerns that, as it currently operates, the Cooperative Group Program is unsustainable (see Chapter 3 for a more detailed analysis).

Inefficient Group Processes and Burdensome Oversight

Recent studies demonstrate that protocol activation in Cooperative Group trials is riddled with inefficiencies, leading to median activation

times of 600 to 800 days (Dilts and Sandler, 2006; Dilts et al., 2006, 2008, 2009). In addition to inefficiencies within the concept development process, extensive and overlapping oversight by NCI, institutional review boards, and FDA contributes to delays in activating trials. Collaborations among Cooperative Groups and industry sponsors largely remain nonstandardized, which also increases the time and complexity of clinical trial planning. Because science can change rapidly, the time that it takes to activate a new trial may render obsolete the research question that the clinical trial was designed to answer and threatens the relevance of Cooperative Group trials (see Chapter 3).

Inadequate Patient and Physician Involvement in Cancer Clinical Trials

Few patients and physicians participate in clinical trials for adult cancers. Of the 1.4 million patients with a new diagnosis of cancer in 2008 (ACS, 2008), it is estimated that no more than 5 percent of patients enrolled in clinical trials,[4] with some estimates suggesting that less than 3 percent of patients enrolled in clinical trials (reviewed by ENACCT-CCPH, 2008). Likewise, reimbursement concerns, a lack of awareness of clinical trials, physician or patient preference for standard therapies, excessive regulatory burdens, and time constraints prevent many physicians from enrolling patients in clinical trials (C-Change and Coalition of Cancer Cooperative Groups, 2006; Mansour, 1994; Somkin et al., 2005). Because of the trend toward the use of targeted therapy and personalized medicine, clinical trials increasingly rely on stratified populations (see Chapter 2), which require large numbers of patients willing to participate. The low rate of involvement of physicians and patients in clinical trials slows accrual and prevents the Cooperative Groups from efficiently translating new knowledge into better patient care. Many trials never reach their accrual goals and thus generate no meaningful results to guide treatment (see Chapter 4 for more details).

Movement of Industry Trials Overseas

In part because of the difficulty of activating and conducting clinical trials in the United States, there is a growing trend for industry to conduct clinical trials overseas (Getz, 2007; Glickman et al., 2009; IOM, 2009). Cost savings and recruitment efficiencies are cited as the primary drivers of the globalization of clinical trials (Agres, 2005; Normile, 2008). With the movement of clinical trials, clinical investigators, and resources away from the United States, the ability of the United States to maintain a critical mass

[4] This is in stark contrast to rate of enrollment for children with cancer, the majority of whom are enrolled in clinical trials.

of expertise to conduct clinical trials is questionable. Without the conduct of clinical trials in the United States, patients could lose access to promising new therapies as they develop, and in some cases, the results of clinical trials may have less relevance to U.S. patient populations (see Chapter 4).

ORIGIN OF THE STUDY

Recognizing the value of publicly sponsored cancer clinical trials and the challenges that currently confront the U.S. clinical trials system, the Institute of Medicine's (IOM's) National Cancer Policy Forum held two workshops to examine these issues and to obtain input from a diverse group of stakeholders. The first workshop, Improving the Quality of Cancer Clinical Trials, held on October 4 and 5, 2007, focused on the science underpinning clinical trials; collaborations among Cooperative Groups, industry, and academia; and the regulatory issues affecting clinical trial development, especially the early stages of development. The second workshop, Multi-Center Phase III Clinical Trials and NCI Cooperative Groups, held on July 1 and 2, 2008, explored the organization and operations of the Cooperative Group Program, patient and physician involvement in Cooperative Group research, and data collection requirements, as well as clinical trial cost and reimbursement issues. The proceedings of both workshops were published by the IOM as workshop summaries (IOM, 2008, 2009).

Invited speakers represented a diverse group of stakeholders, including NCI, FDA, the Centers for Medicare & Medicaid Services, Cooperative Group leadership, clinical investigators from academia and community practice, preclinical research scientists, biostatisticians, bioimaging and biomarker experts, industry participants, insurers, patient advocates, and cancer center administrators. Throughout the workshops, speakers conveyed the importance of Cooperative Group clinical trials in setting the standard of care for cancer treatment, prevention, and detection. However, speakers voiced a number of concerns over the current system, prompting the workshop chair, John Mendelsohn, to note that there was general agreement among workshop participants that the Cooperative Group Program is approaching a state of crisis (IOM, 2009). Other presenters discussed ways in which innovative trial designs, therapeutic combinations, drug-diagnostic codevelopment, molecular imaging, and correlative science have the potential to significantly improve cancer care if the barriers are appropriately addressed.

Based on the input received from these workshops, the director of NCI, John Niederhuber, requested that the IOM conduct a consensus study of cancer clinical trials and the Cooperative Group Program. Funding was obtained from NCI, the Centers for Disease Control and Prevention, the

American Cancer Society, the American Society of Clinical Oncology, the Association of American Cancer Institutes, and C-Change.

COMMITTEE APPOINTMENT AND CHARGE

The NCI asked the IOM to examine a broad a number of topics relevant to cancer clinical trials and the organization and operation of the Cooperative Group Program and to make recommendations that could improve the quality of cancer clinical trials conducted through the program (Box 1-3). To address the charge, the IOM appointed a 17-member committee whose members had a broad range of expertise and experience. Among these individuals were experts in biomedical research, clinical investigation in academia and community practice, statistics, radiology, research and development in the biotechnology and pharmaceutical industries, management research, systems engineering, the health insurance industry, and patient advocacy.

BOX 1-3
Committee Statement of Task

An IOM committee will review the organization and operation of the National Cancer Institute (NCI) Clinical Trials Cooperative Group Program and recommend ways to improve the quality of cancer clinical trials conducted by the groups. Attention will be focused on how to improve, modernize, and streamline the process, with special consideration given to the recent emphasis on targeted therapies due to an improved understanding of the biology of cancer. Given the limits on funding for cancer clinical trials, there is a particular need to improve efficiency and make efficient use of time, effort, and resources. Specifically, the committee will recommend ways to

- improve the design, review, and operation of clinical trials;
- reduce the prolonged period of time currently spent moving from initial concept to final approval;
- prioritize trials and trial sites based on scientific merit and past performance;
- increase participation of both clinicians and patients;
- make greater use of technologies such as imaging and other biomarkers to select therapies for development and testing, to match patients and therapies, and to monitor patient responses;
- define standards for minimal data requirements to establish safety and efficacy of experimental therapies;
- reduce costs and ensure adequate funds for high-quality trials; and
- promote greater collaboration among various stakeholders.

THE COMMITTEE'S VISION FOR CANCER CLINICAL TRIALS IN 2015

The committee recognized that the numerous reviews of the Cooperative Group Program have not resulted in transformative programmatic change. Indeed, a recently published commentary stated that "[i]ts awkward present form evolved because of decades of tinkering with administrative structures at NCI and the National Institutes of Health, reactions to specific events or perceived risks, and changing needs of various governmental and nongovernmental stakeholders" (Steensma, 2009).

With the goal of providing recommendations that result in systemic change, the committee took a broad view of the clinical trials process rather than simply focusing on NCI's role. The committee defined the current system's inadequacies in terms of missed opportunities, misaligned incentives, and collective challenges. Many aspects of the clinical trials infrastructure have not changed dramatically since the 1950s, whereas biomedical discoveries and technology development have been advancing rapidly in recent years. The collective environment in which clinical trials are conducted influences the pace of clinical advances.

The committee then described the needs of an ideal cancer clinical trials system of the near future, circa 2015 (see Box 1-4). The committee envisions a dynamic system that could efficiently respond to emerging scientific knowledge, involve the broad cooperation of stakeholders, and leverage evolving technologies that could provide high-quality, practice-changing research. Clinical trial participation would be the preferred option for patients and physicians because it would provide access to innovative therapies that reflect patient preferences and that are appropriately reimbursed.

This list of ideal characteristics laid the groundwork for the committee deliberations to develop goals and specific recommendations to achieve them. The committee concluded that the academic, governmental, and commercial sectors must join with the public to develop a 21st-century clinical trials system to more effectively leverage scientific advancements and translate them into public health benefits by improving the science, technology, efficiency, and timely completion of the very best cancer clinical trials.

THE COMMITTEE'S CONCLUSIONS AND RECOMMENDATIONS

The committee reviewed the available published literature and obtained input from experts in the field, interested individuals, and institutions to formulate its recommendations. The committee's recommendations support four main goals for achieving the ideal vision of cancer clinical trials: (1) improve the speed and efficiency of clinical trial design, launch, and conduct, (2) incorporate innovative science and trial design in cancer clini-

BOX 1-4
Needs for Cancer Clinical Trials in 2015

Rapid translation of scientific discoveries into public health benefit
- Trials that address questions with significant implications for patient care
- Collaboration among stakeholders, with effective and timely communication, in developing the most promising treatments
- Streamlined procedures for rapid planning, approval, and launch of clinical trials, with accountability for meeting timelines and rewards for productivity
- Efficient incorporation of new technologies and scientific questions, such as the identification and application of biomarkers and molecular imaging, into clinical trials

A strong publicly supported clinical trials system in the United States that complements commercial trials to develop drugs and devices
- A highly efficient and flexible system for innovative, rigorously prioritized clinical trials
- Adequate funding for well-designed, high-quality trials
- Patient access to promising therapies as they develop
- Addresses questions and collects data that are relevant and meaningful to the diverse U.S. patient population

A robust, standardized, and accessible clinical trials infrastructure
- A complete database of active and planned trials
- Standardized electronic data capture
- Publicly accessible tissue repositories with high-quality, fully annotated, and inventoried samples collected and stored in a standardized fashion

cal trials, (3) improve selection, support, and completion of cancer clinical trials, and (4) incentivize participation of patients and physicians in clinical trials.

ORGANIZATION OF THE REPORT

Chapter 2 provides an overview of the science underpinning the development of cancer therapies and the challenges that must be overcome to achieve the goals of personalized medicine for cancer.

Chapter 3 provides an overview of the structure, organization, and funding of cancer clinical trials and the Cooperative Group Program. It also delineates the inefficiencies in the current system and discusses the collaborative nature of cancer clinical trials.

- Broad use of those samples in retrospective studies as new hypotheses evolve
- A consistent and dynamic process for rapidly setting national standards and unified procedures for new technologies such as diagnostics, with reproducibility and effective incorporation into clinical trials

Harmonized and synchronized rules and guidelines across federal regulatory agencies

- Guidance grounded in an understanding of contemporary science as new paradigms develop for therapeutic approaches as well as for clinical trials methodology

Support for clinical investigators

- Training and retention of professionals to efficiently and swiftly carry out important clinical research
- Adequate paid protected research time for active clinical investigators
- Recognition and appropriate rewards for collaborative clinical research in academic advancement and community practice careers
- Adequate reimbursement of costs for actively participating institutions and physicians

Broad patient involvement in clinical trials

- Third-party payor coverage of nonexperimental costs of patient care to ensure that patients do not forgo participation in trials because of financial hardship
- Participation in the design, implementation, and conduct of trials, and in the communication and dissemination of clinical trial results

Chapter 4 examines the incentives and disincentives for participation in cancer clinical trials, for both patients and clinicians.

Appendix A reviews the recommendations from past evaluations of the Cooperative Group Program and ongoing changes in response to those recommendations. It also includes a summary of the recommendations made in March 2010 by the NCI-appointed Operational Efficiency Working Group.

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2

The Science of Developing Cancer Therapy

A revolution is under way in the development of cancer therapy. Over the past decade, personalized medicine has leveraged scientific advancements in fields such as genomics,[1] proteomics,[2] molecular biology,[3] and metabolomics[4] to improve the extent to which medical care is tailored to the individual patient and his or her cancer. This is because most cancer treatments available today are effective in only a minority of patients, in part due to the tremendous variability in the molecular abnormalities that drive tumor formation (IOM, 2007; PCAST, 2008; Spear et al., 2001). As a result, many patients undergo costly treatments and endure the side effects of those treatments without deriving any benefit. Patients also experience an opportunity cost, as an alternative treatment that might be more effective for a patient's particular disease is delayed or forgone. Better tools are therefore needed to reduce the time and costs wasted by delivering ineffective and toxic treatments. Future treatment decisions will depend on the use of tissue biomarkers[5] that can predict outcomes of therapy. By using these

[1] Genomics is the study of the complete genetic material, including genes and their functions, of an organism.

[2] Proteomics is the study of the structure and function of proteins, including the way they work and interact with each other inside cells.

[3] Molecular biology is the branch of biology that deals with the formation, structure, and function of macromolecules essential to life, such as nucleic acids and proteins.

[4] Metabolomics is the systematic study of the unique chemical fingerprints that specific cellular processes leave behind; that is, small-molecule metabolites.

[5] A biomarker is defined as any biological characteristic that can be objectively measured and evaluated as an indicator of a normal biological process, pathogenic process, or pharmacological response to a therapeutic intervention.

new methods, it will be increasingly possible to group individual cancers into subpopulations with similar characteristics to predict patient outcomes for cancer therapies. That will help to ensure that the treatments prescribed for patients will be more effective.

Rising health care costs, the increasing availability of new therapies, and the promise of delivering more effective care make it more important than ever to advance the science underlying personalized medicine (PCAST, 2008). Identifying those subpopulations that are likely to respond to therapies can improve and hasten the success rate for the development of new treatments (PCAST, 2008). Being able to predict the therapeutic response and, therefore, being able to deliver safer and more effective treatments to patients will reduce the number of adverse drug events and thus provide cost savings to the entire health care system.

Advances in personalized medicine are rooted in the discovery, validation, and qualification of biomarkers that can be measured by in vitro diagnostic tests on samples from patients or through in vivo biomedical imaging. For example, cancer biomarkers can be used to develop and deliver improved patient care by predicting the likelihood of the response to treatment or the likelihood that an adverse reaction to the treatment will develop (IOM, 2007). Examples of biomarkers routinely used in the treatment of cancer are shown in Table 2-1.

Most diagnostics that are in use today assess a single target; however, it is widely believed that as technologies in genomics, proteomics, metabolomics, and molecular profiling mature, diagnostic platforms capable of simultaneously examining a large number of potential markers will improve the predictive powers of these tests (IOM, 2007). For example, the cost of DNA sequencing is continually decreasing with advances in sequencing technologies, making it more feasible to identify the gene defects underlying a particular type of cancer. These technological advancements could dramatically change how cancer is diagnosed and treated (Niederhuber, 2009). For instance, by applying new sequencing technologies to genome analysis,

TABLE 2-1 Examples of Validated Biomarkers Routinely Used to Predict Response to Cancer Therapy

Therapeutic Agent	Biomarker	Cancer Type
Endocrine therapies (e.g., tamoxifen)	Estrogen receptor	Breast
Trastuzumab	HER-2	Breast
Imatinib mesylate	BCR-ALB	Leukemia
Cetuximab and panitumumab	KRAS	Colorectal
Irinotecan	UGT1A1	Colorectal

including large-scale genome sequencing, the Cancer Genome Atlas Project[6] aims to catalog the pertinent genetic changes that occur in many types of cancer and identify new potential therapeutic targets.

The technologies used to conduct molecular analyses of tissue embedded in paraffin have also improved dramatically, enabling the large-scale genomic profiling of messenger RNA, the DNA copy number, and focused analysis of mutations on small tissue samples. For example, a recent study demonstrated the feasibility of profiling the expression of all the genes in the entire genome using formalin-fixed, paraffin-embedded tissues. Expression of more than 6,000 genes was assessed in tissues from patients with hepatocellular carcinoma, and 90 percent of the samples tested (including some that had been archived for many years) yielded data of high quality (Hoshida et al., 2008).

THE ROLE OF COOPERATIVE GROUPS IN BIOMARKER DEVELOPMENT

The NCI Clinical Trials Cooperative Groups have a long history of collecting highly annotated specimens[7] from patients with many different forms of cancer in clinical trials, including all the major pediatric and adult cancers, and have in place effective systems for collecting, storing, and tracking specimens to conduct correlative science.[8] Each of the 10 Cooperative Groups has its own repository for biological specimens. These are generally located in group-affiliated academic medical or cancer centers. All the Cooperative Groups' biorepositories use standard operating procedures, but because these repositories were developed to fit the needs of the individual Cooperative Groups, the structure, methods, governance, and access policies differ among the Groups. The Group Banking Steering Committee, which includes representatives from each of the 10 Cooperative Groups and NCI, aims to address many of these issues by improving and harmonizing operations of the Cooperative Group biobanks and by coordinating banking activities among Groups conducting phase III and large phase II clinical trials. Five subcommittees are set up to focus on specific issues (Best Practices and Operations, Informatics, Access and Marketing, Regulatory, and Technology Development). Most of the biological specimens collected from Cooperative Group trials are formalin-fixed, paraffin-

[6] The Cancer Genome Atlas Project is jointly sponsored by the National Cancer Institute and the National Human Genome Research Institute.

[7] Samples of material, such as tissue, cells, urine, blood, DNA, RNA, and protein that are associated with clinical information, such as type of therapy and patient outcome.

[8] Correlative science is a general term referring to research done on biospecimens that are collected during clinical trials.

embedded tumor tissue, but some frozen tissue and body fluid specimens are also collected (Hamilton, 2009).

Because the Cooperative Groups collect specimens under the auspices of a clinical trial, one of their major strengths is that the pathological data and the clinical data for the specimens are linked, making it feasible to conduct retrospective analyses of the clinical and nonclinical factors that influence prognosis and survival. In addition, information on long-term clinical outcomes is often available (Schilsky et al., 2002).

Historically, much of the correlative science performed by the Cooperative Groups focused on the development of prognostic markers (i.e., biomarkers that can predict the progression of disease in the absence of treatment considerations). In recent years, greater emphasis has been placed on identifying predictive markers (i.e., markers that can identify populations that are likely to be sensitive or resistant to specific treatments). Some Cooperative Groups have conducted clinical trials designed to validate the clinical utility of a biomarker, although one (the Marker Validation for Erlotinib in Lung Cancer [MARVEL] trial of lung cancer) was recently discontinued because of a lack of accrual.[9] Lastly, some groups have ongoing efforts in pharmacogenetics to correlate variations in germline DNA with treatment-related toxicity.[10] From 2000 to 2008, that work has resulted in 1,350 publications and 36 patents (Hamilton, 2009).

The work of the Cooperative Groups has also been instrumental in developing some of the cancer biomarker tests in common use in the clinic (see also Chapter 1). For example, the Cancer and Leukemia Group B (CALGB) Leukemia Correlative Science Committee has a long history (25 years) of conducting key correlative studies of adult leukemia. That group initially focused on the use of immunophenotyping for the diagnosis and prognosis of acute leukemia but has more recently focused on the clinical use of cytogenetic and molecular genetic markers in acute and chronic forms of leukemia. The work of that group has had a major impact on the way clinicians currently diagnose leukemia in adults, predict the outcome, select the appropriate treatment, document complete remission, and monitor residual disease (Bloomfield et al., 2006).

Another example of a widely used biomarker test resulting from the efforts of a Cooperative Group is the Oncotype DX breast cancer assay. About half of newly diagnosed cases of breast cancer are estrogen receptor (ER) positive and lymph node negative, and approximately 75 percent of those cases are adequately treated with surgery and hormonal therapy with

[9]The objective of the MARVEL trial was to definitively establish whether the presence or absence of epidermal growth factor receptor activation can help to guide the treatment of lung cancer.

[10]Personal communication, Richard Schilsky, University of Chicago, July 28, 2009.

or without radiation. Although additional chemotherapy benefits less than 5 percent of patients with ER positive lymph node negative breast cancers, chemotherapy adds significant toxicity, so a predictive biomarker test to guide the treatment decision has long been sought. The development of the Oncotype DX breast cancer assay, which measures the expression of 21 genes to predict the likelihood of disease recurrence for women with ER-positive and lymph node-negative breast cancer, would not have been possible without the work of the National Surgical Adjuvant Breast and Bowel Project (NSABP) Cooperative Group. NSABP collected and preserved tissue samples collected in the 1990s to test the benefits of treating breast cancer with chemotherapy. Subsequently, those samples were used for the retrospective clinical validation of the Oncotype DX assay (Wickerham et al., 2008). The results of those retrospective studies showed that the Oncotype DX assay could predict the likelihood of breast cancer recurrence (Paik et al., 2004, 2006). As a result, in the United States today, many ER-positive breast cancer tumors are being tested by use of the Oncotype DX assay (or another multi-gene assay known as Mammaprint[11]), and use of such tests can reduce the rate of chemotherapy use by at least 20 percent (Hayes, 2009). By sparing many women from needless exposure to chemotherapy, the cost savings attained through the use of this test are also substantial (Lyman et al., 2007).

Cooperative Group studies were also instrumental in achieving Food and Drug Administration (FDA) approval for the PathVysion test, which detects amplification of the gene for human epidermal growth factor receptor 2 (HER-2) and is used to select therapies for patients with breast cancer (Mauer et al., 2007).

At present, the Cooperative Groups are actively participating in more than 25 studies of biomarkers (Hamilton, 2009) in five different categories: (1) correlative studies that use clinically annotated biospecimens and research assays; (2) retrospective-prospective studies that use clinically annotated biospecimens, known clinical outcomes, and analytically validated assays; (3) prospective biomarker-drug codevelopment studies; (4) prospective biomarker development studies; and (5) prospective biomarker validation studies (Schilsky, 2009; see also the section on trial design).

[11] The Mammaprint test is another assay that assesses a breast tumor's genetic signature and is used to predict the likelihood of the recurrence of ER-positive lymph node-negative breast cancer. The test, which has FDA approval, uses a dichotomous algorithm based on the expression of 70 genes in freshly prepared tissues.

CHALLENGES IN BIOMARKER DEVELOPMENT

The process for the discovery and validation of predictive biomarkers is complex. Only about 20 cancer biomarkers have been approved by FDA, and many of these are not routinely used in clinical practice (IOM, 2008). Taking discoveries of potential biomarkers from the laboratory to routine use in clinical care entails multiple steps that require substantial resources and include a multitude of complex scientific and regulatory challenges. Although hypotheses about putative biomarkers are often generated preclinically, true biomarker assessment and validation occur during clinical development and require large numbers of patients who have been treated uniformly in randomized trials. Investigators must show that the biomarker is correlated with a specific biological function, outcome, or characteristic, and they must validate its clinical utility by demonstrating that it provides useful information that can effectively inform clinical decisions by studying large numbers of patients who have been treated uniformly. They must also develop an assay that measures the biomarker and demonstrate that it can reliably be used to guide treatment. An increasing number of candidate markers are being identified and are in various stages of development, yet validation and clinical qualification of these markers is not progressing nearly as rapidly.

Advances in information technology and molecular research have enabled large retrospective correlative studies linking clinical data to molecular data, but a number of obstacles stand in the way of effectively leveraging these advances, including inconsistent access to quality, annotated biospecimens; a lack of standards for assays or analysis of samples in a clinical setting; a lack of standards and templates for the design of correlative and other biomarker studies; a lack of clear and consistent policies that define tissue ownership and access to biospecimens; and a lack of adequate funding or funding that is piecemeal and requires multiple reviews.

Biospecimen Collection, Storage, Annotation, and Access

The quality of biospecimens can significantly influence clinical and research outcomes. Poor-quality biospecimens can generate data that are of poor quality or nonreproducible (Compton, 2009). Selection of a therapy on the basis of the results of a diagnostic test performed with a poor-quality biological specimen could result in patients receiving therapies that are unlikely to be beneficial or not receiving therapies that are likely to be beneficial.

The lack of consistent standards for biospecimen collection and storage is an impediment to improving the quality of those specimens. Maintaining the biological integrity of biospecimens outside of their natural environment is complex, specimens can easily be damaged, and there are many variables

in the collection and storage of specimens (Compton, 2009). In addition, a lack of complete annotation of the biospecimens can create challenges for researchers. The information that a scientist has regarding the characteristics of a biospecimen and the patient from whom it was collected can affect the groupings, the analysis, or the conclusions drawn from the data.

Within a collaborative group, there may be well-established standards for its biorepositories, and some programs funded by NCI, such as the Cancer Genome Atlas, have stringent standards for biorepositories. However, the cancer community and NCI currently lack uniform standards for the collection, processing, and storage of biospecimens; the collection and annotation of the associated data; and consents that govern their use. These obstacles compromise the molecular research that is dependent on biospecimens and impedes the progress of personalized cancer treatment (Compton, 2009).

NCI has launched some initiatives to improve the quality and consistency of biorepositories. In 2007, NCI released the final version of NCI Best Practices for Biospecimen Resources. That document defines state-of-the-science practices, promotes biospecimen and data quality, emphasizes access, recognizes the interest of research participants, and supports adherence to legal and ethical rules and guidelines. However, the current NCI Best Practices do not comprise detailed laboratory procedures; rather, they consist of principles by which such procedures should be developed by biospecimen custodians. The document also does not tackle the cost of recovery or transfer of the samples and does not address custodial rights or sample access policies (NCI, 2007a).

The ability to conduct good correlative science is affected by policies regarding access, governance, and documentation; contractual agreements with commercial partners; extensive review systems for sample use; and complex administrative interactions and oversight (Hamilton, 2009). Hundreds of organizations throughout the United States store tissue samples, and among those organizations, the policies on these issues vary widely (Eiseman and Haga, 1999).

One challenge entails patient consent and authorization for the disclosure of protected health information. The informed-consent documents obtained from patients for their participation in a clinical trial may not adequately specify the use of patient samples for additional, future research studies. Therefore, to test the samples, it may be necessary for the Cooperative Groups to re-contact the patients who provided them to obtain consent and authorization[12] (Hamilton, 2009), or to seek permission from

[12] Currently, the Privacy Rule, promulgated under the Health Insurance Portability and Accountability Act, does not allow patients to authorize the use of protected health information for future research. All authorizations must include a "description of each purpose of the requested use or disclosure" (45 C.F.R. § 164.508(b)(4)).

an institutional review board (IRB) to use the samples without consent and authorization.

The stewards of biological specimens have competing interests regarding who owns them, how they are used, and who will benefit from them. Policies regarding ownership and access vary by institution, and this impedes progress. As a result, the means of access to biospecimens for research is inconsistent and can entail complex negotiations with the various custodians of the samples. Pharmaceutical companies, in particular, may be reluctant to share patient samples with academic collaborators and may require agreements regarding intellectual property rights that are unacceptable to collaborators. Many hospitals also discard clinical samples after a period of time, so valuable resources are lost to research. According to NCI, a custodianship plan should consider how the integrity of the biospecimens and their associated data are maintained and monitored; how the rules of access and distribution of biospecimen are defined; what values and responsibilities the biospecimen resource has in place; what legacy or contingency plan, if any, the biospecimen resource has in place; and what circumstances, if any, allow the withdrawal or transfer of biospecimens (NCI, 2008).

Because the Cooperative Groups have a long history of responsible stewardship of biorepositories and well-established networks throughout the country with access to large, diverse patient populations, they are a logical choice for playing a central role in the ongoing efforts of NCI to establish consistent policies regarding ownership and access and could be instrumental in conducting future correlative studies. **Thus, the committee recommends that NCI mandate the submission of annotated biospecimens to high-quality, standardized central biorepositories when samples are collected from patients in the course of Cooperative Group trials. The accompanying clinical data should be reported on standardized forms, and NCI should establish a national inventory of biological samples held in the central repositories. NCI should also have a defined process for access to biospecimens for research that includes a single scientific peer review linked to funding. All data, including biomarker data from sera, tissues, and biological imaging analyses, should be considered precompetitive and unencumbered by intellectual property restrictions and should be made widely available.** This approach would be similar to current practice in the cancer genomics field.[13]

[13] See http://ocg.cancer.gov/.

Lack of Funding for Biomarker Development Within the Cooperative Group Program

There is a growing need for correlative and translational studies that use biospecimen banks, but the funding stream for these studies is inadequate and complex. Funding to support the Cooperative Groups' biorepositories and correlative science studies is cobbled together from a variety of sources, including the Group's core U10 grant,[14] a U24 grant,[15] users' fees; and other grants, contracts, and institutional commitments. Investigators need a better mechanism to cover the considerable cost of maintaining these important resources.

Furthermore, current NCI policies require that research studies that propose to use specimens collected from intergroup protocols undergo scientific review by a scientific steering committee before the specimens are made available. However, such a review is not linked to funding, and thus, investigators often must seek funding through other mechanisms or from other sources. This process creates many review loops, time delays, and significant double jeopardy, in that each proposal requires at least two scientific reviews (each of which involves many people), one to receive specimens and one to receive funding, that are conducted at different times by different review groups. A consistent and adequate funding source, with appropriate peer review, devoted to biomarker studies that use stored samples is imperative. Broader use of high-quality samples from standardized repositories would speed the pace of scientific and clinical advances, at a much lower expense than would be required if new samples must be collected for the study of each new concept. **Thus, the committee recommends that NCI implement new funding mechanisms and policies to support the management and use of Cooperative Group biorepositories for retrospective correlative science.** The Cancer Genome Atlas Project provides a model and precedent for the development and adoption of such policies.

The increased cost of including biomarker tests within trials is also substantial and is not well funded. As discussed in Chapter 3, NCI has taken some initial steps to address this need. **Nevertheless, the committee recommends that NCI adequately fund highly ranked trials to cover the costs of the trial, including biomedical imaging and other biomarker tests that are integral to the trial design.** Although the cost of studying and validating biomarkers is high, the funds are well spent if the effectiveness of therapy is improved and futile therapy can be avoided. Despite the relatively high cost of performing the Mammaprint or Oncotype DX assay (~$4,000),

[14] A cooperative agreement from NCI to support the operations and infrastructure of the cooperative group.

[15] A resource-related research project cooperative agreement, used to support improvements in resources that serve biomedical research.

for example, the cost of chemotherapy is far greater (~$50,000); if only 5 percent of patients assessed by the test would benefit from chemotherapy, then many patients will be spared significant toxicity unaccompanied by any benefit (Hayes, 2009).

Lack of Standards for Biomarker Development and Use

Analytical validation and clinical validation are important for using predictive imaging and other biomarker tests during clinical trials. However, unlike the strategy used for drug development, which has clearly defined preclinical, nonclinical, and clinical milestones accompanied by guidance on how each phase should be conducted, the strategy for biomarker development is significantly less well defined (IOM, 2007; Simon, 2008a). FDA has issued extensive regulatory guidance and procedures to guide drug development, whereas regulatory guidance and procedures for biomarker development are generally lacking. To date, in fact, there are no clear standards for biomarker validation, use, performance, or interpretation (IOM, 2007).

In an effort to improve the efficiency of biomarker development, multiple organizations have developed guidelines and proposed standards for various steps in biomarker development (IOM, 2007). For example, in 2007, NCI released a document titled *Performance Standards Reporting Requirements for Essential Assays in Clinical Trials* for biomarker assays used in Phase II and III clinical trials (NCI, 2007b). Concept proposals and clinical protocols for Phase II and III trials that use such assays must also include standard operating procedures for the proper collection, preparation, handling, and shipping of clinical biospecimens (NCI, 2007b). In addition, several of the Cooperative Groups, such as CALGB, have taken initiatives to standardize methodologies, interpretation of the results, and reporting of the results to ensure accuracy, uniformity, and the completeness of the data set (Compton, 2006).

This ad hoc and piecemeal approach, however, is not ideal, because the processes and rules used for such things as determining the composition of a standard-setting committee and the voting rules for the members of the committee are being reinvented on a case-by-case basis. This can lead to heterogeneous results and delays. A systematic, multidisciplinary, and dynamic approach fostered by the National Institutes of Health (NIH) and NCI would ensure that unified national standards are rapidly and consistently set as the need arises. **Thus, the committee recommends that NCI, in cooperation with other agencies, establish a consistent, dynamic process to oversee the development of national unified standards, as needed, for oncology research. This process should use the input of experts in both subject matter and standards design in the development of standards, and**

it should replicate successful aspects of standards development by other standard-setting bodies, both governmental and nongovernmental (e.g., the American Society for Testing and Materials, the National Standards Foundation, National Institute for Standards and Technology, the International Organization for Standardization, and professional societies). NCI could further assist by facilitating the creation of systems and software to aid the process of standards dissemination and implementation.

This proposal builds on a past IOM recommendation that "government agencies (e.g., NIH, FDA, CMS, and the National Institute for Standards and Technology) and nongovernment stakeholders (e.g., academia, the pharmaceutical and diagnostics industry, and health care payors) should work together to develop a transparent process for creating well-defined consensus standards and guidelines for biomarker development, validation, qualification, and use to reduce the uncertainty in the process of development and adoption" (IOM, 2007).

Uncertain Relevance of Primary Tissue for Patients with Metastatic Disease

Tissue samples from tumor biopsies are generally collected and archived at the time of an initial diagnosis and most often consist of primary tumor specimens. Metastatic or recurrent lesions are biopsied much less frequently. With the move toward targeted and personalized therapy, however, questions about whether the primary tumor is representative of the patient's metastatic disease have arisen, especially in the context of intervening therapy. It is unclear whether primary archived tissue provides biomarker data relevant to predicting the therapeutic response for metastatic cancer or whether another biopsy is required to obtain an accurate and relevant biomarker assessment. It may not be feasible or desirable to ask patients with cancer to undergo multiple invasive procedures to assess recurrent or metastatic disease. However, a second analysis of biological material can also include assessment of samples obtained by noninvasive or less invasive means, such as blood for analysis by blood-based assays (for example, for analysis of serum DNA, the serum protein profile, or circulating tumor cells) or molecular imaging for a relevant target.

Most cancers are not fatal unless they become metastatic, so these questions need to be answered to maximize the effectiveness of cancer therapies. The development of new trial concepts and the provision of funding to compare the molecular pathologies of primary and metastatic tumor tissues and to determine whether it is valid to use archived primary tissue for the selection of therapy for metastatic disease would be helpful. This could be the topic of a Grand Challenge competition, as recommended in Chapter 3.

PROMISES AND CHALLENGES OF COMBINATION PRODUCTS

Developing, testing, and gaining approval for the use of combination products such as multiple therapeutic agents or a therapeutic agent accompanied by a diagnostic test are more difficult than for a single product because of the increased scientific challenges, logistical challenges, unclear regulatory requirements, and high costs. For example, different centers within FDA have jurisdiction over different types of products for use in oncology, and for combination products, more than one center may have jurisdiction (see also Chapter 3 for more details). Furthermore, the traditional and well-established approach to drug development has focused on a single agent (or in some cases, a single agent added to standard chemotherapy), without a paired diagnostic test. In comparison, the stages and important milestones for the development of combination products have not been clearly established by precedent. Although some initial steps have been taken to delineate appropriate development pathways, many challenges remain, as described below.

Diagnostic-Therapeutic Combinations

Cancers have tremendous heterogeneity: even tumors that appear to be the same clinically may have different molecular characteristics and differing mechanisms of development and spread. To deliver effective treatments, it is important to be able to identify the specific molecular characteristics present in a patient's tumor. To do this, it is necessary to develop biomarker tests that accompany treatments targeting those defects. Alternatively, it might be possible to develop therapeutics for which there are multiple biomarkers to choose from or use in combination. Other diagnostics might indicate that a patient's cancer could be treated with multiple therapeutic agents. In addition to baseline biomarkers, which are central to predicting the response to treatment, longitudinal biomarkers (e.g., serial measurements) can help to determine whether a particular tumor is responding to a particular therapy.

A good example of the challenges involved in codeveloping an in vitro diagnostic-therapeutic combination is the targeted drug trastuzumab (Herceptin) and the various assays used to measure the overexpression of HER-2. Tumors that overexpress HER-2 are often sensitive to treatment with Herceptin, a monoclonal antibody that blocks the function of this receptor—one of the most well-known applications of personalized medicine. Genentech used a biomarker assay throughout the drug development process to test the efficacy of trastuzumab, but the company was not able to obtain FDA approval for that test at the time that FDA approved the drug. As a result, the sponsor had to rely on another company to develop a diag-

nostic assay that could be paired with its product and that was approved by FDA (IOM, 2008).

Because of the scientific challenges, the increased financial burden, and the increased risk of developing diagnostics in the early phases of clinical trials of a therapeutic agent, such tests are often not incorporated into clinical trials until late in development or even after a therapeutic agent has received FDA approval. Although the development of successful companion diagnostic tests yields substantial benefits for patients, many technical difficulties limit the development of tests that are reliable and clinically meaningful. Complementary work on diagnostic-therapeutic combinations should ideally begin in the early phases of development of a therapeutic agent (Tan et al., 2009).

The ability to streamline the validation process and develop additional tools will depend on better collaboration and coordination among stakeholders (McClellan and Benner, 2009; PCAST, 2008) and adequate funding. The essential tools and resources include access to high-quality biospecimens accompanied by comprehensive disease annotation and study designs, statistical methods, and standards for determining the clinical validity and utility of biomarkers (IOM, 2007; PCAST, 2008).

Some investigators are conducting clinical trials that use novel methods and collaborations. For example, the I-SPY 2 TRIAL,[16] which builds on the I-SPY 1 TRIAL,[17] is a Phase II adaptive trial that uses Bayesian statistics to predict how the drugs will perform in Phase III studies (see also the section on trial design below). The trial will test various neoadjuvant therapies in patients with primary breast cancer who are at high risk of disease recurrence. The goals of the trial include the identification of biomarkers that predict increased pathologic complete response (pCR) of a therapeutic agent or a combination of agents when added to standard neoadjuvant chemotherapy, modeling of the relationships with imaging to predict pCR, confirmation of the observations to minimize false-positive conclusions, and use of the results to advance biomarker-drug pairs that have a high probability of success to Phase III studies. It is fundamentally a drug screening process and the primary goal is not registration of any particular therapeutic agent or biomarker. A committee determines which therapeutic agents will be tested in the study, and the companies that manufacture the agents then provide them for study. Some of the drug candidates are run through

[16] I-SPY TRIAL: Investigation of Serial studies to Predict Your Therapeutic Response with Imaging And moLecular analysis.

[17] I-SPY 1, a Cooperative Group trial, studied neoadjuvant chemotherapy followed by surgery in patients with breast cancer. Several observations from that trial were taken into consideration when I-SPY 2 was designed. The response to therapy was linked to the prognosis in patients with high-risk molecular features, and imaging was a useful, noninvasive way to measure the response to treatment (Hylton et al., 2007, 2009).

60 tumor cell lines to see if researchers can predict the response. Three standard biomarkers (estrogen receptor, HER-2, and Mammaprint) are used to categorize patients and determine therapy. Many other biomarkers are assessed in the trial and, depending on the results, may be considered for approval as a predictive marker by the FDA Office of In Vitro Diagnostics within the Center for Devices and Radiologic Health (Barker, 2009; Esserman, 2009).

If the trial proves to be a successful demonstration of the process for testing biomarkers, many scientific challenges will still remain. For example, investigators will need to determine whether this research design is portable to other diseases besides breast cancer. Because breast cancer has more established biomarkers than most other types of cancer, identifying suitable markers for similar studies of other cancers may prove more difficult. It is also not clear whether it is financially feasible to test the current model in other settings (Esserman, 2009).

Combination Therapy

Most cancer drugs have traditionally been broadly cytotoxic and nonselective in their mechanisms of action, resulting in significant toxicity to healthy tissues. In recent years, research has elucidated many of the molecular changes underpinning the initiation and progression of cancer (e.g., changes affecting signaling pathways; cell death mechanisms; cancer spread; and DNA synthesis, repair, and modification). Research also shows that a particular cancer may rely on multiple key pathways or functions to survive, grow, or metastasize. In addition, there is often some redundancy in key pathways, such that if one step in the pathway is inhibited, a compensatory step may be upregulated and overcome the inhibition. Treatments that target multiple pathways or more than one node in a pathway are likely to be more effective than those directed toward a single target.

Numerous scientific and medical challenges impede the efficient and successful evaluation of combination therapies. One quandary is prioritizing the combinations of agents to be tested. Preclinical studies, primarily studies that use animal models, may be the best means for determining which drugs are the most effective in combination, but there are limitations to this approach, especially since preclinical models do not always predict effects in patients with cancer.

In the past, little was generally known about the target of the therapeutic agent in the early stages of development. The risk of failure was high because the agent might not interact with the intended target or the intended target might not be relevant for tumor growth. Combining products early in their development increased the risk of failure because little is known about each of the agents alone or in combination. As a result,

it has been rare for two or more investigational products to be combined. Rather, typical combination products include at least one product that has already received FDA approval, along with other approved products or experimental products (IOM, 2008). This could change in the future, as targets for a new drug are better understood. For example, AstraZeneca and Merck recently announced plans to collaborate on a novel cancer regimen using two investigational agents early in development, both allosteric kinase inhibitors (Winslow, 2009). According to Merck, this is the first time that two large pharmaceutical companies have established a collaboration to evaluate the potential for combining candidate molecules at such an early stage of development (Merck, 2009). A unique challenge of this collaboration is that to date, co-registration of two unapproved agents for the treatment of cancer is unprecedented (Huang, 2010). GlaxoSmithKline and Novartis have also initiated a similar early-stage collaboration to evaluate the combination of two investigational kinase inhibitors.[18] While these types of collaborations are just emerging, it is thought that combining targeted agents early in development may accelerate the delivery of promising cancer therapies and ultimately change the drug development paradigm.

If a single sponsor is developing both therapeutic agents, the developmental and regulatory process is less complicated than it would be if multiple sponsors were involved. Having multiple sponsors creates unique data-sharing, intellectual property, logistical, and marketing challenges (Canetta, 2009). These challenges are further discussed in Chapter 3. Numerous regulatory challenges also exist (IOM, 2008). The conventional approach to regulatory reporting is to attribute adverse events (AEs) and efficacy to particular agents. However, studies indicate that some targeted therapeutics that work effectively in concert with other agents may not evince a response as a single agent, so it can be difficult or impossible to measure and delineate the contribution of each agent to the safety and efficacy of therapy when agents are used in combination, as expected by FDA (IOM, 2008; Lutzker, 2009; Woodcock, 2009).

FDA is developing a guidance document to clarify the codevelopment of agents for combination therapy (Woodcock, 2009). This document is likely to require that combination regimens demonstrate much-improved outcomes compared with the small advances that it currently requires for the approval of new therapies (Woodcock, 2009). The codevelopment of two investigational agents will require an improved understanding of their mechanisms of action and will ultimately involve biomarkers (Woodcock, 2009). The availability of biomarkers that are capable of predicting a patient's response could be helpful in interpreting the results of combination therapy trials and in determining the safety and efficacy of each compo-

[18] Personal communication with Perry Nisen, GlaxoSmithKline, March 19, 2010.

nent. However, as noted, finding such markers will require a great deal of research, focused primarily on studying tumor responses to identify markers that predict the response or resistance to the therapeutic agent (IOM, 2008). Input from experts in clinical pharmacology may also be beneficial in designing trials to test novel combinations.

Furthermore, testing all relevant combinations in traditional two-arm trials will be very time-consuming and expensive. Many researchers have proposed novel clinical trial designs that could allow more efficient development of combination therapies (IOM, 2008; Lutzker, 2009; Parmar et al., 2008). FDA has indicated that innovative trial designs (e.g., adaptive designs; see the section on trial design below) could provide faster answers regarding drug combinations (IOM, 2008). However, stakeholders (including industry, FDA, and NCI) have heretofore generally taken a conservative stance on trials with novel designs. All stakeholders should work together to develop innovative and collaborative approaches to this urgent challenge in cancer clinical trials (IOM, 2007; McClellan and Benner, 2009; PCAST, 2008). **The committee recommends that NCI facilitate a process by which stakeholders (NCI, NIH, FDA, industry, investigators, and patients) can define an effective mechanism for the development of targeted cancer therapies, with particular emphasis on combination products.**

TRIAL DESIGN

The increasing complexity of cancer clinical trials, along with the great expense and high failure rate of late-stage clinical trials, has spurred innovations in trial design, with the aim of conducting clinical trials more efficiently and with greater likelihood of success. Experts have proposed numerous trial design innovations, including multi-arm trials, adaptive trials, greater reliance on predictive biomarkers, use of the progression-free survival as an endpoint, testing of multiple agents in the same trial, garnering more information from the early stages of clinical trials, and implementing more randomized Phase II trials in which both safety and efficacy are assessed (Adjei et al., 2009; Berry, 2005, 2006; Bria et al., 2009; Rubinstein et al., 2009; Sargent and Taylor, 2009; Schiller, 2004; Simon, 2008b; Tan et al., 2009; Thall et al., 1988, 1989). An explicit goal in designing clinical trials can be shortening the time to develop and reliably assess therapeutic strategies. This increased efficiency might be possible by utilizing emerging information on biomarkers and other intermediate measures in a more deliberate way. Cooperative groups are in a unique position for developing innovative approaches to clinical trial design and for demonstrating the feasibility and utility of innovative, efficient approaches in their clinical trials.

The randomized controlled trial (RCT) was established as the standard

of practice for evaluating new medical treatments in the middle of the 20th century. Randomization was properly hailed as an enormous advance in empirical science and the RCT is widely recognized to be the gold standard of clinical research. Although many enhancements have been made to trial design and analysis over the ensuing decades, the current explosion of biological knowledge demands increased attention to developing trial designs that can take advantage of this knowledge more fully, with a goal of improving the efficiency of trials without reducing the reliability of results. Many clinical trialists are developing approaches to clinical trials that involve multiple stages or otherwise permit increased flexibility by allowing for changes to be made during the trial, based on emerging results. Such design innovations have potential for decreasing the time to study conclusions and improving the likelihood of offering effective treatment to a greater proportion of trial participants.

Although the committee does not endorse any particular type of trial design, one example of design that may be more flexible than the traditional two-armed RCT that has a fixed sample size is sketched in Figure 2-1. The primary endpoint in this example could be the accepted Phase III endpoint, perhaps overall survival. However, early markers of treatment effect (e.g., tumor response, performance status, disease progression, longitudinal biomarkers) might also be used to make decisions about dropping arms.

The use of the multiarm, multistage (MAMS) trial design has been proposed as a way to evaluate treatments faster and more efficiently than is possible by the use of current standard trial designs. By using intermediate outcomes and testing a number of new agents (and combinations of agents) simultaneously against a single control arm, the MAMS design for RCTs requires fewer patients (Parmar et al., 2008). A performance evaluation of the two-stage, multiarm design using four cancer trials conducted at the Clinical Trials Unit (CTU) of the Medical Research Council (MRC) in the United Kingdom found that such a design performs well with regard to the Type I and II error rates[19] obtained and is an effective way of speeding up the therapy evaluation process (Barthel et al., 2009). The first MAMS trial to use multiple arms and stages synchronously was recently launched by the MRC CTU. The STAMPEDE trial (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) is an open-label, five-stage, six-arm RCT of drug treatments for men with prostate cancer. Although the results of the STAMPEDE trial will not be known for some years, the implementation of this trial may demonstrate the feasibility of

[19]Type I error, also known as a "false positive," occurs when a difference is observed when in truth there is none. Type II error, also known as a "false negative" is the error of failing to observe a difference when in truth there is one.

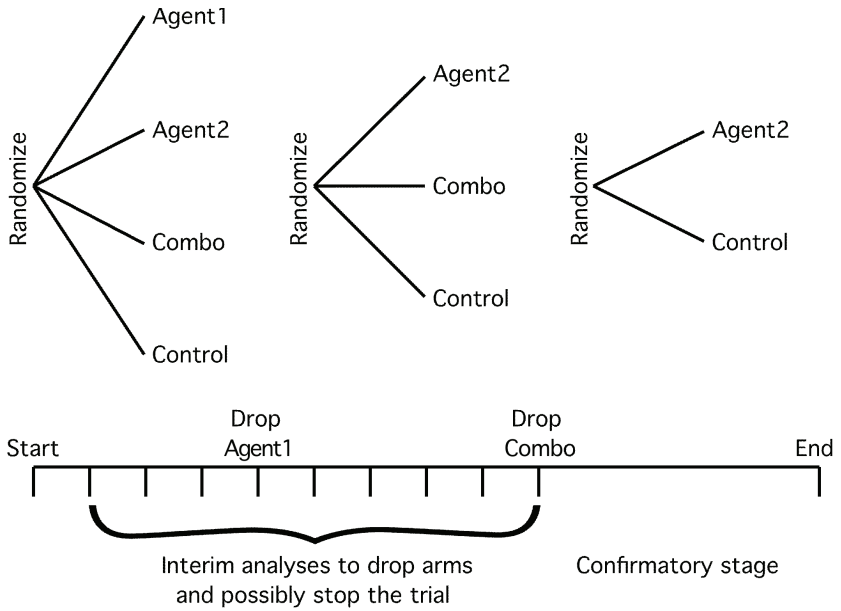

FIGURE 2-1 Example of a Phase II/III trial for investigating several possible treatment strategies. Several treatment arms are considered at the start of the trial (in this case, two individual agents and their combination, but there are many other possibilities). As information accrues, arms that are not performing as well as other arms can be dropped, and if none of the experimental arms are performing well relative to control then the trial can be stopped. A goal may be to reduce to a two-armed trial by particular time points. Accrual continues without stopping for interim analyses, and accrual might be ramped up on the basis of interim analyses as the trial moves into confirmatory mode. The sample size of the confirmatory stage can be determined on the basis of the performance of the experimental arms relative to control in the early stages of the trial.

using the MAMS design to initiate and undertake large-scale trials of cancer therapies (Sydes et al., 2009).

Most clinical trials are designed to employ classical "frequentist" statistical methods.[20] Another approach to clinical trial design and analysis is the Bayesian approach, which considers the treatment effect as a random variable with a probability distribution rather than as an unknown constant that the investigator wishes to estimate. FDA has issued draft

[20]The "frequentist" approach to statistical inference is based on quantifying the frequency with which errors in rejecting or not rejecting a specific hypothesis would be made if an experiment were repeated many times.

guidance on the use of adaptive Bayesian designs for trials of drugs and biologics, and recently issued final guidance on the use of such designs for device trials, with the commissioner of FDA noting, "This final guidance on the use of Bayesian statistics is consistent with the FDA's commitment to streamline clinical trials, when possible, in order to get safe and effective products to market faster" (FDA, 2010a,b,c). The use of Bayesian methods for clinical trials is increasingly being advocated because many statisticians believe that this approach fosters more flexibility in the conduct of a trial and because adaptation can be incorporated more naturally into trials with Bayesian designs than into those with frequentist designs. For example, the performance of Bayesian analyses midtrial can indicate early in the course of the trial the subpopulations most likely to respond to treatment, enabling enrichment of the study population. They can also suggest which among several treatments is the most likely to be effective or ineffective, enabling researchers to drop those treatment arms likely to be failures and to modify the number of subjects needed to show the efficacy of treatments on the basis of midstream analyses. Frequentist designs can also incorporate such opportunities for adaptation, but Bayesian approaches may be more suitable when substantial adaptation is desired, particularly in the earlier stages of drug development. For example, Phase I studies that use Bayesian adaptive designs may enable more doses to be considered and may be more likely to identify the most effective dose with minimal adverse effects than trials with more traditional designs (Berry, 2006). The use of Bayesian designs has been more controversial in the later, confirmatory stages of drug development. An element of subjectivity is an inherent part of this approach.

Bayesian approaches are increasingly being used in exploratory studies. For example, this approach will be used in the I-SPY 2 TRIAL, described earlier in this chapter, to develop paired neoadjuvant cancer therapies and biomarkers (Barker et al., 2009). Improved computational techniques and the widespread availability of high-speed computers enable researchers to more easily conduct Bayesian clinical trials, and the results from Bayesian trials are increasingly being used in clinical trials and to petition FDA for the approval of drugs and devices (Berry, 2006; Biswas et al., 2009; Gonen, 2009; Katsnelson, 2009).

Another aspect of cancer clinical trials that investigators are reconsidering is the reliance on the tumor response rate as an endpoint in Phase II trials. Phase II cancer trials have historically been single-arm trials aimed at demonstrating tumor responses,[21] with the assumption that it will translate into clinical effectiveness in a Phase III trial. However, in many types

[21] "Tumor response" is defined as shrinkage by 50 percent bidimensionally or 30 percent unidimensionally.

of cancer, the tumor response does not reliably predict a survival benefit, and in other types of cancer, the tumor response has proven difficult to measure. In addition, many of the newer molecularly targeted agents are cytostatic rather than cytotoxic and may thus provide a survival benefit in the absence of a significant change in tumor size. For example, some new targeted therapeutic agents, such as sorafenib given to patients with hepatocellular carcinoma, significantly increase patients' time to disease progression compared with patients receiving standard of care, in the absence of tumor shrinkage, presumably by blocking proliferative signals to the tumor such that much of the tumor mass is comprised of inactive or necrotic tissue (Adjei et al., 2009).

The Clinical Trial Design Task Force of the NCI Investigational Drug Steering Committee recently recommended that alternate Phase II endpoints be studied, including the use of novel imaging modalities. Progression-free survival may be an appropriate measure when newer targeted agents are tested, but researchers need to assess this endpoint at the same, pre-specified intervals in both treated patients and control subjects to avoid biased results (Rubinstein et al., 2009; see also the section on FDA data requirements in Chapter 3). New imaging modalities, such as those that use novel positron emission tomography (PET) imaging agents to highlight the biochemical target of a drug or digital contrast-enhanced magnetic resonance (MR) spectroscopy, which can detect the inhibition of angiogenesis, might also provide more valid endpoints for cancer clinical trials than tumor volume.

The task force also recommended the use of a randomized design rather than historical controls in some circumstances (Adjei et al., 2009). Investigators are increasingly conducting randomized controlled Phase II trials to obtain more reliable preliminary estimates of effectiveness. Such trials reduce the possibility for bias and provide more information than uncontrolled Phase II studies for the purpose of deciding whether to progress to Phase III trials (Rubinstein et al., 2009). Randomized trials are also warranted when appropriate historical control data for a tested targeted cancer treatment are not available, especially for patient subsets identified by specific predictive markers for the treatment. To improve the efficiency of Phase II randomized trials, statisticians have proposed a number of innovative trial designs, including randomization of a small portion of patients to a reference arm, the incorporation of a randomized Phase II trial into the first stage of a Phase III protocol, or the use of a Phase II trial that directly compares two experimental regimens to prioritize candidacy for Phase III studies (Rubinstein et al., 2009).

The task force recommended more rational incorporation of biomarkers in Phase II clinical trials as well. The development and evaluation of biomarkers for use in patient treatment decisions also warrants innovative trial designs. The current method of biomarker discovery is largely retrospective.

Various hypotheses about potential biomarkers are generally examined in Phase II studies. Some retrospective biomarker validation is generally required because throughout the development of a therapy and even at the time of FDA approval, researchers may not fully understand the biological implications of a therapy and might not be able to identify subgroups of patients who are likely to respond. However, retrospective studies have inherent limitations. The replication of retrospective studies by multiple investigators can provide informative data, but better strategic planning of biomarker evaluation throughout the development phase, especially in Phase II trials, may enable the design and conduct of more efficient Phase III studies, which could lead to the increased success of new therapies in Phase III studies (McShane et al., 2009).

The use of studies with retrospective/prospective designs is one way to improve biomarker development. That type of design requires randomized patient accrual and the use of prespecified hypotheses, techniques for analyses, patient populations, patient subgroups, and large numbers of patients with biospecimens (Sargent, 2009). Figure 2-2 illustrates one approach that is being used for biomarker validation.

On the basis of data from retrospective-prospective studies, FDA recently added information about testing for mutations in the *KRAS* gene to the labels of two drugs used to treat patients with colorectal cancer (FDA,

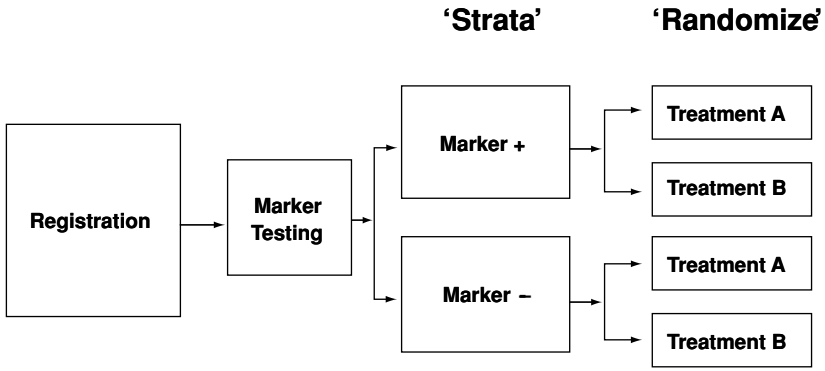

FIGURE 2-2 Example of a retrospective/prospective approach to biomarker validation. The benefit of treatment is tested separately in the two marker-defined patient populations.
SOURCE: Mandrekar, S. J., and D. J. Sargent. 2009. Clinical trial designs for predictive biomarker validation: One size does not fit all. *Journal of Biopharmaceutical Statistics* 19(3):530–542. Reprinted with permission of Taylor & Francis Group, http://www.informaworld.com.

2009). About 10 percent of patients with metastatic colorectal cancer respond to the monoclonal antibodies panitumumab (Vectibix) and cetuximab (Erbitux), which target the epidermal growth factor receptor (EGFR). However, the detection of EGFR protein expression by immunostaining does not reliably predict the clinical outcome of EGFR-targeted treatment (reviewed by Modjtahedi and Essapen, 2009). A search for alternative predictive biomarkers led to the discovery that oncogenic activation of signaling pathways downstream of EGFR, such as mutation of the *KRAS* gene, can render EGFR-inhibiting therapies ineffective (reviewed by Siena et al., 2009). Forty percent of the tumors from patients with colorectal cancer have *KRAS* gene mutations that result in the continuous activation of the *KRAS* protein (Allegra, 2009). Retrospective subset analyses of metastatic colorectal cancer trials demonstrated that patients with this mutation do not receive therapeutic benefit from treatment with cetuximab or panitumumab, but those with wild type *KRAS* do often benefit. In July 2009, FDA announced that the companies that make these two products would be updating the labels so that physicians could use this information to guide treatment (FDA, 2009), although it is not yet clear whether this type of evidentiary data set will lead to similar FDA decisions in the future (Allegra, 2009; Goldberg, 2009).

Prospective randomized clinical trials may be scientifically ideal for the evaluation of predictive biomarkers, but such studies are complex, costly, and challenging to conduct. One reason is that patients may be reluctant to be randomized if they have a biomarker thought to be predictive of benefit from some therapy. Examples of ongoing prospective trials include TAILORx (Trial Assigning IndividuaLized Options for Treatment)[22] and MINDACT (Microarray in Node-negative Disease may Avoid Chemo-Therapy),[23] which are designed to test the validity of the Oncotype DX test and the Mammaprint tests, respectively. The NCI-sponsored TAILORx trial is a prospective study of the Oncotype DX test that will enroll 4,000 ER-positive, lymph node-negative, and HER-2-negative patients to determine whether women with an intermediate score by the Oncotype DX test will benefit from adjuvant chemotherapy (IOM, 2008). MINDACT is a multicenter, prospective, Phase III trial coordinated by the European Organisation for Research and Treatment of Cancer and run under the Breast International Group (BIG) and TRANSBIG[24] networks, which will accrue 6,000 node-negative patients. Patients for whom there is discordance

[22] See http://www.cancer.gov/clinicaltrials/digestpage/TAILORx.

[23] See http://www.breastinternationalgroup.org/Research/TRANSBIG/MINDACT.aspx.

[24] BIG is a nonprofit organization for academic breast cancer research groups that facilitates breast cancer research at international level. TRANSBIG is a consortium within BIG that is focused on translational research.

between the gene signature risk results (high versus low) and the clinical-pathological risk will be randomized to determine which result will be used to make the decision about whether to offer chemotherapy.

Other new strategies being used include "targeted trial designs," which initially test subjects for the presence of predictive markers and include (and randomize) only those subjects whose biomarker status predicts that they will respond to a treatment (Bria et al., 2009). The number of randomized patients needed for such a targeted design is often much smaller than that needed to conduct a trial with a standard design (Simon, 2008b); however, the target population is also smaller, so these trials will not necessarily be completed more rapidly, and they may be more expensive to conduct since many more potential subjects than will ultimately be enrolled will need to be screened for eligibility. Additionally, one must be very sure that the assays measuring the marker are highly accurate before the decision is made to use such a design to avoid unnecessarily limiting a potentially widely effective treatment to a small population. If a predictive marker is not known or is not validated before the start of a clinical trial, an "adaptive signature" trial design could be used. In a trial with such a design, different subsets of data within the Phase III trial are used to develop a predictive marker and to evaluate the effects of the treatment in populations identified by the marker (Simon, 2008b). Another trial design that enriches the patient population with likely responders is the "randomized discontinuation" design, in which all patients receive a cytostatic drug for one or two cycles, and those with stable disease are then randomized to receive either a placebo or the drug (Schiller, 2004).

As Sargent and Taylor (2009) summarize in a recent paper,

> The need to strategically consider drug development as an integrated program as opposed to a collection of isolated studies, the benefits in many cases of randomization earlier in the drug development process, and the need for new endpoints all are challenging the standard paradigms. . . . Our overall premise is that the potential benefits associated with the oncology clinical trial community moving away from the one-size-fits-all paradigm of trial design are great, and that more flexible and efficient designs tailored to match the goals of each study are currently available and being used successfully.

Thus, the committee recommends that the Cooperative Groups lead the development and assessment of innovative designs for clinical trials that evaluate cancer therapeutics and biomarkers (including combinations of therapies). For example, prospective clinical trial designs that randomize patients based on biomarkers or treatments, or both should be explored and evaluated. For targeted therapies, a predictive hypothesis for a biomarker

should be put forward in the preclinical phase and tested in early-phase clinical trials (Phase I-II trials).

COMPARATIVE EFFECTIVENESS RESEARCH

In addition to developing and testing novel approaches to cancer care, the Cooperative Group Program also plays an important role in further evaluating therapies and preventive strategies that are already in clinical use. For example, FDA registration trials may provide evidence of efficacy in a well-defined test population, but physicians would often like to have additional information for making decisions about patient treatment when more than one therapy is available for similar indications. Comparative effectiveness research (CER) is designed to address this data need by generating evidence about the effectiveness of health care options and clinical outcomes that result from different medical interventions for the same condition. CER can span a spectrum of research methods, from data set mining and observational studies to randomized controlled trials, and can include research on preventive interventions, screening tests, diagnostic tests, treatments, follow-up strategies, and end-of-life care. Cooperative Groups often undertake large prospective randomized trials to rigorously compare outcomes for patients treated with cancer drugs that have similar targets, or are indicated for similar patient populations. Evidence generated from such trials can then be used to make treatment decisions based on relative efficacy or toxicity. Pharmaceutical companies have less incentive to undertake such trials because if a competitor's drug fares better in the trial, then they are likely to loose market share.

One type of prospective clinical study that can be used to develop high-quality scientific evidence about real-world effectiveness is a "pragmatic" (or "practical") clinical trial, in which the hypothesis and study design are developed specifically to answer questions faced by decision makers. A pragmatic clinical trial selects clinically relevant alternative interventions to compare; includes a large, diverse population of study participants; recruits participants from heterogeneous practice settings; and collects data on a broad range of health outcomes (although data collection is still greatly minimized compared to standard FDA-style registration trials) (Benson et al., 2009). In some cases, this type of research entails large, simple trials that are constructed to reflect routine clinical practice as closely as possible.

However, the study of biospecimens and biomarkers can greatly increase the value of such trials. If comparisons are studied in a broad, heterogeneous population, it can appear that one treatment is not much better than a comparator, but it may turn out that 10 or 15 percent of the population that has some specific characteristic that results in better outcomes treatment with a particular treatment. Without biomarker studies to identify

the biological subsets of patients, some patients could be at a disadvantage when making treatment decisions.

As noted in Chapter 1, many new cancer therapies have become available in clinical practice in recent years, so the opportunity for developing meaningful CER studies in oncology has never been greater. Congress and the U.S. Department of Health and Human Services have also put a new emphasis on CER as a way to improve the quality of health care.[25] In 2009, Congress requested a study to identify priorities for CER across all fields of health care and provided $1.1B in new funding to support such studies (IOM, 2009; Marshall, 2009). Topics identified as high priorities for CER in oncology include comparing the effectiveness of management strategies for ductal carcinoma in situ, comparing the effectiveness of imaging technologies in diagnosing, staging, and monitoring patients with cancer, and comparing the effectiveness of genetic and biomarker testing and usual care in preventing and treating breast, colorectal, prostate, lung, and ovarian cancer (IOM, 2009). The Cooperative Groups have a history of successful trials to address these types of questions.

BIOMEDICAL IMAGING AS A CANCER BIOMARKER

The quest to incorporate innovative science into clinical trial design and to evolve toward personalized medicine demands a reassessment of the role of biomedical imaging. The use of anatomic imaging to assess changes in tumor size has long constituted the main application of imaging in clinical trials. However, because of advances in computational and molecular imaging techniques, imaging now has the potential not only to provide more refined anatomic endpoints of drug efficacy but also to aid decision making in drug development and patient care by providing molecular information about a patient's cancer.

Imaging studies offer important advantages over in vitro assays for the measurement of biomarkers. Tissue for use in in vitro assays cannot be excised and evaluated for all cancers at all sites at all points along the history of a disease. In contrast, imaging biomarkers can be evaluated for all metastatic sites and have the potential to yield insights into in vivo tumor biology and the heterogeneity of metastatic tumors. Furthermore, imaging can be applied serially, and molecular imaging techniques can provide information about disease activity in real or nearly real time. Thus, expanding the use of imaging biomarkers will play an important role in improving the efficiency of clinical trials and advancing personalized cancer care.

[25] The Patient Protection and Affordable Care Act, H.R. 3590, 111th Cong., 2nd sess., Subtitle D—Patient-Centered Outcomes Research, § 6301; 937; 9511 (March 23, 2010) also calls for CER to improve the quality and lower the cost of health care.

It must be emphasized though, that many of the approaches to molecular imaging discussed in this chapter are being used primarily in the preclinical setting today. Most of these methods must be tested in rigorous clinical trials to prove their utility.

Role of Anatomic Imaging in Clinical Trials

Anatomic imaging is and will remain essential for staging primary cancer, determining the extent of recurrence and metastasis, and assessing the response to treatment in clinical trials. However, enhanced quantification methods could further improve the assessment of treatment response. The standard criteria for assessing treatment response (those proposed by the World Health Organization and the Response Evaluation Criteria in Solid Tumors [RECIST]) rely on one- or two-dimensional tumor size measurements obtained from cross-sectional images (Eisenhauer et al., 2009; Gehan and Tefft, 2000; Miller et al., 1981; WHO, 1979). These criteria can be applied relatively quickly and easily but have substantial limitations. The cutoffs that they specify for identifying response and disease progression were defined when anatomic imaging was considerably less precise than it is now and do not take subtle but potentially important size changes into account. Furthermore, measurement of tumor diameters may be subject to significant interobserver variability (Benjamin et al., 2007; Choi, 2005; Choi et al., 2007; Hohenberger and Wardelmann, 2006; Sevinc and Turhal, 2008; Stacchiotti et al., 2009; Weber, 2009). In addition, one- or two-dimensional tumor size measurements provide reasonable surrogates for the volumes of ellipsoid or spherical tumors but not for the volumes of irregularly shaped tumors, such as those that occur in lung cancer.

Various computerized methods for automated or semiautomated tumor volume measurement have been proposed, and some are now entering clinical use (Galanis et al., 2006). Preliminary studies indicate that volumetric tumor measurement may allow the earlier detection of the response to treatment for lung cancer than conventional tumor measurement techniques (Buckler et al., 2010; Gavrielides et al., 2009; Zhao et al., 2009). Because of its wide availability, CT is likely to remain the standard modality for assessing treatment response in patients with cancer for years to come. Routine use of volumetric CT appears to be feasible in clinical settings, and could allow faster, more accurate assessment of new therapies while sparing patients from the side effects of prolonged ineffective treatments. However, validation, comparison, and standardization of volumetric CT software are needed.

In recognition of the potential of quantitative imaging biomarkers to lead to more efficient, effective clinical research and care (Mulshine and Jablons, 2009), the Quantitative Imaging Biomarkers Alliance (QIBA),

sponsored by the Radiological Society of North America, was formed in 2007. QIBA is a consortium of stakeholders from federal, academic, and commercial institutions whose mission is to streamline the development, validation, and standardization of quantitative imaging biomarkers (Mulshine and Jablons, 2009; RSNA, 2010). Validating and standardizing volumetric CT are among the consortium's highest priorities.

Sometimes, particularly for new therapies that produce cytotoxic or cytostatic effects without substantial tumor shrinkage, tumor size or volume changes alone may not be reliable indicators of treatment response. In such cases, applying conventional imaging techniques in novel, quantitative ways may offer solutions. Thus, to better assess the response of gastrointestinal stromal tumors (GISTs) treated with imatinib mesylate (Gleevec), Choi et al. adjusted the RECIST guidelines and incorporated density changes, as measured by Hounsfield units on contrast-enhanced CT (Benjamin et al., 2007; Choi, 2005; Choi et al., 2007; Hohenberger and Wardelmann, 2006; Sevinc and Turhal, 2008; Stacchiotti et al., 2009). In the long run, however, combining molecular with anatomical imaging is likely to yield even better solutions.

Biological Basis for Improved Cancer Imaging in Oncology

Emerging knowledge about cancer has improved the understanding of the optimal goals for imaging in clinical oncology and clinical trials. First, in vivo, tumors are masses that consist of cancer cells and their supporting nonmalignant cells and blood vessels that are organized into a community of interacting cells. It is this mass that creates the clinical symptoms and that is the target of cancer therapies. This is an important concept and is the biological basis for the continuing value of anatomic imaging, especially volumetric imaging based on ultrasound (US), CT, or MR imaging (MRI).

Second, it is now understood that specific hallmarks of cancer cells cause the clinically evident tumor mass and are fundamental to developing and maintaining the malignant state, including metastases. These include resistance to apoptosis; the ability to replicate indefinitely (immortality); the ability to invade and metastasize; accelerated proliferation, including resistance to growth-stopping signals; and sustained angiogenesis (Hanahan and Weinberg, 2000). The malignant tumor also has an altered metabolism, including accelerated glycolysis, fatty acid synthesis, and lipid synthesis; in short, a metabolic phenotype of malignancy.

Finally, malignancy likely begins as an alteration of key intracellular communications pathways. In some cases there is a transformation of a key gene, the oncogene that encodes a macromolecule that promotes aberrant signaling within the cell. Examples of key modifications include altered EGFR in lung cancer and glioma; HER-2 in breast and gastric cancers;

and c-*kit* in GIST. In some cases, changes in signal transduction molecules further downstream, such as b-*raf* mutations, promote proliferation. These alterations are often the basis for targeted tumor therapy and for molecular imaging of normal and aberrant molecules that accompany the malignant state.

Cancer tissues are distinct from the tissues from which they arise, and the differences may be disclosed by both anatomic and molecular imaging methods. Molecular imaging allows in vivo detection, characterization, and quantitative analysis of the key molecules, molecular events, and cellular components that are fundamental to the development and progression of cancer.

Molecular Imaging and Its Potential Applications in Clinical Trials

Recent revolutionary advances in molecular and cell biology, imaging probe development, and imaging technology have rapidly expanded the actual and potential applications of molecular imaging. Today's sophisticated array of molecular imaging technologies were developed through collaborations across many fields, including radiology, nuclear medicine, chemistry, molecular and cell biology, physics, mathematics, and pharmacology (Bradbury and Hricak, 2005; Grassi et al., 2008; Zakian et al., 2001).

Imaging modalities capable of providing information at the molecular level include PET, single-photon-emission computed tomography (SPECT), MRI, MR spectroscopic imaging, and optical imaging (optical imaging is used extensively in preclinical studies). Apart from diffusion-weighted MRI and MR spectroscopic imaging, which image water molecules and metabolites, respectively, all molecular imaging techniques rely on the use of exogenous probes to provide an imaging signal or contrast. Most probes are composed of an affinity component, which interacts with the target, and a signaling component, which provides image contrast. Although radiolabeled probes are used for PET and SPECT, the signaling component can be a fluorochrome in optical imaging or a chelate containing a paramagnetic atom in MR imaging. Imaging probes can be divided into four main categories, which are described below.

1. Phenotypic imaging probes. Phenotypic imaging probes are used to show general aspects of the physiology of malignant cells and tissues, such as neovascularization (altered blood volume, permeability, perfusion, and vascularity of the tumor tissue) and metabolism. Examples of phenotypic probes include paramagnetic agents such as gadolinium diethylenetriaminepentaacetic acid, which is used for MR imaging of tumor neovascularity, and metabolic probes, such as the radiolabeled glucose analog fluorine-18 fluorodeoxyglucose (^{18}F-FDG), which is used with PET.

2. Targeted probes. Targeted probes are used to localize specific biomolecules that are characteristic of a tumor or class of tumors, such as signal transduction proteins or tumor-associated antigens. The probes include radiolabeled antibodies, peptides, nanoparticles, and small molecules. An example of a targeted probe is 124-iodine-labeled chimeric monoclonal antibody G250, which is used to image carbonic anhydrase IX in renal cancer and which binds with a high affinity to a cell membrane antigen. Targeted probes include activatable probes, which are made with molecules or nanoparticles that undergo inducible changes. Activatable probes are used to localize enzymes, signal transductors, and downstream effectors.

3. Reporter gene probes. Reporter gene probes allow monitoring of the actions of genes in living biological systems. Gene expression imaging has had a revolutionary impact on the laboratory study of cancer biology and is likely to become important in clinical trials in the future as well. Various bioluminescent-, fluorescent-, and radionuclide-based schemes have been developed, and some of these have already been used to image human cancers.

4. Whole-cell tracking probes. Whole-cell tracking probes are used to localize and follow the movement of cells, such as cancer cells, inflammatory cells, or stromal cells, which may be important for sustaining the tumor in vivo. The cells can be labeled with marker genes or other tags, such as green fluorescent protein, bioluminescent markers, or radiotracers.

Phenotypic probes can be used to image characteristics of the hallmarks of cancer and thus have the potential to provide biomarkers for assessing treatment efficacy and response. Specific biological phenomena that can be visualized and, in some cases, quantified include cell proliferation (Bading and Shields, 2008; Conti et al., 2008), hypoxia (Everitt et al., 2009; Krohn et al., 2008), apoptosis (Blankenberg, 2008a,b,c; Strauss et al., 2008), metabolic changes secondary to oncogenic activation (Plathow and Weber, 2008), angiogenesis (Cai and Chen, 2008; Cai et al., 2008), and the expression of receptors or antigens in tumor cells, such as hormone receptors and peptide receptors (Mankoff et al., 2008; Peterson et al., 2008).

Dynamic contrast-enhanced MRI (DCE-MRI) provides data reflective of tumor vascularity and angiogenesis and is one of the phenotypic imaging techniques most often used in clinical trials and clinical practice. Because changes in tumor vascularity tend to occur earlier than changes in tumor size, DCE-MRI is useful for monitoring the effects of or predicting responses to cancer treatments, including chemotherapy for breast and bladder cancers, radiotherapy for rectal and cervical cancers, and androgen deprivation for prostate cancer (Padhani and Leach, 2005). DCE-MRI is also being used as a biomarker in early clinical trials of antivascular drugs (Zhao et al., 2009). MR spectroscopic imaging, diffusion-weighted MRI,

and blood oxygenation level-dependent functional MRI, which are noninvasive, are also promising sources of biomarkers (Evelhoch et al., 2005; Padhani et al., 2009; Torigian et al., 2007). Multiple MRI techniques can be combined in a single examination.

^{18}F-FDG is widely used in clinical oncology as a marker for the elevated level of glucose metabolism that occurs in most cancers (Gillies et al., 2008). In the case of GIST, ^{18}F-FDG-PET and PET-CT have been used to monitor the response to targeted therapies, which are often cytostatic (Contractor and Aboagye, 2009). ^{18}F-FDG-PET or PET-CT has now been successfully used to assess the response to treatment of malignant lymphomas (Bourre and Vuillez, 2009; Hutchings and Barrington, 2009) as well as lung, breast, cervical, colorectal, and esophageal cancers, among others (Avril et al., 2009; de Geus-Oei et al., 2009; Dose-Schwarz et al., 2009; Everitt et al., 2009; Hicks, 2009; Schwarz et al., 2009; Vriens et al., 2009a,b).

One emerging application of molecular imaging is monitoring the use of pathogens as therapeutic agents against cancer. For example, imaging has been used to assess virus dissemination in preclinical and clinical studies of viral therapies (Brader et al., 2009; Msaouel et al., 2009). Molecular imaging is also suitable for monitoring emerging cellular therapies, which employ stem cells or modified or genetically engineered cells (Arbab et al., 2009). Cells can be labeled, and their movement, growth, and death can then be monitored by optical, radioisotopic, or MR imaging (Akins and Dubey, 2008; Dobrenkov et al., 2008; Kang and Chung, 2008).

Codeveloping Imaging Biomarkers and Cancer Therapeutics: Theranostics and Beyond

There is much interest in the codevelopment of novel therapeutics and related molecular imaging biomarkers for use in diagnosis, treatment monitoring, and therapeutic response assessment. However, unlike in vitro diagnostic tests, most emerging molecular imaging methods rely on probes that must be injected, posing concerns similar to those faced in drug development. In some cases, a single entity serves as both a diagnostic imaging probe and a therapeutic agent, or a theranostic (Kassis et al., 2008).

In one example, receptor-targeting radiopeptides are being developed as single agents for molecular imaging and therapy of tumors that overexpress peptide receptors. To balance the clinical benefits and risks of radionuclide-based therapy, biodistribution, dosimetry, and toxicity must be carefully monitored. Imaging with targeted radiopeptides can help to address these and other issues, including detection of metastases, monitoring of the effects of chemotherapy, and detection of tumor progression or recurrence (de Jong et al., 2009; Mankoff et al., 2008).

Similar approaches are also being developed by the use of nanotechnol-

ogy. The unique properties of nanometer-sized particles can be used to target tumors with high affinity and specificity. When nanoparticles are linked with ligands such as monoclonal antibodies, peptides, or small molecules, they may simultaneously serve as therapeutic and imaging contrast agents, so their distribution can be tracked. Polymerized nanoparticle platform technology, which allows nanoparticles to be loaded with different targeting moieties, contrast agents, and therapeutic agents, could allow the development of highly personalized treatment regimens (Li et al., 2002).

Validation and Standardization

Guidelines and standards are urgently needed to validate new imaging biomarkers and related technologies. In addition, better means of standardizing and harmonizing the clinical use of validated biomarkers and technologies must be developed (Boellaard et al., 2010; Hutchings and Barrington, 2009; Wahl et al., 2009).

Serial measurements used to evaluate treatments need to be reproducible and accurate across institutions and trials to allow meaningful comparisons of different patient populations. During the IOM workshop on Improving the Quality of Cancer Clinical Trials, the participants suggested that imaging and image analysis laboratories for clinical trials be established at NCI-designated Comprehensive Cancer Centers. Such laboratories could ensure the proper execution of experimental imaging protocols and use image response assessment teams to interpret the imaging data from clinical trials and assist with the design of clinical trials (IOM, 2008).

The imaging platforms and techniques used in clinical trials vary widely. The need for standardization of anatomic data collection has been described (Strassburg et al., 2008). Furthermore, a framework for standardizing PET Response Criteria in Solid Tumors (PERCIST) has been drafted (Wahl et al., 2009). Such criteria can provide a template for use in the design of clinical trials and quantitative clinical reporting (Wahl et al., 2009). Although standardizing the hardware used at different institutions may be difficult, harmonization of the methods used by equipment vendors could improve the quality and consistency of the results that are obtained.

For emerging imaging approaches to be useful in clinical trials and clinical practice, acquisition and processing must be straightforward and consistent. However, emerging approaches often demand special expertise. For example, commercial manufacturers often collaborate with investigators in research hospitals to develop new MRI acquisition techniques. To apply these techniques in multicenter clinical trials, technical support must be provided to clinical institutions where it is lacking. In the short term, to facilitate multicenter trials, standards might specify only the minimum requirements for image acquisition (Carson et al., 2003).

Industry-academic partnerships could facilitate broad deployment of new data acquisition and quantitation methods. Innovations that academic researchers make could be shared with industry and incorporated into commercially available platforms. In turn, major industry stakeholders could serve as clearinghouses for data acquisition and analysis software and could refine their selections on the basis of feedback from academia (Carson et al., 2003).

Broad cooperation among all stakeholders, including academia, industry, NCI, FDA, and relevant professional societies, could also play a role in establishing standards for validating and applying imaging technologies. Some efforts to standardize and harmonize molecular imaging biomarkers have been undertaken, for example, by the National Institute of Standards and Technology and by the Oncology Biomarker Qualification Initiative sponsored by FDA, NCI, and CMS; but these efforts have not been coordinated (IOM, 2008). The Radioactive Drug Research Committee, which reviews and approves the use of radioactive drugs for research purposes under a mandate from FDA, could potentially play a larger role in establishing standards for validating and translating novel radioactive imaging agents for clinical use (ORS, 2009). For nanotechnology-based agents, standards for validation and translation might be established through the National Nanotechnology Coordination Office (NNCO) and the Nanoscale Science, Engineering, and Technology Subcommittee (NSET), which falls under the Committee on Technology of the National Science and Technology Council. NNCO and NSET are the central points of contact for federal activities related to nanotechnology research and development and so are in a position to coordinate standards across agencies (NNI, 2009).

This piecemeal approach to standards development is less than ideal, however. **The committee therefore recommends that NCI, in cooperation with other agencies, establish a consistent, dynamic process to oversee the development of national unified standards as needed for oncology research. NCI should use this process when standards are required for any important new technology, technique, or breakthrough method, including biomedical imaging and other biomarkers. Standards should be published and updated in a timely manner so that they are useful in clinical trials.**

SUMMARY

The recommendations in this chapter support the committee's goal to incorporate innovative science and trial design into cancer clinical trials. The committee concluded that Cooperative Group clinical trials provide a unique opportunity to enable development of the emerging science of molecular biomarkers through retrospective analyses of archived clini-

cal samples and the prospective evaluation of biomarkers and imaging technologies.

Progress in the treatment of cancer patients depends on the effective incorporation of scientific advances into clinical trials. For example, to achieve the goals of targeted cancer therapy, the use of validated biomarkers will be essential. High-quality annotated biorepositories are needed to gain useful knowledge about the biology of cancer and biomarkers from the analysis of patient samples archived from past trials. The Cooperative Groups have a history of collecting biospecimens from the diverse populations of patients who participate in their clinical trials and maintaining them in repositories with detailed information about patient characteristics, treatment, and outcome. These resources have proven immensely valuable in the development of molecular-based classification schemes and diagnostic tests that now guide decisions on the most appropriate therapy for numerous types of cancer.

However, the maintenance of tissue banks and the analysis of stored samples are costly activities that are not fully covered by the core funding that NCI provides to the Cooperative Groups. Although current NCI policies and funding do support a portion of the costs involved in the collection and storage of samples, the groups must routinely seek supplemental funding to manage and maintain the repositories. Funding mechanisms to conduct retrospective studies of samples that have been collected in previous trials have also been problematic. Current NCI policies require research studies that propose to use specimens collected from intergroup protocols to undergo scientific review by a scientific steering committee before specimens are made available. However, such a review is not linked to funding, so investigators must often seek funding through other mechanisms. This process creates many review loops, time delays, and significant double jeopardy, in that each proposal requires at least two scientific reviews (one to receive specimens and one to receive funding) that are conducted at different times by different review groups.

In addition, access to biospecimens for research is inconsistent and can entail complex negotiations with the various custodians of the samples. Policies regarding ownership and access vary across different institutions, and this impedes progress. Furthermore, many hospitals discard samples after a period of time, so valuable resources are lost to research. Because the Cooperative Groups have a long history of responsible stewardship of repositories, they are a logical choice to play a central role in the ongoing efforts of NCI to establish consistent policies on ownership and access.

The committee recommends that NCI mandate the submission of annotated biospecimens to high-quality, standardized central biorepositories when samples are collected from patients in the course of Cooperative Group trials. NCI should also implement new funding mechanisms and

policies to support the management and use of those resources for retrospective correlative science. For example, all data, including biomarker data from serum, tissue, and imaging analyses should be considered precompetitive, unencumbered by intellectual property restrictions, and be made widely available. NCI should also establish a national inventory of samples held in the central repositories and have a defined process for access by researchers that includes a single scientific peer review linked to funding. In addition, clinical data accompanying biospecimens should be reported using standardized forms.

High levels of evidence are needed to validate and qualify biomarkers for specific uses, and current funding is inadequate to support the research needed to generate that evidence. The availability of a consistent and adequate funding source devoted to correlative studies with stored samples and with appropriate peer review that includes direct input from the group that collected the samples is imperative. The broader use of high-quality, standardized repositories would speed the pace of scientific and clinical advances at a much lower expense than would be required if new clinical samples had to be collected to study each new concept. The creation of a national inventory of samples held by the Cooperative Groups would also greatly facilitate important research in correlative science.

The committee also concluded that the Cooperative Groups are in a unique position to develop innovative designs for clinical trials and to demonstrate the feasibility and utility of using innovative, efficient designs in their clinical trials. The increasing complexity of cancer clinical trials, along with the great expense and high failure rate of late-stage clinical trials, has spurred innovation in trial design, with the aim of conducting clinical trials more efficiently and with a greater likelihood of success. **The committee recommends that the Cooperative Groups lead the development and assessment of innovative designs for clinical trials that evaluate cancer therapeutics and biomarkers (including combinations of therapies).**

The development and use of innovative trial designs could speed progress in clinical trials in numerous ways. For example, prospective clinical trial designs that randomize patients on the basis of biomarkers or treatments, or both, should be explored and evaluated. For targeted therapies, a predictive hypothesis for a biomarker should be put forward in the preclinical phase and tested in early-phase clinical trials (Phase I and II trials). Better Phase II trial designs are needed to more accurately assess which patients benefit from a particular therapy, and thus guide the decisions about whether to move into Phase III trials. Improved designs for Phase III trials, which are the most costly and lengthy trials and entail the majority of Cooperative Group trials, could lead to faster, more accurate conclusions about new therapeutics and in the process reduce costs and conserve resources. For example, recent innovations, such as the use of adaptive

designs for Phase II trials that assess response endpoints during trial accrual in real time, suggest that relevant clinical questions might be addressed more efficiently, with fewer patients required, with less time needed to show differences between groups, and with enhanced confidence in the clinically (and statistically) meaningful differences that are observed between groups. These or related designs may be particularly amenable for the comparison of treatment effects in patients with different biomarker profiles and could hasten the identification of the most promising predictive biomarkers that could be validated in a Phase III trial setting.

As new scientific methods and technologies develop and mature, standards are needed to ensure appropriate and consistent use. However, when new methods or technologies are incorporated into clinical trials, standards to ensure that the results collected at the various trial sites are consistent enough to attain accurate and meaningful conclusions from a study are often lacking. The current approach to standards development is often ad hoc, with the processes and rules for such things as committee composition and voting rules being reinvented on a case-by-case basis. This can lead to heterogeneous and delayed results.

Thus, NCI, in cooperation with other agencies, should establish a consistent, dynamic process to oversee the development of national unified standards as needed for oncology research. This process should be used by NCI when standards are required for any important new technology, tool, or breakthrough method (e.g., biomedical imaging and other biomarkers and biospecimens) and should replicate successful aspects of standards development by other standard-setting bodies, both governmental and nongovernmental (e.g., the American Society for Testing and Materials, the National Standards Foundation, the National Institute for Standards and Technology, the International Organization for Standardization, and professional societies). This process should utilize the input of experts in both subject matter and standards design in developing standards and include consistent operating procedures for developing standards (e.g., representation of stakeholders in committee composition, decision making, and voting rules). The resulting standards should be published and updated in a timely manner so that they are useful for the conduct of clinical trials. A more systematic, multidisciplinary, and dynamic approach to standards development fostered by NIH and NCI would be advantageous for the rapid and consistent setting of unified national standards as the need arises. NCI could further assist by facilitating the creation of systems and software to aid the process of standards implementation.

This need for standards will become increasingly important as the science of cancer research becomes more complex and more dependent on technologies such as imaging and on molecular tools such as biomarkers. In the case of biomedical imaging, many technologies and imaging reagents,

both those in current use and those under development, have the potential to provide information that can aid drug development and clinical decision making by providing improved means of diagnosis and monitoring. However, the lack of standards for image acquisition and quantification of results compromises the validity of the results and the interpretation of those results. In addition, the lack of harmonization of methods among the different vendors of imaging equipment compromises the quality and consistency of results. The consistent development of standard methodologies for established tumor-imaging modalities (e.g., computed tomography, fluorodeoxyglucose positron emission tomography, and conventional magnetic resonance imaging) by expert panels, along with a requirement that manufacturers meet those standards, could significantly improve the accuracy and value of those tests. Validation standards are also needed to continuously evaluate novel imaging methods and modalities to determine their merit and appropriate use.

Similarly, expert panels are needed to establish validation and qualification standards for the development and use of in vitro biomarker tests, to ensure that the results of those tests are consistent and accurate, and for the appropriate interpretation and use of those results. Such standards could also inform FDA guidance for the codevelopment of diagnostic-therapeutic combinations or for the inclusion of a biomarker test on the label for a drug or biologic that is already FDA approved.

Continued progress in the development and incorporation of innovative science into clinical trials will require the efforts of many stakeholders. **For example, NCI, NIH, FDA, industry, investigators, and patients all have a role to play in defining an effective mechanism for the development of targeted cancer therapies.** Effective collaboration among stakeholders will be particularly important for combination therapies, which may hold the key to successful personalized medicine because most cancers have multiple abnormalities. Companies may be reluctant to work with competitors to test promising combinations at an early and risky stage of development. To date, most combinations tested in Phase III trials have involved at least one agent currently approved by FDA. In addition, the steps needed and the data required to bring target therapies and combinations of products are not well defined. Issues relevant to effective collaboration are addressed in more detail in chapter 3.

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3

Operations, Oversight, and Funding of Cancer Clinical Trials

Cancer clinical trials are highly complex and represent a major research undertaking. They require hundreds of steps with numerous decision points and there are multilayered and iterative review processes because multiple oversight bodies have jurisdiction over a trial. The primary focus of the Cooperative Group Program is large, definitive, randomized Phase III studies and the development efforts preceding these trials (NCI, 2006). Phase III trials are considered the "gold standard" for changing medical practice because the results of these trials are used to obtain Food and Drug Administration (FDA) approval, establish practice guidelines, and make insurance coverage decisions. They are also the most complex and costly trials to conduct. These large-scale clinical trials necessitate interactions among numerous stakeholders, including multiple governmental agencies, academic medical centers, community practices, patients, and industry. To improve the system as a whole, a revision of the roles of all these stakeholders must be considered.

This chapter describes the organization, oversight, and funding of the National Cancer Institute (NCI) Cooperative Group Program, as well as the processes and collaborations needed to develop, launch, and complete a large-scale cancer clinical trial. The chapter identifies inefficiencies and limitations of the current system and describes the committee's recommendations, which aim to improve the speed, efficiency, and effectiveness of cancer clinical trials, especially those that the Cooperative Groups undertake.

ORGANIZATION OF THE COOPERATIVE GROUP PROGRAM

The Cancer Therapy Evaluation Program (CTEP), which is part of the Division of Cancer Treatment and Diagnosis (DCTD) of NCI, administers the Cooperative Group Program, which represents a major component of DCTD's extramural research activities. The NCI Cooperative Groups were originally organized by geographic area or, in some cases, by type of disease or therapeutic modality. Each Cooperative Group includes a large network of physicians, statisticians, nurses, clinical research associates, pharmacists, patient advocates, and other affiliated investigators. The Groups operate independently and have their own administrative structures, operating procedures, and committees. Each Group has an operations office and statistical center overseen by the Group chair and Group statistician, respectively. To be involved with a Cooperative Group, institutions must apply for membership and meet that Group's eligibility criteria, including accrual potential and the ability to comply with Group standards and federal requirements. Each institution participating in a Cooperative Group is represented by a principal investigator, who manages the institution's activities within the Group (Mauer et al., 2007).

Institutions participate in the Cooperative Groups as main member institutions, affiliates of a main member institution, or members of participating Community Clinical Oncology Programs (CCOPs). The main member institutions are generally academic medical centers or other major medical centers that are centrally involved in Cooperative Group activities. Main member institutions enroll a significant number of patients in clinical trials and also contribute scientific expertise and other resources to Group activities. Affiliate members, designated by the main member institutions, include community-based organizations and physicians' practices and have lower patient accrual rates.

Created in 1983, "the CCOP network allows patients and physicians to participate in state-of-the-art clinical trials for cancer prevention and treatment while in their local communities," according to NCI (2009b). The CCOP network can include hospitals, clinics, health maintenance organizations, groups of practicing physicians, or a consortium that agrees to work with a principal investigator through a single administrative unit (Mauer et al., 2007). Each CCOP chooses to join one or more CCOP Research Bases, which are NCI-designated Cancer Centers or Cooperative Groups that design, develop, and conduct clinical trials (NCI, 2009b).

OVERSIGHT OF CLINICAL TRIALS

Cancer clinical trials are highly regulated activities. Multiple agencies of the U.S. Department of Health and Human Services (HHS) review and

provide oversight of cancer clinical trials, including NCI, FDA, the Office for Human Research Protections (OHRP), and the Office for Civil Rights (OCR). Many reviews are required before a Cooperative Group clinical trial can begin. These include reviews undertaken by the disease site and other scientific committees of the Cooperative Groups, various committees and branches of NCI, institutional review boards (IRBs), comprehensive cancer centers, CCOPs and their affiliates, and, in some cases, FDA and industry sponsors (Table 3-1). Additional oversight is required during the conduct of the trial and at the closure of the trial. The many oversight bodies have different objectives and responsibilities, and thus, they seek similar and overlapping but not identical information and action for compliance. This section provides a brief overview of Cooperative Group clinical tri-

TABLE 3-1 Types of Reviews Required to Develop a Cooperative Group Clinical Trial, by Stakeholder

	CTCG	CTEP	CCC	CCOP/Affiliates	Others
Scientific Review	Disease Site Committee Executive Committee Protocol Reviews (2–4)	Steering Committee/ CRM PRC CTEP Final	Protocol Review	Feasibility Review Site Surveys	Industry Sponsor
Data Management	CRF Reviews (2–4) Database Review	CDE Review			
Safety/Ethics	Informed Consent		Local IRB	Informed Consent	CIRB
Regulatory	Regulatory Review	PMB Review RAB Review			FDA
Contracts/ Grants	Budget Language				Industry Sponsor
Study Start-up	Start-up Review		Start-up Review	Start-up Review	

NOTES: CCC = Comprehensive Cancer Centers; CCOP = Community Clinical Oncology Program; CDE = Common Data Element; CIRB = central institutional review board; CRF = case report form; CRM = Concept Review Meeting; CTCG = Clinical Trials Cooperative Group; CTEP = Cancer Therapy Evaluation Program; FDA = Food and Drug Administration; PMB = Pharmaceutical Management Branch; PRC = Protocol Review Committee; RAB = Regulatory Affairs Branch.
SOURCE: Dilts, 2008.

als oversight, with emphasis on issues that the committee considered most relevant to improving the clinical trials system.

NCI Oversight of Cooperative Group Trials

The cooperative agreements that provide funding to the Cooperative Groups stipulate NCI review and oversight at each step of the clinical trial process, including selection of trials to be conducted, protocol development, and trial operations (NCI, 2006). The role of CTEP staff, as described in the NCI clinical trials Cooperative Group Program Guidelines (NCI, 2006), is to "assist, facilitate, and assure optimal coordination of Group activities. CTEP staff have very specific and well-defined responsibilities for the oversight and review of Group clinical trials and for investigational agent development." **Given this central position of NCI in the clinical trials system, the committee recommends that the current roles of NCI as well as the Cooperative Groups be reevaluated.**

The 2005 report by the Clinical Trials Working Group (CTWG) recommended several ways to improve NCI oversight of cancer clinical trials (NCI, 2005b; see also Appendix A). In response to the recommendations of the CTWG, NCI created a number of offices, committees, and subcommittees, as indicated in Table 3-2 and Figure 3-1.

Trial Concept Selection

Investigators within the Cooperative Groups develop ideas for new cancer clinical trials, and these suggestions percolate through Cooperative Group committees to the Group leadership. Funding for the Cooperative Groups is based on past accomplishments but is not provided on a per trial basis or on the basis of specific trial proposals (see the section on funding for cancer clinical trials). However, all trial concepts that the Groups generate must be reviewed and approved by CTEP before they are launched. Because an excess of trials with poor enrollment raised concerns that prioritization of the trials was inadequate, the CTWG recommended the creation of a network of scientific steering committees (Box 3-1) that would leverage Cooperative Group, inter-Group, Specialized Programs of Research Excellence, and Cancer Center structures to work with NCI staff on the design and prioritization of Phase III trials to better allocate resources, increase scientific quality, and reduce duplication (NCI, 2005b; see also Appendix A). With this new organizational setup, principal investigators submit the concept for a clinical trial to CTEP for review and approval by the appropriate steering committees, with the goal of prioritizing them.

This approach to concept review remains inefficient and is not sufficiently effective in prioritizing trials. Since the steering committees were formed, the lengths of concept proposals have increased significantly (they

TABLE 3-2 NCI Oversight of Cancer Clinical Trials

Office, Committee, or Subcommittee	Role
NCI Office, Coordinating Center for Clinical Trials	Established in 2006; supports the implementation of the initiatives of the CTWG and the Translational Research Working Group (TRWG)
NCI Committees	
Clinical and Translational Research Operations Committee (CTROC)	Established in 2005; an internal committee that provides strategic oversight for NCI clinical trials and translational research
Clinical Trials and Translational Research Advisory Committee (CTAC)	Established in 2007; provides extramural oversight for implementation of the CTWG and TRWG initiatives, including steering committees
CTAC Subcommittees/Working Groups	
Investigational Drug Steering Committee (IDSC)	Provides strategic input into the clinical development (early phase) plans for new agents for which the Cancer Therapy Evaluation Program holds the investigational new drug application
Disease-Specific Scientific Steering Committees (SCs)	Prioritize concepts for Phase III and selected Phase II therapeutic clinical trials; refine and collaborate on concepts by the use of task forces, when appropriate
Patient Advocate Steering Committee	Develops and shares best practices for patient advocate participation in steering committees; identifies common concerns and needs and proposes potential solutions; disseminates information from steering committees to the appropriate communities; ensures that the concept evaluations consider the patient community at large and includes a special focus on minority and underserved populations
The Clinical Trials Management System (CTMS) Steering Committee	Provides strategic advice for the CTMS work space, advising on project selection, prioritization, and oversight
Ad Hoc Coordination Subcommittee	Provides advice on how to foster collaboration among the various components of the NCI-sponsored clinical trials infrastructure, to develop a fully integrated clinical trials system
Ad Hoc Public/Private Partnership Subcommittee	Provides advice on how to enhance NCI-sponsored clinical trials through collaborative interactions with the private sector
Cooperative Group Clinical Trials Funding Model/Complexity Model Working Group	Charged with developing a model for aligning reimbursement of Phase III treatment trials with complexity, to compensate the additional costs
Correlative Science Working Group	Charged with developing validation standards and prioritization criteria of correlative science studies associated with Phase III trials
Operational Efficiency Working Group	Charged with developing approaches to cut timelines in half

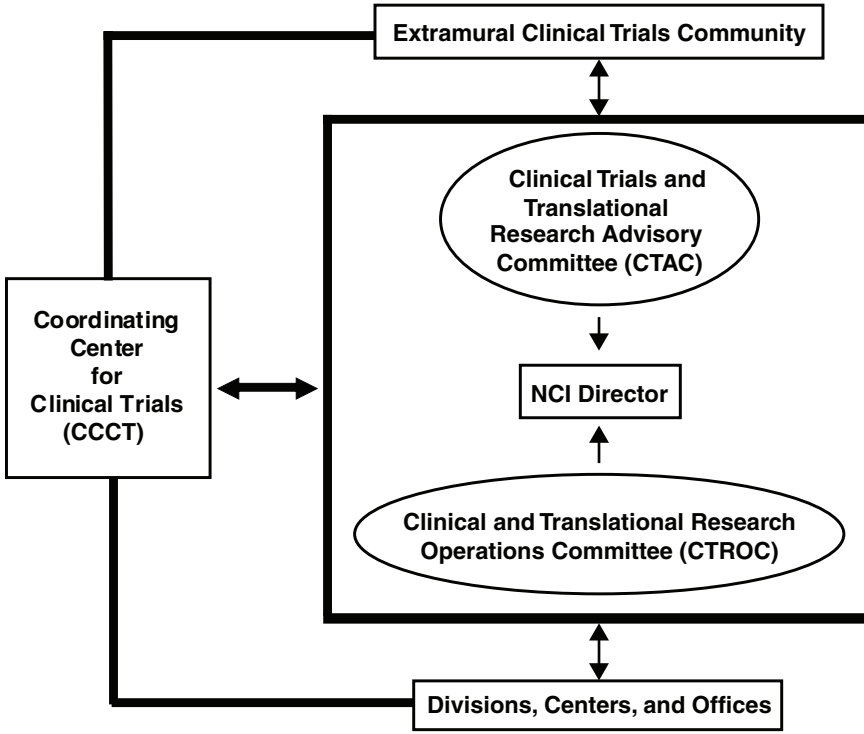

FIGURE 3-1 Integrated management of NCI cancer clinical trials.
SOURCE: Doroshow, 2008.

are now about 25 pages long), making the review process more arduous. Multiple layers of review still slow the process, and trial concepts are still not ranked against each other, as is usually done in peer review. Steering committees review and vote up or down on trial concepts as they are submitted, and NCI staff actively participate in the review process, unlike other NCI peer review groups. As of January 1, 2010,[1] 62 percent of concepts for Phase III trials reviewed by the steering committees had been approved,[2] whereas the historic approval rate was about 65 percent before

[1] The various steering committees have been phased in gradually, with start dates as follows: Gastrointestinal Cancer, January 2006; Gynecologic Cancer, June 2006; Head and Neck Cancer, January 2007; Genitourinary Cancer, February 2008; Breast, September 2008; Lung, Fall 2008; Hematologic Malignancies, December 2009.

[2] Of 45 concepts, 28 (62 percent) were approved, 15 (33 percent) were disapproved, and 2 (4 percent) were pending.

BOX 3-1
Clinical Trials and Translational Research Advisory Committee Steering Committees

Investigational Drug Steering Committee (IDSC) for Early-Phase Trial Prioritization

Membership includes principal investigators of NCI's early-phase U01 grants and N01 contracts and representatives from Cooperative Groups and other content experts. The committee has nine task forces in the areas of signal transduction, biomarkers, angiogenesis, clinical trial design, pharmacology, immunotherapy, PI3K/Akt/mTOR (PAM), cancer stem cells, DNA repair, and programmed cell death. The Group has developed recommendations for:

- Toxicity management of antiangiogenic agents
- Novel Phase I and Phase II clinical trial designs
- Prioritization of agents for immunotherapy trials
- Guidelines for the incorporation of biomarkers into early-phase trials

Disease-Specific Scientific Steering Committees

NCI established disease-specific scientific steering committees with the goal of increasing information exchange at an early stage of trial development; increasing the efficiency of clinical trial collaboration; reducing trial redundancy; and developing, evaluating, and prioritizing trial concepts. These committees are charged with prioritizing, refining, and collaborating on concepts for Phase III and selected Phase II therapeutic clinical trials. The committees use task forces when appropriate, convene planning meetings to identify the critical issues and questions about the disease to be studied, and periodically review accrual and unforeseen implementation issues.

The initial committees included the Gastrointestinal Cancer, Gynecologic Cancer, and Head and Neck Cancer Committees. Subsequent committees included the Genitourinary Cancer, Breast Cancer, and Thoracic Malignancy Committees and three committees for adult Hematologic Malignancies (Leukemia, Lymphoma, and Myeloma). Committees on brain cancers and pediatrics are in development. The full transition to disease-specific steering committees is expected in 2010.

SOURCES: NCI, 2009a,f.

the implementation of the committees.[3] The approval rate for Phase II trial concepts was 53 percent. In addition, there is little interaction among the disease-specific steering committees to determine trial priorities across disease categories, nor is there consideration of how the trial portfolio should be balanced with regard to Phase II or Phase III trials, although

[3]Personal communication, Margaret Mooney, National Cancer Institute, December 9, 2009.

they are charged with guiding the development of "strategic priorities" (NCI, 2005b). A possible alternative approach might be for the steering committees to identify research priorities and then issue requests for proposals to address them. **However, the trial concept review process should be strengthened and streamlined, and it should entail the evaluation of concise proposals (including the intended statistical design) that are ranked against each other. The emphasis should be on scientific strength and opportunity, innovation, feasibility, and importance to improving patient outcomes. In addition, steering committees should operate independently from NCI staff,** with NCI taking a more traditional role of facilitating the review process rather than actively participating in it; **and they should have a primary focus on the prioritization of clinical needs and scientific opportunities and on facilitating communication and cooperation among the Cooperative Groups.**

Protocol Development

After CTEP approval for a trial concept is achieved, the principal investigator and other key staff develop a full study protocol that must again be reviewed and approved by various branches within CTEP (Table 3-1). Although the Cooperative Group guidelines state that protocols can be "approved with recommendations," in which investigators are requested to give serious consideration to any recommendation included in the consensus review but are not obligated to amend the study, reviewers generally do not distinguish between major and minor review concerns. **The committee recommends that all review bodies distinguish between major review concerns (concerns regarding patient safety and critical scientific flaws, which must be addressed) and minor concerns (which should be considered, but are not obligatory).**

Moreover, if changes are made before activation of the study, the investigators must send CTEP a revised protocol for review that details any changes in the previous CTEP-approved document. This policy includes changes to the protocol that are requested by an IRB subsequent to CTEP approval (see also the section on oversight of trials by IRBs). Similarly, minor changes requested by NCI can trigger iterative reviews by IRBs. Additional duplicative and iterative reviews can further slow the process when a trial involves an investigational new drug (IND) or an investigational device exemption (IDE), as both FDA and NCI are involved in protocol review and development (see also the section on FDA oversight). **The committee recommends that federal oversight be more flexible in allowing minor amendments to the protocol or consent form to fast-track the chain of reapprovals.**

In sum, the protocol development process is arduous and time-consuming.

Months are often consumed by multiple re-reviews that sometimes address only minor changes. Given the funding limits and voluntary nature of the Cooperative Group Program, it can be difficult for the Groups to devote sufficient staff time to rapidly develop and amend a protocol as the process proceeds, further compounding delays due to expectations for revisions and re-review (IOM, 2009c). The provision of funds for professional project managers could ease the workloads of principal investigators and greatly facilitate a rapid review process and adherence to timelines. As described in subsequent sections of this chapter, improved processes are also needed to reduce the time required for protocol development and trial launch. For example, use of standardized templates for some portions of the protocol might result in fewer iterative reviews and speed the review process.

Trial Operations

Once a trial is launched, NCI takes a direct role in overseeing quality control, data and safety monitoring, data management and analysis, and compliance with federal regulatory requirements (NCI, 2006). For example, an NCI program director assisted by the Biometric Research Branch (BRB) staff assesses Cooperative Group compliance with NCI-established policies on data and safety monitoring boards for all Cooperative Group Phase III trials. At the request of CTEP, the BRB staff also review mechanisms established by the Cooperative Group for data management and analysis. BRB staff make recommendations with the goal of ensuring that data collection and management procedures are adequate for quality control and analysis yet are sufficiently simple to encourage maximum participation of physicians entering patients into studies and to avoid unnecessary expense. Data must be made available for external monitoring as well, as required by NCI's agreement with FDA relative to NCI's responsibility as sponsor of a therapeutic agent (NCI, 2006).

The Clinical Trials Monitoring Branch (CTMB) of CTEP provides direct oversight of each Cooperative Group's monitoring program, which includes on-site auditing. CTMB is responsible for establishing guidance for the conduct of quality assurance audits and for overseeing and monitoring the compliance of the Groups, the CCOP research bases, and the Cancer Trials Support Unit (CTSU) with NCI's monitoring guidelines. CTMB also monitors compliance with applicable federal regulations. CTMB staff may attend certain on-site audits, and they review audit reports and findings and assess the adequacy and acceptability of any corrective actions. CTMB staff also review and provide advice regarding the mechanisms established by the Group for quality control of the therapeutic and diagnostic modalities that it uses in its trials (NCI, 2006).

In addition to overseeing the conduct of Cooperative Group clinical

trials, NCI also provides some logistical support (NCI, 2006). For example, the Pharmaceutical Management Branch provides for the distribution of investigational new agents for which DCTD is the sponsor. However, NCI does not provide those services for other agents. Faster trials could be fostered through more active and consistent support from NCI. **Thus, the committee recommends that NCI file more IND applications for agents to be tested in approved protocols and that NCI devote more funds to the distribution of drugs for approved protocols to ensure an adequate drug supply for high-priority studies.** These tasks entail time- and resource-intense activities. An expanded support role for NCI would help Group investigators gain access to more experimental therapeutic agents and reduce the time that the Groups spend in negotiation with industry to acquire agents before the launch of a trial and also ensure the availability of the agent during the trial.

NCI could facilitate the more timely completion of clinical trials in other ways as well. **NCI should provide resources and technical assistance to facilitate the rapid adoption of a common patient registration system.** For example, the Oncology Patient Enrollment Network[4] would provide a standardized Internet-based environment for the enrollment of all patients in all Cooperative Group trials. **NCI should also provide a common remote data capture system.**[5] The availability of such a system would permit sites to enter patient-level data into a clinical database over the Internet. The implementation and adoption of these structured electronic tools would increase consistency across trials, Groups, and sites; conserve resources by reducing the workload associated with patient enrollment and follow-up; allow more timely data review; and enhance the knowledge gained from a trial. However, these transitions can be costly and temporarily disruptive, so support from NCI to facilitate rapid implementation is important.

NCI should also facilitate the establishment of more efficient and timely methods for ensuring that trial data are complete and accurate while the trial is ongoing. Many Groups wait until completion of a trial before beginning the necessary steps to ensure data quality because they lack the resources to check the data more frequently, but this can result in significant delays in analyzing and publishing the results**. NCI should also develop standardized case report forms that meet regulatory requirements.** The language for most clinical data elements in NCI-sponsored trials has been standardized by the NCI Common Data Elements,[6] but standardized report formats would also simplify the reporting across multiple trials and multiple sites.

[4] See https://open.ctsu.org.
[5] See https://www.ctsu.org/RDC_project_page.asp.
[6] See https://wiki.nci.nih.gov/display/caDSR/CTEP+Common+Data+Elements.

Oversight of Trials by IRBs

In the 1970s, concern about the inadequate protection of human subjects in research led to federal regulations and the establishment of IRBs[7] (Beecher, 1966; HEW, 1979). At that time, most clinical research was done at single sites by single investigators. Since then, the increasing emphasis on evidence-based clinical practice has greatly increased the number of clinical trials. There has also been substantial growth in the number of multicenter trials as well as an increase in the complexity of clinical trials. In addition, the purview of IRBs has been expanded as additional regulations regarding human subjects research have been developed, such as the Privacy Rule promulgated under the provisions of the Health Insurance Portability and Accountability Act (HIPAA). These combined changes have overburdened IRBs and have fostered long delays in the review of study protocols and informed-consent forms (ICFs) (IOM, 2002).

IRB Oversight of Multicenter Trials

In many cases, each site participating in a multicenter trial will have its own IRB review of a study, which causes "unnecessary duplication of effort, delays and increased expenses in the conduct of multi-center trials," as noted in a recent FDA guidance (FDA, 2006). For example, one study (Greene and Geiger, 2006) found that one-quarter of the 20 trials reviewed experienced delays (of up to 8 months) because of multiple IRB negotiations.

Multiple IRB reviews do not necessarily improve patient protection, as evidenced by the numerous inconsistencies in the rulings of local IRBs reviewing the same study (Gold and Dewa, 2005; Greene and Geiger, 2006). One survey of participating sites in a multicenter genetic epidemiology study found that the participating local IRBs used different evaluation criteria, which resulted in requirements for the use of different numbers of consent forms at each institution participating in the trial (McWilliams et al., 2003). Another analysis found that of 20 multicenter clinical trials reviewed, 17 experienced inconsistencies both in the IRBs' review processes and in their recommendations (Greene and Geiger, 2006). McWilliams and colleagues concluded, "Lack of uniformity in the review process creates uneven human subjects protection and incurs considerable inefficiency" (McWilliams et al., 2003). The lack of consistency in consent requirements among IRBs can also lead to selection bias and decrease statistical power (Jamrozik, 2000).

In addition, the bulk of the changes that IRBs request are often minor changes to ICFs that increase the reading level of the forms, thus making

[7] 45 C.F.R. § 46.103.

them more difficult to understand (Burman et al., 2003). Furthermore, local IRBs often ask for changes that are not local in nature (Burman et al., 2003; Tully et al., 2000). One review found that less than 2 percent of the changes made to consent forms were due to local context issues (Burman et al., 2003).

Many local IRBs also lack the expertise needed to evaluate certain studies with complex scientific and ethical dimensions, such as those using genetic tests (McWilliams et al., 2003). Finally, the integrity of patient protections is also threatened by excessive IRB work loads (HHS, 1998).

Recognizing these shortcomings, in 1998 the deputy inspector general of HHS published a report requesting the reform of IRBs (HHS, 1998). This was followed by the Armitage report from the NCI Clinical Trials Program Review Group commissioned by the NCI director (NCI, 1997), which recommended that NCI streamline or eliminate redundant processes and procedures (see also Appendix A). NCI responded in 2001 by establishing two central IRBs (CIRBs) for NCI Phase III multicenter trials (first, one for adult trials and, later, one for pediatric trials), to avoid the need for such a trial to be reviewed extensively by dozens of IRBs throughout the country. The members of the CIRBs comprise patient advocates, physicians, nurses, pharmacists, statisticians, and an ethicist.

The CIRB does the initial and continuing review of national studies (without charge) while allotting to local IRBs the responsibility of ensuring that the protocol and ICF are appropriate for the local population and institutional requirements. With this "facilitated review," a local IRB reviews the CIRB-approved study for considerations that apply only to the local context. A subcommittee or the chair can therefore perform the local IRB review, so there is no need to wait for the next meeting of the full local IRB.

Such facilitated reviews should allow local sites to open studies within days, making it easier to conduct trials of treatments for rare diseases and for patients nearing the end of the eligibility window to participate in clinical trials. In theory, a CIRB also enhances the protection of research participants by "providing consistent expert IRB review at the national level before the protocol is distributed to local investigators" (Adler, 2009). A centralization of ethical review is ongoing in other countries for similar reasons. For example, the United Kingdom has transitioned to a more centralized system that is faster and has freed up resources for reviewer training to ensure consistent quality ethical reviews.[8] Clinician investigators and academic and commercial sponsors in the United Kingdom generally agree that this new, more centralized ethics system has been a major improvement. However, it should also be noted that faster and more consistent Ethics

[8] See http://www.nres.npsa.nhs.uk/aboutus/building-on-improvement/.

Committee reviews had the effect of highlighting delays that subsequently arose with other aspects of regulatory review (research and development [R&D] approval) at each participating site. In effect, the delays previously seen in ethics review were shifted to what is now the slowest component of the full system. The latter delays are now being addressed with a more centrally coordinated R&D review system, but that transition is not yet far enough along to demonstrate whether the total study start-up time will have been shortened substantially.[9]

Several evaluations have revealed the benefits of NCI's CIRB. A survey in 2006 found that 80 percent of primary investigators who responded to the survey believed that participation in the CIRB saved them some or a lot of time and effort, with 65 percent rating their overall experience with the review board as good or very good (RTI International, 2007). Another analysis of the costs and benefits of CIRBs showed that the CIRB saves the local IRB and investigators time and effort (Wagner et al., 2009). Wagner and colleagues estimated that institutions using the CIRB for the initial review save $563 per study. One study that compared the use of the NCI CIRB to the use of local IRB methods found an "increase in productivity with fewer staff hours after initiation of the Central IRB" and that the CIRB process "is most efficient and provides increased benefits in terms of time, costs, and patient safety as well as other measures" (Hahn, 2009). Another study found that although a CIRB increased the workload for IRB administrators, IRB chairs, and others who conduct facilitated reviews, it improved the efficiency of the review for local IRB members, investigators, and research coordinators (McArthur et al., 2008). In addition, the study found that the use of the CIRB enabled local IRBs to focus on high-risk (earlier-phase) trials.

The NCI CIRB has been sanctioned by OHRP, which helped NCI develop its CIRB, and is officially endorsed by the American Society of Clinical Oncology. In addition, FDA wrote a guidance in 2006 stating that "use of a centralized IRB review process is consistent with the requirements of existing IRB regulations" (FDA, 2006) and urged those involved in multicenter clinical research to consider the use of a CIRB.

NCI data indicate that, as of April 2009, more than 300 institutions had enrolled to participate in the CIRB, nearly 9,000 facilitated reviews had been used for adult or pediatric studies, and the number of accepted facilitated reviews has steadily increased over the past decade (Adler, 2009). However, although more than half of NCI Cooperative Group pediatric sites participate in the central IRB, only about one-quarter of the adult sites do (IOM, 2009c). An American Association of Medical Colleges (AAMC)

[9]Personal communication, Richard Kaplan, United Kingdom Clinical Research Network, March 10, 2010.

survey of U.S. medical schools found that most had never used a CIRB (Loh and Meyer, 2004).

Numerous reasons have been given for the lack of participation in a CIRB, including concerns about liability and accountability, an unwillingness to take the additional steps or provide the additional documentation needed for a facilitated review, and local concerns (AAMC, 2006; McArthur et al., 2008; McNeil, 2005; OHRP et al., 2005). On the basis of the information gathered by the Science and Technology Policy Institute (STPI), the major barriers to the use of a CIRB were divided into two categories: those that could be mitigated through efforts by NCI and its CIRB, and those that would be more difficult to resolve. In regard to the former, a number of suggestions were made, including working with OHRP to develop official guidance on implementing the CIRB process at local sites, developing a set of best practices for CIRB implementation at sites, including model standard operating procedures, decreasing the time required to post materials, posting complete review materials, improving the response time for questions, and designating a single point of contact for each CIRB site (McArthur et al., 2008). NCI is taking action on many of these suggestions.[10]

The barriers identified as being more difficult to resolve included the increased workload for the local IRB chair and administrative staff, legal issues, and a loss of full local control. For example, the STPI analysis found that about half of the Cancer Centers that responded cited the main barriers to using a CIRB were the increased workload for IRB administrators, legal liability, regulatory compliance or control concerns, and local issues. In addition, the U.S. Department of Veterans Affairs (VA) chose not to allow VA hospitals and other sites enrolling veterans to use NCI's CIRB (McArthur et al., 2008) but, instead, recently implemented its own CIRB.[11] This variability, even among federal agencies, makes it more difficult to undertake clinical research.

Unless contractual agreements state otherwise, many local IRBs view themselves as being accountable and legally liable for any harm incurred to patients during a trial that had a facilitated review. This makes some IRBs resistant to parceling out any of the review responsibilities to a CIRB that will not be responsible for any patient harm that develops (Wechsler, 2007). There also is concern about the potential for regulatory noncompliance, given the inconsistencies between federal regulations regarding the protection of human research subjects (AAMC, 2006; McArthur et al., 2008; OHRP et al., 2005). As noted above, multiple agencies within HHS review or have regulatory jurisdiction over cancer clinical trials, including NCI,

[10] Personal communication, Jeffrey Abrams, National Cancer Institute, September 23, 2009.
[11] See http://www.research.va.gov/programs/pride/cirb/.

FDA, OHRP, and OCR; and at times, different federal regulations conflict with one another, as well as with state regulations. Indeed, the HHS Secretary's Advisory Committee on Human Research Protections (SACHRP) and the Institute of Medicine (IOM) have recommended harmonization of the regulatory language, guidance, and policies associated with the Common Rule[12] and the HIPAA Privacy Rule[13] because of the difficulties that investigators and IRBs encounter when they try to reconcile discrepancies between the two (IOM, 2009a; SACHRP, 2005). For example, the Common Rule allows patients to provide consent for future research to be performed with the biosamples collected from the patient in a clinical trial, whereas the Privacy Rule does not. In addition, the definitions of "deidentified data" are quite different between the two rules.

At a national conference on alternative IRB models in 2006, participants called for harmonization among federal laws and regulations and "recommended that regulatory agencies give clear signals that alternative forms of review are acceptable." The executive summary of that conference also called for HHS to consider policies akin to those of FDA, which link regulatory liability to the organization responsible for the alleged problem, as opposed to the current OHRP policy that holds institutions responsible for all compliance issues that occur under their Federalwide Assurance, regardless of where the alleged violation occurred (AAMC, 2006). Alternatively, OHRP could issue a statement that "when institutions use due diligence in selecting an external IRB, they will not be held responsible for that IRB's decisions" (AAMC, 2006).

OHRP is considering making a rule that will "enable OHRP to hold IRBs and the institutions or organizations operating the IRBs directly accountable for meeting certain regulatory requirements." That could encourage institutions to rely on CIRBs or other IRBs operated by another institution or organization, when appropriate, which OHRP believes will reduce the administrative burdens of ensuring adequate protection of human subjects in research without diminishing that protection (OHRP, 2009). SACHRP also believes that OHRP "should continue its efforts to develop guidance on IRB models," including model agreements for use by institutions considering a CIRB review (SACHRP, 2008). In a letter to the HHS secretary, SACHRP requested that the secretary encourage the NIH director "to explore more widespread use of collaborative IRB models, including expanded use of Centralized IRBs for NIH-sponsored

[12] The Common Rule is the term used by 18 federal agencies that have adopted the same regulation governing the protection of human subjects of research (Subpart A of 45 Code of Federal Regulations [C.F.R.] part 46).

[13] The HIPAA Privacy Rule ("Standards for Privacy of Individually Identifiable Health Information: Final Rule") can be found at 45 C.F.R. parts 160 and 164.

research" (SACHRP, 2008). The NCI director's Consumer Liaison Group also believes that OHRP should provide more guidance that enhances the acceptance of CIRBs (Director's Consumer Liaison Group, 2008). The committee concurs. **The committee thus recommends that OHRP develop guidance that clearly establishes the accountability of the NCI CIRB to encourage its wider use and acceptance by local institutions.**

Informed Consent

Two HHS regulations[14] require researchers supported by HHS funding to obtain and document informed consent from patients participating in their clinical trials. In addition, researchers who want to use and report on protected health information may have to obtain HIPAA authorization from research subjects.[15] Both consent processes are designed to "inform potential subjects about the research, and the use and sharing of their health information in terms that the patients can understand" (AHRQ, 2009).

Despite the requirement that ICFs be written in "understandable" language,[16] one study of 107 oncology ICFs found that all of them were written above the recommended eighth-grade reading level (Sharp, 2004), which is the reading level of nearly half of the U.S. population (Kirsch et al., 2002). One study showed that even IRBs failed to meet their own standards for readability (Paasche-Orlow et al., 2003). Several studies confirm that research subjects often do not understand fundamental concepts required for their participation in clinical trials (Coletti et al., 2003; Joffe et al., 2001; Sudore et al., 2006).

The HIPAA authorization form is also typically written at a higher reading level than that which most Americans have. One study assessed the readability of HIPAA authorization forms from the 125 academic medical centers that receive the most funding from NIH and found that the median reading level for the authorization templates was the 13th grade (i.e., freshman year in college) (Breese et al., 2004). A similar study found that NIH's model authorization form was written at a 12th-grade reading level (Nosowsky and Giordano, 2006). The authors concluded that many research participants cannot understand the forms that they are required to sign.

Not only are HIPAA authorization forms and ICFs written at a higher level of reading than most of the public has attained, but they also are often too lengthy, which is a burden for both the research subjects who need to read and understand them and the physicians who need to spend

[14] 45 C.F.R. 46.116 and 45 C.F.R. 46.117.
[15] 45 C.F.R. 164.
[16] 45 C.F.R. 46.116 (a).

extra time explaining them to their patients. Studies show that the length of informed-consent documents has increased over time (LoVerde et al., 1989; Tarnowski et al., 1990). The HIPAA authorization form alone adds an average of two pages of additional material to the ICF. At a recent IOM workshop, one clinical researcher noted that because of the increasing complexity of cancer clinical trials, his average ICF is between 30 and 35 pages long, which is too long for patients to digest without medical staff devoting a considerable amount of time to verbally summarize them (IOM, 2009c). The extra time required to do this, he pointed out, can deter physicians from engaging in clinical research.

ICFs that are too long and complex also hinder patients' understanding of them and often prevent patients from reading the forms completely, research confirms (Dresden and Levitt, 2001; Sharp, 2004). This can hamper efforts to adequately protect research subjects, as studies involving greater risk tend to have longer and more complex ICFs (Dresden and Levitt, 2001). Several researchers have tried to address the shortcomings of ICFs by creating simpler or shorter forms that are easier to read. Most of those studies have found that these simpler forms foster a better comprehension by the potential research participants (Campbell et al., 2004; Dresden and Levitt, 2001; Epstein and Lasagna, 1969; Kaufer et al., 1983; Tait et al., 2005; Young et al., 1990). One particularly telling study found an inverse relationship between the length and degree of detail of an ICF and the study subjects' comprehension of the form (Epstein and Lasagna, 1969). Those subjects who received the shorter, less detailed form scored the highest on comprehension. As an AAMC report concluded, "This study reinforced the concept that ICFs are most comprehensible when they are as concise as possible" (AAMC, 2007a).

Several organizations have tried to remedy the ICF comprehension problem by creating guidelines and templates that call for ICFs to be more concise and written in simpler language. These organizations include the Agency for Healthcare Research and Quality (AHRQ), AAMC, the Coalition of Cancer Cooperative Groups, the Children's Oncology Group (COG), NCI, and the Group Health Center for Health Studies (Table 3-3). In addition, participants at a recent IOM workshop suggested providing a short form that can be layered on top of a long, complicated consent form (IOM, 2009c). The short form would state in a few words what is going to happen to the patient and then provide links to the rest of the document for those who want more detail. AAMC is trying to develop such a short-form approach to consent forms. SACHRP is also examining ways to improve ICFs and the consent process (HHS, 2007).

Current regulations and guidance (HHS, 2009), however, do not allow the use of a shortened summary document to obtain informed consent. **The committee concluded that guidance from OHRP and OCR to allow simpli-**

TABLE 3-3 Examples of Past and Ongoing Efforts to Simplify Informed-Consent Documents and Improve the Informed-Consent Process

Organization	Activity to Simplify Informed Consent	Year
AHRQ	Developed sample documents and guidance for the informed-consent process	2009
AAMC	Has an ongoing project to promote universal use of short and simple informed-consent documents	2007
SACHRP	Has an ongoing panel that will make recommendation on how to improve the informed-consent form and process	2007
Group Health Center for Health Studies	Developed a "readability tool kit" that includes template language for common topics in informed-consent forms	2007
Coalition of Cancer Cooperative Groups	Published *About Clinical Trials: Informed Consent*	2007
COG	Developed informed-consent document templates with simple language for Phase I, II, and III trials	2004
NCI	Published *Guide to Understanding Informed Consent*	2005
	Joint project with the Office for Protection from Research Risks (now OHRP) to simplify informed-consent forms	1998

SOURCES: AAMC, 2007b; AHRQ, 2009; caBIG, 2007; CCCG, 2007; Ridpath et al., 2007.

fied summaries of consent forms would improve patient communication and decision making.

FDA Oversight of Cancer Clinical Trials

Part of FDA's mission is to ensure the safety and effectiveness of therapeutics and diagnostics on the market. To achieve this mission, FDA reviews clinical trial data on therapeutic agents and diagnostics that sponsors provide and then approves or clears those products that meet the agency's standards for safety and efficacy. Before the launch of some clinical trials, FDA may also review and provide advice about a study's protocol or a sponsor's data collection proposal, including annotated case report forms (FDA, 2001).

According to Margaret Mooney, chief of CTEP's Clinical Investigations Branch, initiatives undertaken in response to the recommendations in the CTWG report aim to increase cooperation and communication among NCI, FDA, and the pharmaceutical industry (CTAC, 2008). Cooperative Group Phase III trial concepts that are specifically identified as supporting a licensing indication are forwarded to FDA at the concept stage, and some efforts have been made to integrate and coordinate special protocol assessments with the CTEP review processes. However, other concepts for Phase

III trials with INDs or commercial agents are also forwarded to FDA for informational purposes, even if the study has not been specifically identified as supporting a potential licensing indication. The intent is to allow FDA to provide input at the agency's discretion, but FDA does not have the staff or resources to examine proposals for trials that may or may not have registration implications. **The committee recommends that NCI do more to coordinate reviews and oversight with FDA in trials involving an IND or investigational device exemption to eliminate iterative review steps.**

FDA is a complex agency comprising five product centers and many offices. More than one FDA unit is often involved in reviewing Cooperative Group cancer clinical trials. Although the Office of Oncology Drug Products was recently established within the Center for Drug Evaluation and Research to review most oncology drugs, some cancer therapeutics and diagnostics may be reviewed by several offices of the Center for Biologics Evaluation and Research,[17] or the Office of In Vitro Diagnostic Device Evaluation and Safety within the Center for Devices and Radiological Health (FDA, 2009).

Because more than one center may have jurisdiction over an oncology product, there may be conflicting regulatory expectations. In addition, no single FDA center or office offers the full range of specialized oncologic expertise needed to review all types of cancer therapeutics and diagnostics, including biologics (such as monoclonal antibody-based products), standard chemotherapies, genetic tests and other in vitro diagnostics, or imaging modalities. The Office of Combination Products is charged with facilitating reviews that involve more than one center. However, that office is not oncology specific, and more than coordinated review is needed. A coordinated cancer program at FDA would bring together relevant areas of science and regulation to both advise sponsors and enable the efficient review of applications that involve either combinations of agents (some of which might not have independent activity, as described in Chapter 2) or drugs that are developed together with diagnostic devices to facilitate their use. Such a program could provide more consistency and expertise in the review of oncology products (Epstein, 2009). FDA has committed in principle to the formation of such a cancer program to "facilitate cross agency expert consultation," but it has yet to follow through on that commitment (FDA, 2004). A major challenge of putting all responsibility for all aspects of the regulation of cancer products in one place within FDA is that the many types of expertise needed, which currently reside in differ-

[17] For example, cancer vaccines are reviewed in the Office of Vaccine Research and Review, whereas cellular and gene therapy products are reviewed in the Office of Cellular and Gene Therapies. Both of these offices are part of the Center for Biologics Evaluation and Research.

ent parts of FDA, would have to be duplicated in the new oversight unit, possibly requiring substantial additional resources for FDA. Nonetheless, **the committee recommends that FDA establish a coordinated Cancer Program across its centers that regulate oncology products to improve both efficiency of and consistency of regulatory standards for review of oncology products.**

FDA Data Requirements

To gain FDA approval, FDA requires data that indicate the effectiveness of the tested product for a specific indication, as well as data on adverse effects. The types and amounts of data required, however, are not specified in detail in FDA guidance because expectations may vary according to what is already known about a drug and how different a proposed new use of the drug is. A guidance document developed in 2001 noted that fewer data may be necessary if extensive safety data on a drug already exist because it has been on the market for another indication, if a drug has been tested in other trials with similar patient populations, or if the proposed new use of the drug is similar to that of already approved uses of the drug (FDA, 2001). However, that guidance document has had little influence on FDA's data requirements.

The lack of a standard required data set leads to inconsistency in the data collected for cancer trials that can affect the quality of the study and limit cross-study comparisons (Curt, 2009; Epstein, 2009; McClellan and Benner, 2009). For example, studies on the collection of data on adverse events (AEs) find that the rates of reported AEs depend on how information is gathered. Patients reported more AEs if they received a checklist of AEs rather than asked open-ended questions related to AEs (Bent et al., 2006). Other factors that may affect the reporting of adverse events include the frequency of follow-up visits (Ioannidis et al., 2006).

The validity of progression-free survival as an indicator of treatment effectiveness can also vary according to the frequency of assessment and can be further confounded by the variability of tumor measurements, as noted in Chapter 2, particularly in unblinded trials (Amit et al., 2009). The use of blinded independent central review (BICR) of imaging to assess tumor progression in randomized clinical trials has been advocated to control the bias that might result from errors in progression assessments. A review of the literature for studies of breast, colorectal, lung, and renal cell cancer using retrospective BICR found high rates of discrepancy between the local and the central reviews, but these differences did not lead to different conclusions about treatment efficacy. The authors concluded that although BICR reduces some potential biases, it does not remove all biases from evaluations of treatment effectiveness. Furthermore, they found that BICRs,

as typically conducted, may introduce bias because of informative censoring,[18] which results from having to censor unconfirmed locally determined progressions (Dodd et al., 2008).

Although the data requirements are not detailed in guidance, industry sponsors often expect the collection of more data than may be needed for FDA approval so that they "cover all bases." There is an inherent tradeoff, however, in determining how much data to collect in a trial. Although investigators intuitively wish to collect as much data as possible, there is a risk that the magnitude of data collection may compromise the overall quality of the data by creating an enormous burden on investigators and clinical study sites (Schilsky et al., 2008). The collection of excess data increases the cost and duration of clinical trials, and the administrative burden not only for data collection but also for ensuring the quality control procedures for all these data contributes to the reluctance of investigators to participate in trials and enroll patients. The extensive collection of unused data can be detrimental to the overall quality of the data and the subsequent data analysis (Abrams et al., 2009). For example, all data collected must be quality controlled and edited, if necessary, so the collection of nonessential data is a drain on limited resources. In a poll of several Cooperative Group and industry trial sites, more than 85 percent noted that data optimization would moderately or significantly impact the resources of the trial site, allowing the collection of higher-quality, targeted data and greater participation in clinical trials (Abrams et al., 2009). **The committee recommends that FDA update its regulatory guidelines for the minimum data required to establish the safety and efficacy of experimental therapies (including combinations of products).**

Standards for data collection that differ according to whether the clinical trial is for a primary or a secondary indication could reduce the collection of excess data and improve the quality of the data collected, studies suggest. A retrospective review of the data sets from completed Phase III cancer trials, many of which were used for FDA supplemental approvals, found that gathering toxicity data for a subsample of the participants in a trial for a drug for which a substantial toxicity profile already exists led to the same conclusions that were reached in the original study that gathered this information for all patients enrolled (Abrams et al., 2009).

A similar retrospective analysis of the Avastin Non-Small Cell Lung Cancer Trial found that if toxicity data on Grade 1 and 2 AEs were collected from a subset of 200 patients per arm rather than from all 650 trial participants, there would have been a time savings of 2,500 hours and no

[18] Standard analyses assume that the progression course of censored individuals is the same as that for patients remaining under observation; if not, censoring is informative and will bias the results.

important AE in those categories would have been missed. The collection of Grade 3 and 4 AE data from a subset of such patients found that those AEs that occurred at least 5 percent more frequently in the study drug arm were almost always seen in the smaller subset, whereas those AEs that occurred at an increased frequency of 2 percent were missed about half the time (Schilsky et al., 2008).

Whether such subset analyses will be adequate depends on what is already known about the safety of the drug and is likely to be sufficient for many clinical trials undertaken for supplemental indications. At a recent IOM workshop, Richard Pazdur of FDA concurred that a clearer definition of an optimal safety database would be helpful (IOM, 2009c), and FDA is currently developing new guidance material on this issue.

A panel of experts convened at the Brookings Institution concluded, "Clinical trials could be designed and conducted more efficiently, and the regulatory review process could be more uniform and rapid if a set of data collection and reporting standards were consistently applied to clinical trials conducted by industry, academia, and the NCI's Cooperative Groups" (McClellan and Benner, 2009; Schilsky et al., 2008). That panel suggested that a core set of data elements be identified, along with how those data elements need to be modified for certain situations. Ideally, such standards would be recognized by regulatory agencies worldwide. Increased investment in regulatory science studies that assess how best to craft regulations on the basis of the scientific evidence, as recently advocated by the FDA commissioner, might aid with the determination of such data standards (Christel, 2009; Grant, 2009).

OPERATIONAL INEFFICIENCIES IN TRIAL DEVELOPMENT, LAUNCH, AND CONDUCT

The complexity of the collaborative process and multi-institutional oversight of Cooperative Groups has fostered inefficiencies and long start-up times for clinical trials, with many investigators raising concerns about burdensome bureaucratic procedures that create undue delays (NCI, 2005a). To provide insight into the organizational challenges in the development of clinical trials, several studies have been undertaken to document all the steps and time required to launch Cooperative Group clinical trials opened by the Cancer and Leukemia Group B (CALGB) (Dilts et al., 2006) and the Eastern Cooperative Oncology Group (Dilts et al., 2008), as well as the steps and timing required for CTEP and the CIRB to evaluate and approve Phase III clinical trials (Dilts et al., 2009).

Many of the steps in the startup process are redundant and do not improve the value of the study, according to these analyses (Dilts et al., 2006, 2008, 2009).The problem is not how much time each step takes but

how many repetitive steps with looping there are, such that the same person or institution keeps reviewing the same study after minor alterations that other reviewers required were made. These repetitive steps result in an inefficient system that could be made more efficient by getting all parties (e.g., FDA and IRBs) to discuss a proposed trial at the same time. Often, there is also "scope creep," which occurs when one group or organization expands the scope of its authority or power beyond what was originally intended, triggering re-reviews by the other review bodies. Furthermore, minor changes often do not significantly improve the clinical trial yet trigger another lengthy series of reviews. Contributing to the inordinate amount of time required to develop a clinical trial is the fact that many of the steps are conducted serially rather than in parallel.

Although synchronicity is an issue for any clinical trial, it is exacerbated in Cooperative Group trials because of the need to deal with multiple external agencies (Dilts et al., 2008). Startup times for Phase III Cooperative Group trials ranged from 1.25 to almost 7 years (Dilts and Sandler, 2006; Dilts et al., 2006, 2008), during which time the science can change tremendously. Because of these scientific developments, the protocol may no longer be relevant when the trial is launched. New scientific findings might also require additional changes to the protocol be made, and these changes, in turn, require additional reviews. The length of the development process for a clinical trial also appears to affect the accrual success of the trial. The longer that trials take to be developed, the less likely it is that they will meet their minimum accrual goals (Cheng et al., 2009) (Figure 3-2). The ultimate inefficiency is a clinical trial that is never completed because of insufficient patient accrual, and this happens far too often. One analysis[19] found that 40 percent of CTEP-approved trials (Phase I-III) failed to achieve minimum accrual goals. A total of 8,723 patients (17 percent of the accruals) accrued to those studies that were unable to achieve the projected minimum accrual goal (Cheng et al., 2009). Among the Phase III trials, 63.9 percent (n = 39) did not achieve accrual success, and a large number of Phase III trials (49.2%, n = 30) closed to accrual with enrollments less than 25% of the originally stated accrual goal. It should also be noted, however, that some trials close early because of unanticipated side effects or because the results from another trial unexpectedly make it no longer ethical to continue the trial. Another study, a survey of study chairs and lead statisticians for 248 phase III trials by five national cooperative groups

[19]The analysis considered all trials that began and closed between 2000 and 2007. As a result, trials that had begun during that time but were still ongoing were excluded. In addition, some trials were closed for a planned interim analysis for positive or negative results. A more detailed analysis over a longer period is ongoing (personal communication, Jeffrey Abrams, National Cancer Institute, September 22, 2009).

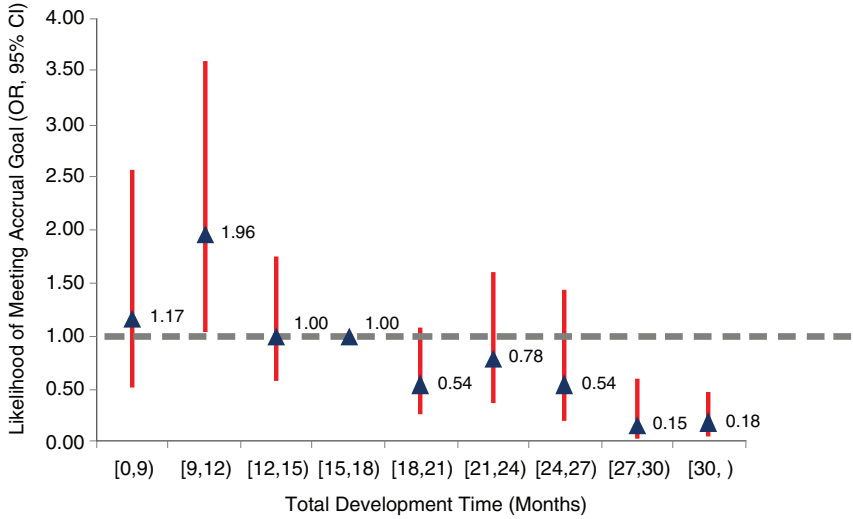

FIGURE 3-2 Likelihood of achieving sufficient accruals compared with the total time of development for CTEP-sponsored trials, 2000 to 2007. The graph shows the relative odds that a clinical trial with the indicated development time will meet its accrual goals. The dotted line indicates the median development time. Triangles above the dotted line indicate greater success in meeting accrual goals; triangles below the line indicate less success. Trials with a development time of 9 to 12 months were significantly more likely to achieve their accrual goals, whereas those whose development times exceeded 27 months were significantly less likely to achieve their accrual goals.
NOTE: CI = confidence interval; OR = odds ratio.
SOURCE: Cheng, S., M. Dietrich, S. Finnigan, A. Sandler, J. Crites, L. Ferranti, A. Wu, and D. Dilts. 2009. A sense of urgency: Evaluating the link between clinical trial development time and the accrual performance of CTEP-sponsored studies. *Journal of Clinical Oncology* 27(18s):CRA6509. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved.

open in 1993-2002 (response rate, 62%), found a 65% accrual success rate (Schroen et al., 2009). The findings in these studies are congruent with to those of Ramsey and Scoggins (2008), who reported that 59 percent of the clinical trials performed by NCI-supported clinical trials networks had been published during a similar time period.

A computer model that was developed on the basis of those analyses found that if individual Cooperative Groups or CTEP singly tried to improve its processes, each would cut only a few days off the trial development timeline, but if they worked together to improve the entire process, the timeline could be substantially shortened. For example, a process map

for CALGB showed that 63 percent of the decision-making steps reside with multiple organizations and agencies, none of which is under the direct control of the Cooperative Group (Dilts et al., 2006).

NCI funded those analyses in response to the CTWG report (NCI, 2005b). NCI also established the Operational Efficiency Working Group (OEWG), which was charged with identifying ways to reduce the study activation time for Cooperative Group and Cancer Center trials by 50 percent. That Group established specific, measurable goals that the IOM committee endorses. The OEWG's report recommends strategies and implementation plans that aim to reduce the time from submission of the trial protocol to final approval of the protocol to 300 work days for Phase III trials (Figure 3-3) and 210 work days for Phase II trials (Doroshow and Hortobagyi, 2009). Those recommendations include staffing changes, more coordinated, parallel reviews, and improved project management and protocol tracking (see also Appendix A for more details). The recommendations also include time-date goals that specify, for example, that a clinical trial must open and accrue patients within 18 calendar months for Phase II trials or 2 years for Phase III trials or it will be closed (although some exceptions may be necessary, for example, in the case of rare diseases). **The IOM committee concurs with the findings of the OEWG and recommends that NCI work with the extramural community to coordinate and streamline the protocol development process, as recommended by the OEWG.**

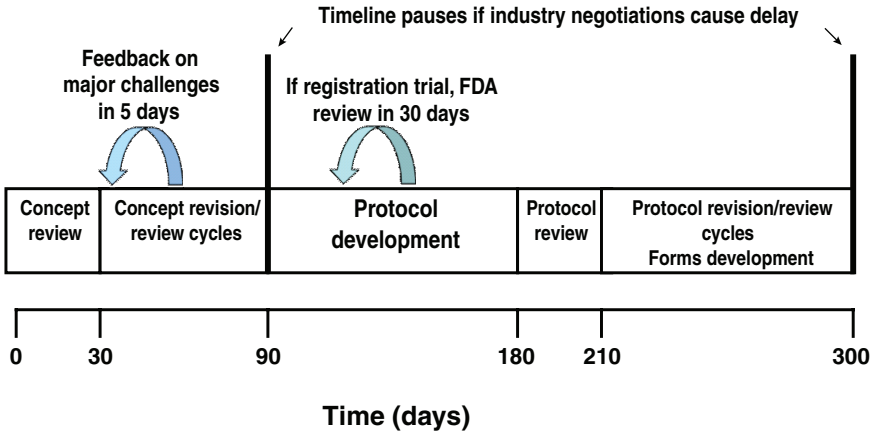

FIGURE 3-3 The target timeline for Phase III clinical trials proposed by the NCI's Operational Efficiency Working Group. The timeline excludes IRB review, as well as contracting and drug supply activities. Protocols would be terminated if not activated within 2 years.
SOURCE: Doroshow and Hortobagyi, 2009.

Potential Ways to Improve Trial Quality and Efficiencies

Reports indicate that the review of operational data on the development of clinical trials can reveal steps that are redundant and do not add value to the resulting protocol, and could thus be eliminated (Kurzrock et al., 2009; McJoynt et al., 2009). For example, when the Mayo Clinic reviewed the steps and time taken from receipt of a new trial protocol through submission to an approving authority such as NCI or the IRB, it discovered numerous redundant review steps, as well as delays caused by waiting for e-mail responses. It then eliminated steps that added no value and provided deadlines for responding to e-mails. A review of 64 protocols submitted since the implementation of this streamlining process revealed that the mean turnaround time for both internally and externally authored protocols dropped by about 60 percent (McJoynt et al., 2009). The M.D. Anderson Cancer Center used a similar approach to streamline the steps needed to initiate Phase I trials, once FDA approved the IND. In one recent Phase I trial at the center, the study was activated and the first patient enrolled 46 days after completion of the final study protocol and about 48 hours after final FDA approval of the IND, reducing the overall timeline by about 3 months (Kurzrock et al., 2009). Real-time electronic tracking of the steps in trial protocol development, with the same protocol tracking number for each review step, would help with these evaluations and enable problems to be detected more quickly as trial development proceeds (Steensma, 2009).

The creation of standard operational metrics and best practices for the clinical trial development process for use across institutions could further facilitate improvements in the process. The operational processes used to conduct clinical trials are idiosyncratic to individual institutions or Cooperative Groups, with little sharing of best practices or lessons learned. Although Good Clinical Practice guidelines (ICH, 1996) provide an international ethical and scientific quality standard for designing, conducting, recording, and reporting on the results of clinical trials that involve the participation of human subjects, there is currently no mechanism for the systematic identification of best management and administrative practices that can be used as benchmarks by a clinical trials office in a Cancer Center or a Cooperative Group, nor can such best practices be used to aid up-and-coming Cancer Centers. Furthermore, there are few standard processes or metrics of what constitutes operational quality in the development or management of clinical trials. Organizations need to know how they are performing, independently over time and in comparison with their peer institutions. Thus, the operational performance metrics used to evaluate Cancer Centers and Cooperative Groups need to be enhanced and redefined to include metrics for the measurement of quality, outcomes, and timing.

The committee recommends that NCI work with governmental and non-governmental agencies with relevant expertise to facilitate the identification of best practices in the management of clinical research logistics and develop, publish, and use performance, process, and timing standards and metrics to assess the efficiency and operational quality of a clinical trial.

There is also a need to make interagency processes more efficient. For example, simplifying and harmonizing regulatory methods (such as reporting of AEs), to the extent possible within the constraints of the responsibilities of the different agencies involved, could be beneficial. Inefficiencies could also be improved by standardizing the information technology infrastructure as well as data elements, collection, and reporting, as noted above in the section on trial oversight.

Some steps are already being taken to streamline reviews. For example, NCI recently created a parallel approval process for initial IRB review for adult clinical trials. Once CTEP approves a study protocol, the CIRB review can be done concurrently while the Cooperative Group Operations Office makes final study arrangements and submits the protocol to local IRBs that do not use the CIRB. In addition, no post-CIRB review is required from CTEP to activate the study. As a result, final approval of the initial review by CTEP could potentially be received 8 to 12 weeks earlier, and local IRBs that are not CIRB members should be able to begin their reviews sooner (Abrams, 2008a).

However, there is a need for bolder changes. For example, some consolidation of the Cooperative Groups and of common activities could increase operational efficiencies and conserve resources, ease the workloads of the Cooperative Groups, and offer more consistency to providers enrolling patients in trials launched by different Cooperative Groups. Each Cooperative Group devotes significant resources to support similar administrative structures and activities in what is defined in the operations management literature as "back-office operations" (Chase and Tansik, 1983). Back-office operations, such as information technology support and payroll systems, primarily occur outside the view of customers and do not differentiate the product or the service provided to the customer, so they have been the focus of consolidation in many industries and other organizations, including banking, nonprofit organizations, and governmental agencies (Dare and Reeler, 2005; Davis, 2009; Grosser, 2008; Kraus and Marjanovic, 1995; Lacity et al., 2003; Leith, 2002; Rhoades, 1998; Shortell et al., 1998; Taheri et al., 2000).

In clinical trials, back-office operations include activities such as data collection and management, data queries and reviews to ensure that the data collected are complete and accurate, patient registration, audit functions, processing of case report forms, training of clinical research associates, image storage and retrieval, drug distribution, and credentialing of

sites. Although the ways in which the Cooperative Groups accomplish these functions vary, there is little technical rationale for why they must be unique to the scientific focus of each Group. The consolidation of offices and personnel to conduct these information-based activities across all the Cooperative Groups should help to streamline the operations, reduce redundancy, lead to greater consistency, and conserve resources. **The committee recommends that NCI require and facilitate the consolidation of these back-office administration and data management operations of the Cooperative Groups.** It will be essential, however, to maintain high-service-quality work and a high level of responsiveness to the principal investigators and Cooperative Groups.

In addition, some consolidation of the current front-office operations of the Cooperative Groups, which primarily entail the Groups' committees that generate and vet potential concepts for clinical trials, as well as the experts responsible for statistical design and analysis, would further reduce redundancy in the Program, enable the pooling of resources, and reduce competition for enrollment in trials on the basis of Group-specific priorities. **The committee thus recommends that NCI facilitate some consolidation of the Cooperative Group front office operations to conserve resources while still maintaining rigorous competition for trial ideas.**

One possible way to reorganize the Group front offices would be by disease type. For example, there could be four multidisciplinary Groups dedicated to adult cancers, with the task of performing trials for different diseases and with true cooperation occurring among all the Groups. Each Group could perhaps have four disease-specific committees to ensure broad coverage and some overlap for each disease. In other words, two Groups would undertake trials for lung cancer, two for colon cancer, two for breast cancer, two for head and neck cancer, two for hematology, and so on. One way to achieve consolidation would be to alter the peer-review process for the Cooperative Groups to focus on the accomplishments of disease committees. **The committee recommends that the Cooperative Groups be reviewed and ranked using defined metrics on a similar timetable and that funding be linked to the review scores. The key planning and scientific evaluations should be at the disease site committee level, with a focus on the quality and success of the clinical trial concepts developed and on the committee's record of developing new investigators. Committees that do well in review should be funded, and committees with low scores should be eliminated. Committees should be organized with a multidisciplinary focus on disease sites, and Group leaders should consolidate disease site committees from different Groups to strengthen their productivity and review scores.** This approach would ensure that only the most innovative and successful disease site committees would thrive and expand their membership. The logical extension of the proposed consolidations will be a reduction in the number

of Cooperative Groups. For example, Groups focused on a single disease site or modality would likely need to merge with multidisciplinary Groups under this system. It will, however, be important to preserve a sense of community among the investigators focused on a particular disease.

The recent consolidation of the four Cooperative Groups focused on pediatric cancers into a single new Children's Oncology Group is informative in this regard (Box 3-2). The goal of that merger was to consolidate talent and resources to minimize duplication, make better use of dwindling funds, and increase the efficiencies of conducting clinical trials (Benowitz, 2000; Murphy, 2009). Although concerns were raised about creating a scientific monopoly that would stifle innovation and deter involvement by young investigators who would have fewer opportunities for leadership and recognition (Benowitz, 2000), according to current Group leadership, there is still competition at the international level (Reaman, 2009). In addition, the total accruals have increased and the national childhood cancer mortality rate continues to fall. To nurture young investigators, COG has developed a formal mentoring program, and each study must have an early career investigator as the chair, with a more seasoned investigator being the cochair or vice chair. Another recent example of program consolidation with the goal of improving the design, conduct, and support of clinical studies that involve large numbers of patients from multiple centers is the recent merger of the National Marrow Donor Program and the Medical College of Wisconsin's International Bone Marrow Transplant Registry and Autologous Blood and Marrow Transplant Registry to form the Center for International Blood and Marrow Transplant Research (CIBMTR) (2008).

Although some could argue that consolidation is unnecessary because it is now possible for members of one Group to enroll patients in trials undertaken by another Group via NCI's Cancer Trials Support Unit (CTSU)[20] and cross-group accruals have increased as a result,[21] current Cooperative Group peer-review guidelines and priorities still favor the recruitment of patients into trials that originated within that Group (NCI, 2006). Furthermore, the CTSU does not address the issue of redundancy in the activities supported by the front offices of the Cooperative Groups.

Other Informative Models and Ongoing Activities

Several organizations may serve as models for the efficient conduct of clinical trials. One is the Multiple Myeloma Research Consortium (MMRC), which integrates the research efforts of 15 member institutions and whose mission is to accelerate the development of novel and combination treat-

[20] See https://www.ctsu.org/.

[21] Personal communication, Margaret Mooney, NCI, November 2009.

BOX 3-2
Overview of Creation of Children's Oncology Group

The first pediatric cancer clinical trials group was the Children's Cancer Group (CCG), one of the original Groups formed in the 1950s, previously known as CCGA or Group A, to distinguish it from Group B, the forerunner of Cancer and Leukemia Group B (CALGB). The Southwest Cancer Chemotherapy Study Group, the forerunner of the Southwest Oncology Group (SWOG), was originally organized as a pediatric oncology group in 1956 and only later expanded to include evaluation of adult malignancies. In 1979–1980, the pediatric division of SWOG elected to separate and seek independent status, and thus, the Pediatric Oncology Group (POG) was formed. POG grew to be virtually equal in size to CCG in terms of institutional members and patient accruals. Both POG and CCG were multidisciplinary, multidisease Groups. There were also two single-disease pediatric cancer Cooperative Groups, the National Wilms' Tumor Study Group and the Intergroup Rhabdomyosarcoma Study Group, whose members actually comprised the investigators and member institutions of both POG and CCG, although they each maintained separate Cooperative Group statistical centers, had their own chairs, and underwent separate peer review. By the late 1990s, the four pediatric Groups had a long history and tradition of both friendly competition and close collaboration.

In 1998, the leadership of all four of the pediatric Groups, including the chair, vice chair, statisticians, and Cooperative Group administrators, gathered to discuss ways to improve the efficiencies of the intergroup process. There had been long-standing frustration with the cumbersome intergroup process, and a number of ongoing changes led to the decision to eliminate the intergroup mechanism entirely and merge into one Group. First, because of the significant success with the treatment of all forms of childhood cancer, survival rates had successively improved, such that larger and larger numbers of patients were needed to enroll in randomized clinical trials to achieve reasonable study objectives of demonstrating significant improvements in overall results within a reasonable time frame. Given the relative rarity of pediatric cancers in general and the increasing sophistication of the stratification of trials into smaller and smaller risk-adapted subgroups, it had become necessary to increase collaboration to accrue sufficient numbers of patients. By merging, the Groups would provide a seamless geographical coverage of North America, which also enabled epidemiological studies not possible as separate entities, including the formation of a national children's cancer registry.

Second, at that time, NCI was requiring all of the cancer Cooperative Groups to make extensive changes to their informatics infrastructures, to adopt common toxicity codes and data dictionaries, to streamline and harmonize data reporting, and to migrate from the use of paper forms to electronic forms. This work was both onerous and expensive, and the Group leaders thought that it would be better to work together to accomplish all the upgrades to the informatics systems. Third, the Groups hoped that providing a single source for pediatric clinical trials, a single point of service, and the promise of increased accruals and more rapid completion of Phase I and II trials would improve interactions

with the pharmaceutical industry, which was necessary to gain access to promising new agents for testing. This process of working with industry was inherently challenging because the pharmaceutical industry had relatively little interest in developing and licensing drugs for childhood cancers due to the small market. Fourth, the Group leaders believed that by working together, they could articulate a stronger case to the public for pediatric cancer clinical trials. Parents, the public, and philanthropic foundations and individuals were often confused about why there were multiple Groups and what the differences were.

The merger took 3 years and proved to be very challenging, with perhaps the biggest challenge being the merging of the very different cultures of the Groups. A transition team was created and consisted of the Group chairs, vice chairs/executive officers, administrators, and Group statisticians; the heads of the committees in surgery, pathology, radiation therapy, and nursing; and clinical research associates. The merger was labor-intensive, entailing the development of a memorandum of understanding, the creation of an interim governing council, the creation of a new constitution, the development of transitional committees for every disease and discipline, a new membership committee to review the performance and qualifications of each institutional member, new rosters, greatly increased communications, and many additional interim meetings. NCI provided some additional funding to cover some of the additional travel costs associated with interim meetings, but no extra staff was hired, and it was difficult to retain valued staff who were concerned that their jobs would be eliminated by the merger (many ultimately were).

Reaching consensus on Group data management and statistics was a major challenge. The transition team sought external assessment and guidance, and the result was a distributed network of statistical offices and staff. Another major challenge was the merging of disease-specific committees, which had historically been competitive, often on the basis of competing scientific strategies developed over the course of serial studies. Of necessity, compromises were reached and some stakeholders were not satisfied with the outcome. A great deal of work was also involved with revising the budgeting for the Group U10 grants during the transition, but an additional challenge entailed merging the foundations that CCG and POG had established for private funding, which had very different structures for their 501c3 corporations. POG's foundation was very simple, with no additional paid staff, but CCG had established a corporation with a fairly large staff, the National Children's Cancer Foundation (NCCF), to act as its grantee organization and to engage in active fundraising from the public. Thus, POG had to merge with both NCCF and CCG.

The resultant Group, the Children's Oncology Group is now the world's largest childhood cancer research organization and united with NCCF under the umbrella 501c3 to form CureSearch, with offices in Arcadia, California; Gainesville, Florida; Omaha, Nebraska; and Bethesda, Maryland, and 235 member institutions throughout the United States and Canada plus five other countries. COG now has more than 5,000 individual members.

SOURCE: Murphy, 2009.

ments for multiple myeloma by facilitating clinical trials and correlative studies (MMRC, 2009). As described at an IOM workshop, MMRC has assessed and devised solutions to many of the inefficiencies commonly encountered in the clinical trials process (IOM, 2009b). MMRC has also implemented metrics and reward systems into its clinical research endeavors to improve its processes. For example, a scorecard tracks the time required to open and accrue clinical trials. It also tracks the level of engagement of the principal investigators, which is determined by monitoring their participation in monthly calls and face-to-face meetings and how often they bring new ideas to the consortium. Those centers performing in the top one-third receive funding to cover the full salary of a clinical research coordinator, who provides dedicated oversight of all MMRC clinical trials (100 percent full-time equivalent [FTE]). The second tier receives 50 percent of an FTE, and the third tier receives 25 percent of an FTE (IOM, 2009b). After the release of the first scorecard results at the end of 2007, 100 percent of the principal investigators participated in the monthly call for the first time. The speed and efficiency of its clinical trials are also priorities, with MMRC setting aggressive goals in this regard: only 3 months is allotted for protocol development or for IRB approval, 2 months is allotted for contracting, and 8 to 14 months is allotted for patient accrual (IOM, 2009b).

Other informative examples include the Center for International Blood and Marrow Transplant Research mentioned in the previous section and the HIV Prevention Trials Network,[22] a worldwide collaborative clinical trials network that develops and tests the safety and efficacy of primarily nonvaccine interventions designed to prevent the transmission of HIV.

Several initiatives and centers are dedicated to studying and improving the efficiencies of clinical trials (Box 3-3).

COST OF CANCER CLINICAL TRIALS

It has been difficult to accurately document the costs of all the various components and procedures of clinical trials. These costs vary significantly, depending on the nature of the trial. Additionally, there is a great deal of unfunded volunteerism in developing and conducting trials, particularly by investigators who are deeply committed to the assessment of cancer therapies. The investigators are not fully compensated for this time and effort.

Several groups have attempted to discern the various steps involved in the successful conduct of a clinical trial and the costs linked to carrying out those steps. Clinical trials can be broken down into seven basic functional steps (C-Change and Coalition of Cancer Cooperative Groups, 2007):

[22] See http://www.hptn.org/index.htm.

BOX 3-3
Initiatives to Improve the Efficiency of Clinical Trials for Cancer and Beyond

AACI Clinical Research Working Group and Clinical Research Initiative

To support the improved operation of clinical trials and expand patient enrollment, the Association of American Cancer Institutes (AACI) has launched a communications forum for administrative leaders and managers of cancer center clinical research facilities across the AACI network. The forum, called the Clinical Research Working Group, will examine the systems and procedures that clinical trials offices use to perform management and oversight functions and compare the office metrics used for clinical trials: benchmarking, evaluation, and best practices. The forum aims to promote efficient use of resources and personnel. AACI has also established a network for cancer center clinical research leaders called the AACI Clinical Research Initiative (CRI). The AACI CRI will examine and share best practices that promote the efficient operation of cancer center clinical research facilities and will leverage the ability of the AACI cancer center network to advocate for improvement in the national clinical trials enterprise (http://www.aaci-cancer.org/).

FDA Clinical Trials Transformation Initiative

The recently created FDA Clinical Trials Transformation Initiative (CTTI) brings together all interested stakeholders to identify practices that, through their broad adoption, will increase the quality and efficiency of clinical trials. CTTI is currently assessing ways to improve the system of reporting and interpreting serious adverse events. In addition, CTTI's Clinical Trial Monitoring project aims to identify best practices and to provide sensible criteria for effective monitoring while eliminating practices that may not be of value for ensuring reliable and informative trial results or human subjects protection.

Clinical and Translational Science Awards Network

The Clinical and Translational Science Awards (CTSA) program, led by the National Center for Research Resources (part of the National Institutes of Health), creates a definable academic home for clinical and translational research. CTSA institutions work together as a national consortium with the goal of improving human health by transforming the research and training environment to enhance the efficiency and quality of clinical and translational research across the country. This consortium includes 46 medical research institutions located throughout the nation. When fully implemented by 2012, about 60 institutions will be linked together to strengthen the discipline of clinical and translational science. To set a national research agenda, the CTSA consortium established five overarching strategic goals that will guide consortium-wide activities: (1) Build National Clinical and Translational Research Capability; (2) Provide Training and Improve the Career Development of Clinical and Translational Scientists; (3) Enhance Consortium-Wide Collaborations; (4) Improve the Health of Communities and the Nation; and (5) Advance T1 Translational Research.

continued

BOX 3-3 Continued

Tufts Center for the Study of Drug Development

The Tufts Center for the Study of Drug Development (Tufts CSDD) has a mission to develop strategic information to help drug developers, regulators, and policy makers improve the quality and efficiency of pharmaceutical development, review, and utilization. An independent, academic, nonprofit research group affiliated with Tufts University, Tufts CSDD provides independent analyses on the nature and pace of new drug development. This center has conducted studies on drug development operational processes, including a benchmark analysis of activities related to the initiation of clinical research studies.

Center for Management Research in Healthcare

The Center for Management Research in Healthcare was designed with the focus of providing advances in management disciplines for health care-related applications by integrating theory founded on academic principles and industry best practices. The goals include the transfer of management knowledge to health care settings and the dissemination of findings that arise between the intersection of health care and management.

Sensible Guidelines for the Conduct of Clinical Trials

In 2007 several clinical trials groups from McMaster, Duke, and Oxford Universities in the United Kingdom organized an international meeting called "Sensible Guidelines for the Conduct of Clinical Trials" to discuss the difficulties involved in initiating and running randomized trials efficiently. The organizers concluded that solutions to many of the problems would require a coordinated response from academic trialist groups, regulatory agencies, pharmaceutical companies, and health care providers worldwide. A follow-up meeting of the Sensible Guidelines group took place in Oxford on September 5–6, 2009. The principal aims were to (1) update the review of the main barriers preventing efficient trials; (2) share the experiences of those who are attempting to deal with these barriers; and (3) agree to possible solutions to the main difficulties and encourage their promotion through international collaboration.

SOURCES: AACI, 2009; CMRHC, 2009; CTSI, 2010; CTSU, 2010; CTTI, 2009; NCI, 2009a; Tufts University, 2009; Yusuf et al., 2008.

- Protocol selection and development
- Study and site feasibility assessment, including scientific review and evaluations of budgets and timelines
- Regulatory submission of the protocol and ICFs to IRBs and the trial sponsor(s)
- Legal and financial review and approval
- Site activation, including site approval and preparation for study execution

- Study execution and data collection and review (accrual and follow-up)
- Study closure, including document retention

Of these seven steps, four are related to federal regulations: regulatory submission of the protocol, site activation, study execution and data review, and study closure. An average of 35 percent of clinical research costs is spent on compliance with such regulations (C-Change, 2005).

The time and effort spent on all these steps of a clinical trial can be considerable, with one study estimating that the time required to conduct a 12-month randomized, placebo-controlled trial of a new chemotherapeutic agent was, on average, more than 4,000 hours, with the costs for nonclinical activities amounting to between $2,000 and $4,000 (in 2002) per study subject, when overhead costs were excluded (Emanuel et al., 2003).

About half of the time spent on a clinical trial is devoted to study start-up endeavors (IOM, 2009c). Startup costs for clinical trials include staff training, IRB approval, time for reviews, and staff time for startup visits and the completion of forms (C-Change and Coalition of Cancer Cooperative Groups, 2006). For Cooperative Group trials, some startup costs may be somewhat lower because of the existing infrastructure and operating procedures, but many unique aspects of each clinical trial also contribute to these costs. Many of the startup steps can involve several iterations, because changes made in response to one review body trigger re-reviews by other bodies. For example, protocols and ICFs often undergo multiple reviews by local or central IRBs, as well as by NCI and FDA. Contracts among multiple parties can require many layers of review that may take months to complete, and the financial review of a study may be done separately from a contract review (C-Change and Coalition of Cancer Cooperative Groups, 2007). Numerous steps are also involved in the initial execution of clinical trials, including on-site training of personnel, the establishment of billing and budget procedures, and the screening and recruitment of patients (C-Change and Coalition of Cancer Cooperative Groups, 2007). These fixed startup costs are independent of the number of subjects enrolled in a clinical trial and are more economically efficient when large numbers of patients are enrolled in the trial.

Only about half of open government-sponsored trials, however, have subjects enrolled, one study found (C-Change, 2005), and an NCI study of four NCI-funded Comprehensive Cancer Centers found that many trials accrue few or even no patients. As noted earlier in this chapter, a review of these four Cancer Centers along with two large Cooperative Groups and CTEP revealed that the amount of time it takes to start up a study is nearly 3 years (Dilts and Sandler, 2007; Dilts et al., 2006, 2008, 2009). The substantial startup costs of trials with low rates of accrual often

go unappreciated. One assessment found that Cooperative Group trials accruing two patients or less cost more than $700 annually, but it did not consider the $5,000 to $8,000 of startup costs documented in other studies (nor did it include the costs for research nurses or long-term follow-up) (Waldinger, 2008).

Once a clinical trial is under way, in addition to administering the experimental treatment to patients, much time is spent on patient follow-up. This follow-up is much more involved for clinical studies than it would be for standard patient care, as detailed case report forms, as well as forms that report adverse events must be filled out (C-Change and Coalition of Cancer Cooperative Groups, 2007). In addition, new requirements from OHRP specify that if a substantial new toxicity becomes apparent during a clinical trial, the trial must again be reviewed by the IRB at the local institution, and the written consent form must then be modified accordingly (Abrams and Mooney, 2008; Goldberg, 2008). Even billing is more complex for patients in clinical trials, with Medicare requiring the costs for routine care of the patients to be listed separately from the research costs on the bills submitted to Medicare (IOM, 2009c). The data centers also have many tasks, such as quality control efforts (editing data, sending out queries, updating the database), creating and circulating reports on the progress of the study to investigators and funders, and preparing reports to data and safety monitoring boards.

Many of the costs of clinical trials are overlooked or understated (Waldinger, 2008), such as the costs of specimen collection, processing, and shipping, especially if the processing of the specimens is time sensitive and the specimens must be shipped individually, as well as the costs of standard imaging and pathology evaluations. These are increasingly important economic issues, as Cooperative Group studies are doing more genetic and other analyses of tumor or blood samples in the movement toward personalized medicine, which depends on the collection and analysis of such samples. This focus on personalized medicine increases the complexity and cost of clinical trials, as there is a greater need for the documentation of patient characteristics, imaging, and biomarker tests (see also Chapter 2).

In addition, for trials that Cooperative Groups undertake with industry support, there can be lengthy negotiations over the ownership and use of the biological specimens collected during the trial because they might be useful for future studies (IOM, 2009c). The use of such biospecimens can also require additional time to craft more complex ICFs and explain them to patients. Furthermore, current NCI policies require that research studies that propose to use specimens collected from intergroup protocols undergo scientific review by a scientific steering committee before specimens are made available. However, this review is not linked to funding, and thus, investigators must often seek funding by other mechanisms. This process

creates many review loops, time delays, and significant double jeopardy, as each proposal requires at least two scientific reviews; one to receive specimens and one to receive funding, by different review groups involving many people and conducted at different times.

The increasing number of global clinical trials adds more complexity and costly bureaucratic burdens as researchers try to comply with the wider range of regulations that vary from country to country (C-Change and Coalition of Cancer Cooperative Groups, 2006). Even variations in local regulations can add to the complexity and can be burdensome in multicenter trials, especially because many participating sites contribute 10 patients or less, yet they must still undergo cumbersome regulatory reviews. One study estimated that 30 to 40 percent of all funding for cancer clinical trials is used to cover the costs of local regulatory compliance (C-Change and Coalition of Cancer Cooperative Groups, 2006). For example, an investigator who participates in just one clinical trial over 7 years may be required to have between 35 and 50 interactions with the IRB, each of which requires about 100 hours of staff preparation time (C-Change and Coalition of Cancer Cooperative Groups, 2006). As one research group summed it up, "Regulations governing the conduct of clinical research have become more and more complex, placing a greater burden on investigators in terms of compliance, documentation, and training" (Glickman et al., 2009). In addition, the workload associated with audits, data queries, and blinded central reviews has been increasing (see also the previous section on oversight of clinical trials).

Further insight into the costs involved in conducting Cooperative Group trials in particular is expected in 2010, when NCI will publish its analysis of the costs of Cooperative Group clinical trials. This comprehensive study will document the Groups' infrastructure costs linked to operational functions, statistics and data management, scientific leadership, and core support services, including specimen bank and laboratory services. The analysis is expected to identify areas of inadequate funding, as well as to identify best practices and opportunities for enhanced efficiency. The ultimate goal of the study is "to develop an improved funding model for the Cooperative Group Program that aligns funding more closely with actual costs and enhances overall cost effectiveness" (Hautala, 2008). Preliminary results indicate that most groups spend about 50 percent of their budgets on infrastructure and about 50 percent on accruing and managing patients. Most allocate the largest portion of their infrastructure to statistics and data management, but there is large variability in the percentage allocated to various other infrastructure components and subcomponents, such as administration costs. Some of this variation may be due to the way in which expenses are described in the grant applications. The analysis also found that the amounts of funds awarded were always less than the amounts requested and that no group spent the funds that it was awarded at exactly

the same percentage allocation that was originally requested (CTAC, 2008; Hautala, 2008).

Research and patient care costs must be met if the trial is to be efficiently and effectively completed. As one participant at an IOM workshop noted, it may be unethical to attempt to do a clinical trial when those who are running it are not getting paid enough to do it well (IOM, 2009c). However, despite the long history of accomplishments of the NCI Cooperative Group Program (as described in Chapter 1), the program has been chronically underfunded because of limitations in NCI funding and the increasing complexity and costs of clinical trials. The lack of sufficient funds for the program was noted with concern more than 10 years ago, in the 1997 Armitage report (NCI, 1997), but the funding situation for the program has not substantially improved since that report recommended increased funding. When the budget for NIH was doubled between 1998 and 2003, the Cooperative Group Program experienced a 40 percent growth in funding (when adjusted for inflation), although the Program's share of the total NCI budget actually decreased, and in 2008 was slightly less than 3 percent.[23] Furthermore, because of NCI budget constraints, funding for the Cooperative Groups has been flat or declining in recent years. Funding for the Program declined after 2002 and leveled off at about $145 million a year (Figure 3-4). This figure reflects a 20 percent decline in funding since 2002 when the effects of inflation are considered. In real dollars, the current funding level is less than it was in 1999. The CCOP funding that many Cooperative Groups rely on also is declining. This situation is increasingly unsustainable. **The committee recommends that NCI allocate a larger portion of its research portfolio to the Clinical Trial Cooperative Group Program to ensure that the Program has sufficient resources to achieve its unique mission.**

FUNDING FOR CANCER CLINICAL TRIALS

Overview of Federal Funding for Cancer Research

The U.S. Congress determines the total funding allotment for NCI each year, but the NCI director is responsible for proposing a budget and for allocating the available funds among the various programs and funding mechanisms within NCI. Unlike other institutes at the NIH, NCI's budget priorities and allocations are independent of those of the NIH director because of the budgetary bypass provision of the National Cancer Act of

[23] The Cooperative Group Program's share of the NCI budget decreased by 10 percent, from 3.8 percent in 1998 to 3.4 percent in 2003. By FY2008, the Program's share of the NCI budget had decreased to 2.98 percent. See http://www.cancer.gov/aboutnci/servingpeople/snapshot and also Figure 3.4.

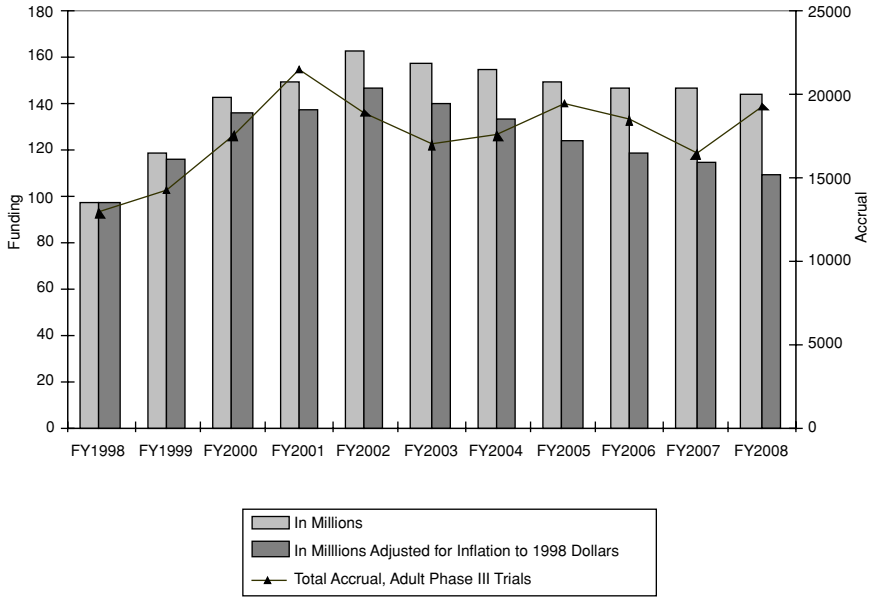

FIGURE 3-4 Funding for NCI Cooperative Group Program, fiscal years (FY) 1998 to 2008, and total accrual in adult Phase III trials during the same time span. SOURCE: Margaret Mooney, National Cancer Institute, 2009.

1971. This provision permits the NCI director to submit NCI's annual budget request directly to the U.S. president. The NIH director and secretary of HHS may comment on the NCI bypass budget, but they cannot change the proposal (reviewed by IOM, 2003).

Allocation of NCI funds among the competing needs of its various programs is a major challenge for the NCI director, who must take many factors into consideration. Decisions must be made about how much funding to devote to basic, laboratory research versus clinically oriented research across several major categories that include cancer causation, prevention, and control; cancer biology; detection, diagnosis, and treatment; and resource development (reviewed by IOM, 2003). Furthermore, the clinical trials program supported by NCI is multifaceted, with the Cooperative Group Program being just one of several clinical research endeavors that NCI supports (Figure 3-5). In addition to its intramural Clinical Center, NCI has grants that can support either investigator-initiated studies or the Cancer Centers at which trials are conducted, as well as U10 cooperative agreements, such as those that underlie the Cooperative Group Program and CCOP (Box 3-4).

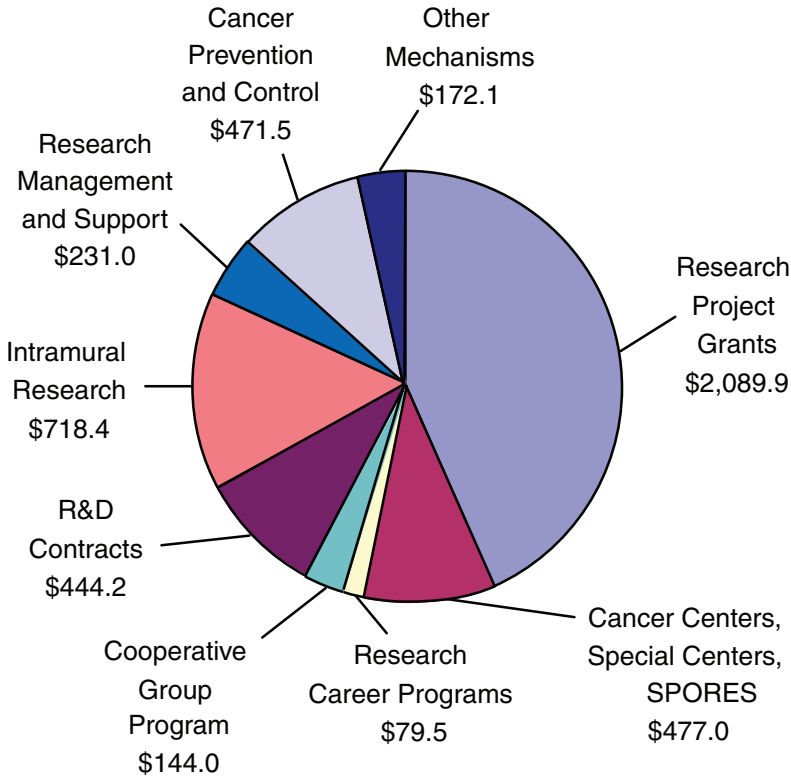

FIGURE 3-5 Allocation of the NCI budget in fiscal year 2008. The actual obligations of NCI funds by mechanism are shown, in millions of dollars. The allocation for the NCI Cooperative Group Program represents approximately 3 percent of the total NCI budget.
SOURCE: See http://www.cancer.gov/aboutnci/servingpeople/snapshot.

To determine how funding should be parceled out among the many intramural and extramural programs of NCI, the NCI director can, in principle, draw on the expertise of external advisory boards (IOM, 2003; NCI, 2009c). Notably, the National Cancer Advisory Board (NCAB) is charged with advising "the NCI director with respect to the activities carried out by NCI, including reviewing and recommending for support grants and cooperative agreements, such as the agreement that funds the Cooperative Groups, following technical and scientific peer review." All members of this group are appointed by the president, with the intent of providing oversight for all NCI activities to ensure that NCI programs maintain goals focused on the nation's interests and needs in cancer

BOX 3-4
Funding Mechanisms for NCI Clinical Trials Program

Extramural Research Activities

- **Grant mechanisms:** R01, R03, R21, R37, and P01 grant-supported trials in treatment, control, and prevention
- **Cancer Center support 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 and sites, 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**

NOTES: R01 = research project grant, R03 = small research grants, R21 = exploratory/developmental grant, R37 = method to extend time in research (MERIT) award, P01 = research program grants, P50 = specialized center grant (see http://deainfo.nci.nih.gov/flash/awards.htm).
SOURCE: Abams, 2008b.

research. The Board of Scientific Advisors (BSA) could also influence allocations within the NCI budget, as one of its charges is to advise the NCI director on the policy, progress, and future directions of the extramural scientific research program within each division. This includes evaluations of awarded grants, cooperative agreements, and contracts and examination of extramural programs and their infrastructures to evaluate whether changes are necessary to ensure that NCI is positioned to effectively guide and administer the needs of science research in the foreseeable future (reviewed by IOM, 2003).

However, NCAB and BSA currently have little input in setting budget priorities and ensuring that the Cooperative Group Program has sufficient funds to operate effectively. **The committee recommends that these external advisory boards have a greater role in advising NCI on how it allocates its funds to support a national clinical trials program.** This would help to ensure the most rational distribution of funds, in light of such factors as scientific opportunity and clinical need.

Funding of the Cooperative Group Program

The NCI Cooperative Groups receive funding from NCI's Division of Cancer Treatment and Diagnosis. In 1980–1981, the mechanism of support for the Cooperative Group Program was converted from a grant to a cooperative agreement (U10 award). This was a major change for the program because the cooperative agreement funding mechanism is intended to be a cross between a grant and a contract and thus allowed NCI to have a much more active role in the conduct, management, and oversight of research than grants typically require. Investigators funded through other grant mechanisms (the bulk of NCI extramural funding) based on peer review are not subjected to such oversight. There is considerable variability across the NIH with regard to the balance between oversight and support of trials by the sponsoring institution, and unlike many other NIH clinical trials arrangements, funding for the Cooperative Groups is not linked to specific clinical trials but, rather, to the infrastructure that supports the trials. The U10 award supports the operations, statistical offices, and committees of the Cooperative Groups (CTEP, 1996; IOM, 2009c).

Funding for the CCOP infrastructure is independent of the budget of the Cooperative Groups and comes from the Division of Cancer Prevention rather than the Division of Cancer Treatment and Diagnosis. In fiscal year 2009, the program supported 47 community oncology sites and 12 research bases, as well as 14 minority-based CCOP sites. NCI has proposed increasing the number of CCOP sites to 50, with 1 additional research base, at a cost of $13.6 million over 5 years, and increasing the number of minority-based CCOP sites to 20, at a cost of $6.2 million over 3 years (Goldberg, 2009).

The Cooperative Groups are evaluated at a maximum of 6-year intervals on the basis of various performance criteria. The criteria include the numbers of publications and accruals, the scientific merit and innovation of their trial proposals and whether they meet national priorities, timeliness of study completion, leadership, and whether there is a strong commitment to active, meaningful participation in NCI Phase III treatment trials (NCI, 2006). However, the Cooperative Groups have different timelines for review and so are not compared directly with each other in the evaluation process. In addition, the amount of funding received is not directly linked to the review score, and because of NCI funding limitations, the Cooperative Groups usually receive 30 to 50 percent less than the total grant money requested on their applications and approved by peer review.

CCOP grantees get funds for research costs in advance and earn credits against this funding by enrolling patients into trials (NCI, 2009b). CCOP grants also undergo a peer-review process, largely on the basis of accruals and data quality, different from the review process for the Cooperative

Groups that they have joined (NCI, 2006). CCOP funding also covers only about two-thirds of the actual costs of conducting clinical trials in community settings (IOM, 2009c).

Such insufficient funding has become unsustainable as trials have become more complex. For example, as noted above and in Chapter 2, the funding does not adequately support the collection and molecular characterization of tumor specimens and their storage in biospecimen banks, so Cooperative Groups must supplement support for these activities from a variety of sources, including repository users' fees, other grants, contracts, and institutional commitments. As noted in Chapter 2, such activities are increasingly part of Cooperative Group clinical trials to assess patient subgroups for whom therapy is especially effective or especially toxic. Recognizing the increasing importance of correlative studies that use biospecimens collected during clinical trials to realize the promise of targeted therapies and personalized medicine, NCI set aside $1.6 million in 2007 for biomarker studies run by the Cooperative Groups. However, that funding may be insufficient for these efforts, as tests may cost thousands of dollars per patient. NCI also recently introduced the Biomarker, Imaging, and Quality of Life Supplemental Funding Program to support correlative science and quality-of-life studies that are integral to Phase III clinical trials, with $5 million being allocated for this program in 2009 (NCI, 2008).

Another major factor contributing to the underfunding of Cooperative Groups is inadequate reimbursement of per patient costs. This shortfall was recognized in the U.S. House of Representatives appropriations report for fiscal year 2010,[24] albeit only in regard to gynecologic oncology trials. NCI provides per patient reimbursements to individual Cooperative Group sites in addition to the funding that it provides for the Cooperative Group's infrastructure. However, since 1999, the reimbursement for sites has remained fixed at $2,000 per patient in treatment trials, which is about one-third to one-quarter of the amount of financial support needed to support the cost of these studies (C-Change and Coalition of Cancer Cooperative Groups, 2006). Although the average per patient cost in industry trials is higher (median costs range from $4,700 for Phase III trials to $8,450 for Phase II trials [C-Change and Coalition of Cancer Cooperative Groups, 2006]), industry-sponsored trials may provide $15,000 or more in reimbursement per patient enrolled (Comis, 2008). A recent survey of Cooperative Group sites found that of the 155 respondents (32 percent) who were planning to limit their Cooperative Group participation, three-quarters cited inadequate per case reimbursement for the decline in their level of participation (Blayney, 2009). Some cancer centers have also

[24] See House Report (H. Rpt. 111-220) at http://www.access.gpo.gov/congress/legislation/10appro.html.

capped the number of accruals in Cooperative Group trials because it is too much of an economic burden and because Cooperative Group accruals are not highly valued in reviews for the renewal of Cancer Center support grants, which place more emphasis on individual investigator-initiated, NCI-funded research undertaken by center personnel (IOM, 2009c). **The committee recommends that NCI increase the per case reimbursement and adequately fund highly ranked trials to cover the costs of the trial, including the costs for biomedical imaging and other biomarker tests that are integral to the trial design.**

In addition, the new focus on targeted and combination therapies tends to make the process for obtaining informed consent more difficult and to increase the structural complexity of trials, as well as the complexity of data collection and analysis, all of which increase the costs and personnel time devoted to a trial (NCI, 2009e). Recognizing this, NCI recently implemented a trial complexity and scoring model, under which studies deemed "complex" on the basis of various elements described in the complexity model, may be eligible to receive additional funds (if they are available) to supplement their base capitation. The complexity elements evaluated include the informed-consent and randomization process, the complexity and length of the course of investigational treatment, the duration of follow-up required and the follow-up testing to be done, the complexity of data collection, and whether ancillary studies (such as correlative science or quality-of-life studies) will be conducted (NCI, 2009e). This initiative is designed to align reimbursement for Phase III treatment trials with their complexity to compensate the trial sites for additional expenses. However, the maximum reimbursement under the new system for trial complexity payments is $3,000 per study subject. For many cancer clinical trials, this amount appears to be inadequate to cover most labor costs, per subject enrollment costs, and additional research-related paperwork and reporting requirements (ACS CAN, 2009).

The lack of adequate reimbursement is further exacerbated by the refusal on the part of many health insurers to pay for the health care costs linked to a clinical trial, even though many of the same costs would be reimbursed if the patient were not receiving experimental treatment. The costs linked to treatment within cancer clinical trials are substantial and include physician visits, blood work, and X rays (IOM, 2009c). This issue is addressed in more detail in Chapter 4.

Because of insufficient funding from NCI, the Cooperative Groups must leverage other sources of funding to accomplish their work. The Cooperative Groups are permitted to accept funds from nongovernment sources for research activities not supported by NCI (NCI, 2006). Via this mechanism, the Cooperative Groups can accept support for their trials from industry or charitable organizations. A 2004 survey found that, on

average, 29 percent of a U.S. Cooperative Group site's clinical research revenue originates from sources other than the trial sponsors. These sources include donations, contributions from philanthropic organizations, and community and non-trial-specific grants, as well as institutional discretionary funds of the institutions conducting the research (C-Change, 2005). Private funding, however, is usually allocated to specific trials and not to support the infrastructure of the Cooperative Groups. Consequently, private funds cannot always compensate for insufficient public funding (IOM, 2009c).

The committee recommends that to ensure sufficient funding of high priority clinical trials, the total number of trials undertaken by the Cooperative Groups should be reduced to a quanity that can be adequately supported.

COLLABORATION AMONG STAKEHOLDERS

As noted throughout this chapter, cancer clinical trials often necessitate effective collaboration among diverse stakeholders, but numerous challenges to achieving such collaborations remain (NCI, 2005a). By leveraging the strengths and abilities of different partners, effective collaborations can offer many benefits, including greater efficiency, by pooling skills, technologies, and other resources and by sharing costs and risks. Public-private partnerships in particular can more effectively leverage public funding and resources, increase the breadth and depth of research, and effect a more rapid translation from basic discoveries to public health applications. Industry, government, and nonprofit organizations all have a potential role to play in such partnerships and could each make important and unique contributions to the endeavor. NIH, NCI, and FDA have all recognized the value of these collaborative activities (Niederhuber, 2009; NIH, 2009; Woodcock and Woosley, 2008). As noted in Table 3-2, CTAC recently established an ad hoc Public-Private Partnership Subcommittee charged with providing advice to the director of NCI on how to enhance NCI-sponsored clinical trials through collaborative interactions with the private sector.

Two recent reports from the President's Council of Advisors on Science and Technology also acknowledge the importance and value of strengthening public-private collaborations to enhance innovation (PCAST, 2008a,b). The latter report noted that "the accelerating speed of technological development requires new methods of knowledge exchange between universities and industry so as to capture the societal and economic benefits of these innovations" (PCAST, 2008b). That council recommended that guidance and educational tools on intellectual property and technology transfer practices be developed for university and private-sector partners (PCAST, 2008b).

One recent example of a situation in which multiple stakeholders worked for a common good is the recent meeting sponsored by the Brookings Institution, in which professional societies and a cancer advocacy organization provided a "safe harbor" to facilitate an evidence-based review of safety data from several pharmaceutical groups and a Cooperative Group to better determine what safety data are needed for supplemental FDA approvals (Curt, 2009; McClellan and Benner, 2009).

Collaborative Funding Mechanisms

Inadequate funding of the Cooperative Groups combined with the growing interest by industry in developing and clinically testing new therapeutics and diagnostics for cancer has also led to more industry-Cooperative Group collaborative cancer clinical trials in the past decade. Both parties stand to benefit from such public-private partnerships. Industry provides Cooperative Group investigators access to their new agents and supplements the currently insufficient per-case payments that NCI provides for those enrolled in a Cooperative Group trial. The Cooperative Groups provide industry with their extensive infrastructure, expertise, and scientific credibility that enables companies to conduct high-quality, large-scale, multicenter clinical trials without the burden of vetting and contracting with multiple academic or private institutions. In addition, industry can use some of the public resources of the Cooperative Groups, such as NCI's central IRB (Bressler and Schilsky, 2008).

As noted at an IOM workshop, when a clinical trial done by an NCI-funded Cooperative Group has regulatory implications (e.g., if it will be a trial for registration of a drug), the added costs linked to regulatory requirements are increasingly borne by the drug's sponsor (IOM, 2008). With judicious negotiation and planning with industry, the Cooperative Groups could perhaps use this model to double their budgets so that half comes from drug companies and half comes from NCI. A similar model for the funding of clinical trials is already in use in Canada (IOM, 2008). To avoid perceptions of bias because of industry involvement, it would be important for Cooperative Groups to retain control of the design and analysis of such clinical trials and to ensure that industry partners, just as trial investigators, are not allowed access to the clinical trial database until the trial is completed. Several Cooperative Group-industry clinical trials have successfully used such a procedure (Bressler and Schilsky, 2008; IOM, 2009c).

One Cooperative Group, the National Surgical Adjuvant Breast and Bowel Project, has used a similar approach to industry-Cooperative Group clinical trial collaborations (Wickerham, 2009). It has used a hybrid model to fund Cooperative Group trials, whereby NCI provides funds for fixed

infrastructure costs, such as the costs for the design, production, conduct, and analysis of clinical trials, but industry funds variable costs, such as per case costs at trial sites, the cost of nonstandard patient care, and the cost of ancillary studies. The potential advantage of using this collaborative model is that it allows the Cooperative Groups to maintain the ability to independently design, conduct, and publish the findings of clinical trials and make biospecimens available for public access; provides NCI and FDA review and oversight; and provides adequate resources for the proper conduct of studies in a timely fashion without avoidable fiscal barriers. Another example of a hybrid funding arrangement is the international partnership between CALGB and Novartis to test a leukemia drug within select genetic populations. While CALGB is the IND holder for the United States and North America, Novartis holds the IND for the rest of the world. Novartis organized international sites while CALGB organized the North American sites (IOM, 2009c). **The committee recommends that NCI do more to facilitate the use of appropriate hybrid funding models, in which NCI and industry support clearly defined components of trials that are of mutual interest.**

This approach is common in other countries as well. The United Kingdom uses a form of collaborative hybrid funding for most of its medical research, and the European Organisation for Research and Treatment of Cancer (EORTC) has used a collaborative funding model for years. **Multicenter cancer trials groups in the United Kingdom and Europe generally** use methods of organization that are somewhat different from those that the U.S. Cooperative Groups use.[25]

In the **United Kingdom, for instance, a government agency (the Department** of Health) covers the costs of laboratory and imaging services and the administration of therapeutic agents at no charge for approved clinical trials, and provides the required national infrastructure in the form of salaries for research staff and clinical research associates at National Health Service hospitals. The **United Kingdom disease groups can then work collaboratively** with pharmaceutical and biotech companies in one of two ways: either with the industry partner covering all costs for a study primarily intended to support registration of a drug and done under commercial sponsorship, or with only partial support (or even just the provision of a drug at no cost) from a company for a trial that has been developed by the investigator and that may or may not ever support drug registration. In the latter situation, the database and the analysis are entirely controlled by the academic investigators and the company involved otherwise remains at arms length from the trial. A set of characteristics is used to identify which trials funded by industry should be considered commercial and which should be considered

[25] Personal communication, Richard Kaplan, United Kingdom Clinical Research Network, December 22, 2009.

"investigator-initiated" and effectively academic research. An academic trial usually has most or all of the following characteristics:

- The primary purpose of the trial is not for licensing. (After completion, a company may decide that it wants to use the data for licensing, but if so, new financial and practical arrangements will need to be negotiated.)
- It usually does not collect as full and complete a data set as commercial trials (e.g., concomitant medications, detailed data on less critical blood tests), and it does not employ on-site monitoring beyond the usual standard (such as CTEP's 10 percent auditing every 3 years).
- The database, analysis, and publication are independent of the company and the data are only released to them after an independent data monitoring committee has agreed.
- These studies almost always have an academic or public sponsor (sponsorship is very formally defined in EU regulations), not the company.

These criteria almost always clarify which studies are investigator-initiated studies (even if the company may have provided considerable advice). When a trial doesn't fit the above characteristics, it is considered a "commercial" study, and the company must reimburse full costs of all aspects of the study to the National Health Service. A costing template ensures appropriate reimbursement. This system provides value to the public/taxpayer because the resultant trials are considered scientifically of interest and potentially beneficial for improving patient care, but are less likely to be conducted by industry on its own.

EORTC generally works in a similar way, although it does not have the level of funding support for staff, imaging, and so on, that is available in the United Kingdom. Most EORTC studies therefore require industry support at a higher level than studies in the United Kingdom do. It nonetheless generally uses a model whereby investigators independently control the study database and analysis and may do so even for studies with full funding from commercial sources and with the goal of product registration.

Other public-private models have also been developed or proposed, including that of the Foundation for the National Institutes of Health (FNIH), which was established by the U.S. Congress in 1996 to support NIH's mission of improving health through scientific discovery. According to its website (FNIH, 2009), "The foundation identifies and develops opportunities for innovative public-private partnerships involving industry, academia, and the philanthropic community. A non-profit corporation, the foundation raises

private-sector funds for a broad portfolio of unique programs that complement and enhance NIH priorities and activities." The Foundation, which receives between $70 million and $100 million in revenues per year from such benefactors as pharmaceutical companies and the Bill and Melinda Gates Foundation, has funded large-scale initiatives, such as the Grand Challenges in Global Health and the Collaboration for AIDS Vaccine Discovery, as well as smaller-scale endeavors, such as the Biomarkers Consortium of the FNIH (FNIH, 2009). Under the auspices of this Biomarkers Consortium, several pharmaceutical and biotechnology companies are collaborating with NCI, FDA, and academic investigators to further the use of biomarkers in breast cancer treatments; the I-SPY2[26] trial aims to simultaneously and serially test several different targeted treatments and biomarker tests to more rapidly assess which biomarkers best predict the likelihood of a therapeutic response (Barker et al., 2009; see also Chapter 2).

If funding is provided in a transparent way, both industry and foundations could make important contributions to the publicly funded clinical trials system. If the clinical trials system was streamlined and less complicated (through the adoption of the recommendations in this report and those of the OEWG), these stakeholders might be more willing to support trials conducted by the Cooperative Groups. Similarly, if the core funding provided by NCI adequately supported the clinical trials infrastructure, industry and foundations would be more willing participants, as they could just cover the costs of individual studies. **The committee recommends that NCI facilitate more public-private partnerships and precompetitive consortia, guided in part by successful models.**

Contract Negotiations and Intellectual Property

A major stumbling block to the development of potentially fruitful private-public partnerships is the complex, multiparty contractual negotiations that can be extremely lengthy and consume substantial staff resources of all parties involved (Dilts and Sandler, 2006). These negotiations often stall over issues related to intellectual property, publication rights, and data or biospecimen ownership and access (Bressler and Schilsky, 2008). NCI has provided guidelines for Cooperative Group-industry collaborations that broadly outline the relationship between the two parties and NCI with regard to confidentiality, publication rights, access to data, indemnification and liability, and intellectual property rights (NCI, 2009d). Although the guidelines do specify some rights, such as the right of an industry collaborator to review a manuscript of the study prior to submission but not

[26] I-SPY TRIAL stands for Investigation of Serial studies to Predict Your Therapeutic Response with Imaging And moLecular analysis.

to edit or require changes other than to request the removal of proprietary information, much of the detail in the guidelines is left for negotiations. For example, the guidelines state that "when a clinical protocol involves either an agent, which is proprietary to another company, or involves another NCI collaborative effort, the NCI, the Collaborator, and all other Collaborators will jointly determine a reasonable and appropriate mechanism for data access and sharing prior to initiation of the clinical trial" (NCI, 2009d).

To expedite the negotiations required between industry and the publicly funded investigators before the launch of a collaborative trial, NCI and the CEO Roundtable on Cancer[27] recently reviewed copies of 78 clinical trial agreements from participating organizations and identified 45 key concepts related to intellectual property, study data, subject injury, indemnification, confidentiality, and publication rights. They then gleaned from those agreements the exact language that embodied the key concepts and used it to create standardized and harmonized clauses for clinical trial agreements that are designed to serve as a starting point for contract negotiations (CEO Roundtable on Cancer and NCI, 2008). The U.S. Department of Justice gave the proposed clauses a favorable review and indicated that it had no intention to challenge the initiative (DOJ, 2008). However, its adoption is not yet widespread.

Nevertheless, no proposed clauses in this document specifically detail the ownership of and access to biospecimens and related data collected during a clinical trial. In addition, drugmakers must still negotiate the rights to patented discoveries stemming from biomarker research involving their agents. In November 2009, NCI proposed language for technology transfer agreements, which states that sponsors would obtain a royalty-free, worldwide, nonexclusive license for commercial purposes and a time-limited first option to negotiate an exclusive or coexclusive, if applicable, worldwide, royalty-bearing license for commercial purposes for inventions arising from clinical or nonclinical studies involving a collaborator's therapeutic agent (Ansher et al., 2009). **The committee recommends that NCI develop standard licensing language and contract templates for material and data transfer and intellectual property ownership in biospecimen-based studies and trials that combine intellectual property from multiple sources.**

The Life Science Consortium of the CEO Roundtable on Cancer has also initiated the creation of a precompetitive pool of intellectual property for cancer drug development (Curt, 2009). This effort is modeled in part on the successful example of SEMATECH (SEmiconductor MAnufacturing TECHnology) in the semiconductor industry, in which the U.S. government and 13 firms representing 80 percent of the U.S. semiconductor manufac-

[27] This roundtable was established in 2001 and consists of 17 representatives from 11 pharmaceutical companies and 26 representatives from NCI-designated Cancer Centers.

turing capacity contributed $500 million over 5 years to a public-private partnership to solve the critical problems in computer chip manufacture (reviewed by Curt, 2009). That group developed new ways to standardize the equipment, supply chain, and manufacture of semiconductors in a way that benefited all companies.[28] A lack of standardization and qualification of biomarkers has been cited as a major impediment in the development of targeted cancer treatments as well (IOM, 2007). More private-public collaboration in a precompetitive environment could facilitate the development and use of biomarkers in cancer therapeutics, and the codevelopment of a biomarker diagnostic with a targeted cancer drug.

Recognizing this, the Life Science Consortium has been working to establish a new precompetitive environment in which major drug companies can present their biomarker programs for cancer drug development, under confidentiality, to NCI (Curt, 2009). This precompetitive safe harbor allows NCI to gain a unique perspective unobservable to its individual industry partners and to identify areas of overlap and redundancy as well as gaps. By selecting the most promising partners for further biomarker development and then sharing the validated markers with the academic and industry communities at large, NCI provides a neutral platform that can enable cancer drug development across companies and academia because the risks are shared and collaboration replaces competition. This new approach has already come to fruition. NCI identified a promising assay for measuring the activity of poly(ADP-ribose) polymerase (PARP) inhibitors and worked to further develop and validate the assay, which has since been used in a Phase 0 human trial (Kinders et al., 2008; Kummar et al., 2009; Yang et al., 2009).

Grand Challenges to Stimulate Innovation

Philanthropic and government challenge prizes are undergoing a renaissance because of the growing awareness that, when such prizes are properly applied, they can be a powerful tool for change that can tap new, multidisciplinary, and widespread resources to solve problems (McKinsey & Company, 2009). In addition, the growing science on prizes is improving prize economics and practices for managing execution challenges and risks. Unlike Nobel Prizes, which recognize prior achievement, a growing number of big-prize challenges focus on achieving a specific future goal, and they are often awarded to those who help solve complex problems that have not responded well to activities funded by standard grants. Challenge grants may be especially useful for solving problems for which the goals are clear, but the ways to achieve them are not. By attracting diverse talent and

[28] See http://www.sematech.org/.

a range of potential solutions, challenge grants can foster innovative and often unexpected solutions (McKinsey & Company, 2009).

Grand challenge grant competitions are increasingly being used with great success to help solve large-scale problems or achieve goals that improve society at large (McKinsey & Company, 2009). For example, the X PRIZE Foundation is offering a multimillion-dollar award to the first team to improve the speed of human genome sequencing to better realize the promise of personalized medicine. Another X PRIZE has been established to find ways to change health care delivery, financing, and incentives to measurably improve the health value in a 10,000-person community during a 3-year trial.[29] Rather than directly funding research, an X PRIZE aims to spur innovation by tapping into competitive and entrepreneurial spirits. A report on such incentive prizes concluded that they are unique and powerful tools that can produce change not only by identifying new levels of excellence and by encouraging specific innovations but also by changing wider perceptions, improving the performance of communities of problem solvers, building the skills of individuals, and mobilizing new talent or capital (McKinsey & Company, 2009). Examples of technology development that was spurred by this mechanism include the first commercial space flight, increased super computer speed, and the first autonomous vehicle to drive 100 kilometers.

The use of new and novel approaches and application of the best minds in multiple disciplines (engineering, social science, management, marketing, etc.) could help to solve some of the well-known problems described in this report. The potential for impact can often be a strong motivator to good science, and competition can foster both innovative solutions and rapidity in their discovery, much like what occurred with the sequencing of the human genome. Thus, one promising novel approach would be to develop a major, influential grand challenge to improve cancer clinical trials.

The National Institutes of Health Reform Act of 2006 specifies that

> the Secretary of HHS, acting through the Director of NIH, may allocate funds for the national research institutes and national centers to make awards of grants or contracts or to engage in other transactions for demonstration projects for high-impact, cutting edge research that foster scientific creativity and increases fundamental biological understanding leading to the prevention, diagnosis, and treatment of diseases and disorders. The head of a national research institute or national center may conduct or support such high-impact, cutting edge research [using the previously described awards].

[29] See http://www.xprize.org/.

The committee recommends that NCI use this authority to implement a grand-challenge grant competition with the goal of dramatically increasing the efficiency and innovation of critical cancer clinical trials and clinical trials processes.

SUMMARY

The recommendations in this chapter support the committee's goal to improve the speed and efficiency of the design, launch, and conduct of clinical trials as well as the goal to improve prioritization, selection, support, and completion of cancer clinical trials. The committee concluded that a robust, standing cancer clinical trials network is essential to effectively translate discoveries into clinical benefits for patients. Multi-institutional collaborations are necessary to conduct large Phase III trials for indications such as adjuvant therapy, first-line therapy of metastatic disease, and prevention; single institutions are not capable of undertaking such large-scale trials. Because cancer encompasses more than 100 different diseases, the treatment regimens are complex and diverse (and becoming more so), and hundreds of experimental therapies for cancer are in development, there is a continuous need for the design and implementation of new trials, and it would be highly inefficient to fund and develop infrastructures and research teams separately for each new clinical trial.

If NCI is to achieve the goal of improving outcomes for patients with cancer, it is imperative to preserve and strengthen the unique capabilities of the NCI Clinical Trials Cooperative Group Program as a critical component of NCI's translational continuum. However, the current structure and operating processes of the entire trials system need to be reevaluated to reduce redundancy and improve effectiveness and efficiency. Clinical oncology research has changed a great deal since the early days of the Cooperative Group Program in the 1950s. The process of conducting large-scale trials has become highly complex, with the incorporation of new technologies and trial designs, the increasing number of therapeutic agents to be tested, the increase in the number of Cooperative Groups, and the evolving regulatory environment. All of the stakeholders, including NCI and other federal agencies, such as FDA, as well as the Cooperative Groups need to reevaluate their current roles and responsibilities in cancer clinical trials and work together to develop a more effective and efficient multidisciplinary trials system. Modifying any particular element of the Program or the clinical trials process will not suffice; changes across the board are urgently needed.

Implementation of the committee's recommendations would move the Cooperative Group Program beyond cooperation to integration for many functions, and would significantly alter the definition, structure, and opera-

tions of Cooperative Groups. First, some consolidation of the Cooperative Group front offices would reduce redundancy in the Program, enable the pooling of resources, and reduce competition for enrollment in trials on the basis of Group-specific priorities. **NCI should facilitate front office consolidation by reviewing and ranking the Groups by the use of defined metrics on a similar timetable and by linking funding to review scores. Key planning and scientific evaluations should be at the level of multidisciplinary disease site committees, with a focus on the quality and success of the clinical trial concepts developed and the committee's record of development of new investigators. Committees that do well in review should be funded, and committees with low review scores should be eliminated. Group leaders should consolidate disease site committees from different Groups to strengthen their productivity and review scores.** Changing the timeline and focus of the review process to facilitate direct comparisons of the front office operations would ensure that only the most innovative and successful disease site committees would thrive, expand their membership, and maintain a sense of community. The logical extension of the proposed consolidations will be a reduction in the number of Cooperative Groups. For example, Groups focused on a single disease site or modality would likely need to merge with multidisciplinary Groups under this system. Such a system would ideally maintain strong competition for trial concepts among a smaller number of disease site committees and thus help to ensure that only the highest-priority trials are undertaken.

Second, **NCI should require and facilitate the consolidation of administration and data management operations across all of the Cooperative Groups (the back office operations) including such activities as data collection and management, data queries and reviews to ensure that the data collected are complete and accurate, patient registration, audit functions, submission of case report forms, training of clinical research associates, image storage and retrieval, drug distribution, credentialing of sites, and funding and reimbursement for patient accrual.** Each Cooperative Group devotes significant resources to support similar administrative structures and activities, but consolidated back office operations work very successfully in other industries. The consolidation of offices and personnel to conduct these information-based activities across all the Cooperative Groups would streamline the operations, reduce redundancy, conserve resources, and offer greater consistency to providers enrolling patients in trials launched by different Cooperative Groups. However, it will be imperative to ensure high service quality and responsiveness to the principal investigators and Cooperative Groups, through periodic peer review of formal metrics of performance.

In addition, NCI should work with the extramural community to make process improvement in the operational and organizational management

of clinical trials a priority. For example, NCI should work with governmental and nongovernmental agencies with relevant expertise to facilitate the identification of best practices in the management of clinical research logistics and develop, publish, and use performance, process, and timing standards and metrics to assess the efficiency and operational quality of clinical trials. The operational processes used to conduct clinical trials are idiosyncratic to individual institutions or Cooperative Groups, with little sharing of best practices or lessons learned. Because these operational issues can significantly delay clinical trials and the evaluation of innovative therapies for all types of cancer, the operational performance metrics used to evaluate Cancer Centers and Cooperative Groups need to be enhanced and redefined to include quality, outcome, and timing metrics for clinical trials. A transparent process that could be used to measure and reward the conduct of meaningful and efficient clinical research would greatly facilitate the adoption and use of best practices and metrics.

One of the most time-consuming and complex activities in the clinical trials process is the development of a scientific concept into a viable and approvable clinical trial protocol. NCI's Operational Efficiency Working Group, which was charged with identifying ways to reduce the study activation time for Cooperative Group and Cancer Center trials by 50 percent, has recently put forth specific, measurable goals that include reducing the time from protocol submission to final protocol approval to 300 workdays for Phase III trials and eliminating trials that do not open and accrue patients within 2 years. To achieve those goals, the working group recommended staffing changes, more coordinated, parallel reviews, improved project management, and better tracking of the trial protocol. **The IOM committee endorses these recommendations.**

More active and consistent support from NCI to facilitate trial operations would also be beneficial. **For example, NCI should devote more funds to drug distribution, provide resources and technical assistance to facilitate the rapid adoption of a common patient registration system as well as a common remote data capture system, facilitate more efficient and timely methods for ensuring that trial data are complete and accurate, and develop standardized case report forms that meet regulatory requirements.** However, all these activities will require additional NCI staff and resources to support the Cooperative Group Program.

Compliance with regulatory requirements for the conduct of clinical trials is another major challenge for clinical investigators. Multiple agencies and institutional bodies of HHS review and provide oversight for cancer clinical trials, including NCI, FDA, OHRP, OCR, and IRBs. The many oversight bodies have different objectives and responsibilities and thus seek similar, overlapping, but not identical information and action for compliance. Moreover, the review processes are serial and iterative. This

delays the trial process and increases the burdens on investigators. The committee recommends that **HHS lead a transagency effort to streamline and harmonize government oversight and regulation of cancer clinical trials. For example, all review bodies should distinguish between major review concerns (regarding patient safety and critical scientific flaws, which must be addressed) and minor concerns (which should be considered, but are not obligatory). Also, NCI should coordinate with FDA for the review and oversight of trials involving an investigational new drug or investigational device exemption to eliminate iterative review steps.** Harmonizing, coordinating, and streamlining the oversight and review processes could significantly improve the speed and efficiency of clinical trials, ease the burden on investigators, and better protect patients.

Changes within individual agencies would also be beneficial. For example, FDA may have multiple centers with jurisdiction over trials testing combination products, such as drug-biologic combinations or therapeutic-diagnostic combinations. **Thus, FDA should establish a coordinated Cancer Program across its centers that regulate oncology products** to reduce the conflicting expectations that may arise when sponsors seek approval through multiple centers. FDA committed in principle to the formation of such a cancer program in 2004, but it has yet to follow through on that commitment. In addition, **FDA should update its regulatory guidelines for the minimum data required to establish the safety and efficacy of experimental therapies (including combinations of products) and eliminate requirements for nonessential data, particularly for supplemental new drug and biologic license applications.** Defining a core set of data elements, along with guidance on how those elements could be modified under certain circumstances, would speed the FDA review process and lead to greater uniformity in data requirements. Eliminating unnecessary and onerous data requirements would also conserve resources and result in the testing of more combination therapies in particular.

A major challenge unique to large multi-institutional studies is the involvement of many local IRBs. Regulatory language is often complex and subject to interpretation, so decisions by IRBs can be highly variable, which can cause delays and lead to protocol variations at different sites. Local IRBs can defer to a central IRB (CIRB), but in practice, many institutions are reluctant to rely on decisions made by the NCI CIRB, in large part because of concerns about being held accountable for the decisions that the CIRB makes. **The committee recommends that OHRP develop guidance that clearly establishes the accountability of the NCI CIRB, to encourage its wider use and acceptance by local institutions.** This would increase the efficiency and reduce the costs of clinical trials, as well as increase consistency in patient protections across sites. Another way to better protect patients, through improved patient communication and decision making,

would be to develop federal guidance that allows the use of **a shortened and simplified summary to enhance the provision of informed consent,** as consent forms have become very lengthy and complex. **Federal oversight should also be more flexible in allowing minor amendments to the protocol or consent form to fast-track the chain of reapprovals.**

The progress of clinical oncology research is also impeded by numerous obstacles that are well-known but have eluded solution, despite decades of discussion and multiple reports by review panels. A new and novel approach is required to solve these well-known intractable problems, with application of the best minds in multiple disciplines. The potential for impact can often be a stronger motivator to good science than money per se, and competition can foster rapid and innovative solutions, much like what occurred with the sequencing of the human genome. **Thus, NCI should implement a highly visible grand challenge competition to engage experts in cancer and noncancer fields (e.g., engineering, social science, management, and marketing) and to reward significant innovation leading to increased efficiency in clinical trials processes.** Models for the development of such grand challenges exist and have shown some successes. A recent report on such incentive prizes, which spur innovation by tapping into competitive and entrepreneurial spirits rather than directly funding research, concluded that they are unique and powerful tools that can produce change not only by identifying new levels of excellence and by encouraging specific innovations but also by changing wider perceptions, improving the performance of communities of problem solvers, building the skills of individuals, and mobilizing new talent or capital.

Cancer clinical trials often necessitate effective collaboration among diverse stakeholders, but there are numerous challenges to achieving such collaborations. **Thus, NCI should take steps to facilitate more collaboration among the various stakeholders in cancer clinical trials.** For example, negotiations to reach contract and licensing agreements to transfer or share materials, data, and intellectual property (IP) are complex and can cause lengthy and costly delays in the launch of clinical trials. Pharmaceutical companies in particular may be reluctant to share IP or data and patient samples with academic collaborators and may require IP rights that are unacceptable to collaborators. However, valuable insights and discoveries may be lost and progress toward clinical advances may be slowed if important data or samples are withheld from collaborating institutions that could explore novel, additional hypotheses with those resources. **Thus, NCI should develop standard licensing language and contract templates for material and data transfer and for intellectual property ownership in biospecimen-based studies and trials that combine intellectual property from multiple sources.**

It is also necessary to examine the contributions of and interactions between NCI and the Cooperative Groups in developing and implementing

large-scale cancer clinical trials. NCI's coordination role within the current environment is quite complex and challenging, and inefficient interactions between NCI and the Groups contribute to delays in the system. To improve the speed of advances in oncology care, streamlined processes are needed for the prioritization, selection, and support of trials and for rapid patient accrual after a trial is launched. **Thus, NCI should reevaluate its role in the clinical trials system.** NCI has crucial responsibilities in the clinical trials system, for example, by providing a framework for both cooperatively and competitively organized interactions between Groups and their committees and in the management of IND sponsorship. Helping Group investigators gain access to more experimental therapeutic agents for high-priority trials by filing an IND application would reduce the time that the Groups spend in negotiations with industry to acquire agents before a trial is launched and also ensure the availability of the agent during the trial. **NCI should file more investigational new drug applications for agents to be tested in high-priority trials and provide a leadership role to ensure the success of those studies.**

However, in cases in which NCI does not hold the investigational new drug application, the primary focus of NCI should be on supporting high-priority trials, with less emphasis on oversight of the selection and implementation process and greater focus on facilitating the launch and execution of the trial. Since the funding mechanism for the Cooperative Group Program was changed from grants to cooperative agreements in 1980, NCI has exercised oversight of every aspect of the clinical trials process, including trial selection, protocol development, and trial operations. But this is not the best use of NCI's limited funds. A Cooperative Group whose trial concept has scored well in peer review should be able to request assistance from NCI as needed to develop and implement the protocol, but it should have the necessary expertise to develop and run the trial without extensive oversight by NCI, which can delay the process. Specific research projects funded through other grant mechanisms on the basis of peer review (the bulk of NCI extramural funding) are not subjected to such oversight.

The role of the steering committees should also be reevaluated. A major challenge that the Cooperative Group Program faces is the prioritization and selection of trial concepts before a trial is launched. The effective prioritization and selection of trial concepts is critical to ensure that limited public funds are used in ways that are likely to have the greatest impact on patient care. However, the disease-specific steering committees set up in response to the CTWG report do not appear to have fully achieved that goal. The approval rate for trial concepts has not changed substantially since implementation of the steering committees, but the length of concept proposals has increased considerably, making the review process more arduous. Moreover, multiple layers of review still slow the process, and

trial concepts are still not ranked against each other with consistent criteria, as is usually done in peer review. Steering committees review and vote up or down on trial concepts as they are submitted and NCI staff actively participate in the review process, unlike other NCI peer review groups. In addition, there is little interaction among the disease-specific steering committees to determine trial priorities across disease categories, although the steering committees are charged with "guiding the development of strategic priorities." **The committee recommends that steering committees administered by NCI operate independently of NCI staff. These committees should focus on the prioritization of clinical needs and scientific opportunities, selection of trial concepts proposed by the Cooperative Group disease site committees, and facilitation of communication and cooperation among the Groups. In addition, the process of peer review for trial concepts should be strengthened and streamlined and should entail the evaluation of concise proposals (including the intended statistical design) that are ranked against each other. The emphasis should be on scientific strength and opportunity, innovation, feasibility, and the importance to improving patient outcomes.** Launching only the highest-ranked trials would improve quality, speed advances, and ensure that patients are enrolling in the most meaningful and potentially beneficial trials.

Prioritization alone, however, is not sufficient. At present, only about 60 percent of cancer clinical trials supported by NCI are completed and published. This represents a tremendous waste of very limited resources, including time, effort, and money. Once a priority trial has been launched, resources and effective procedures are needed to ensure rapid patient accrual and completion of the study.

The NCI Clinical Trials Cooperative Group Program has been chronically underfunded for the work that it performs, and current funding does not cover the cost of the clinical trials undertaken. For the past 3 years, the annual budget for the Program has been held at about $145 million, but in real dollars it has declined to less than the 1999 funding level of $119 million, when the funding is adjusted for inflation. Despite this decrease in funding, the Cooperative Group Program has maintained patient accrual, with several hundred clinical trials ongoing at any given point. This level of funding is simply not sufficient to support the number of trials that the Groups undertake. As a result, the Cooperative Group Program is highly dependent on the voluntary efforts of participating investigators and on supplemental funding from other sources, such as foundations, the pharmaceutical industry, and the institutional contributions of Cooperative Group members. Especially in light of the new focus on targeted therapy and personalized medicine, which raises the complexity and cost of clinical trials, the Cooperative Group funding process is becoming increasingly unsustainable.

High-priority trials must be adequately funded to efficiently and effectively attain results that can move the field forward. NCI has an obligation to adequately fund trials identified as being of high priority. NCI should increase the total funding allocation for the Cooperative Group Program to ensure the effective translation of discoveries made with public funding to improved clinical care. Thus, **NCI should allocate a larger portion of its research portfolio to the Clinical Trial Cooperative Group Program to ensure that the Program has sufficient resources to achieve its unique mission.** The allocation of NCI funds among the competing needs of its various programs is a major challenge for the NCI director, who must take many factors into consideration. Greater input from the broad expertise and experience of external advisory boards would be helpful to ensure the most rational distribution of funds across the major NCI programs, in light of such factors as scientific opportunity and clinical need. **External advisory boards, such as the National Cancer Advisory Board and the Board of Scientific Advisors, should have a greater roles in advising NCI on how it allocates its funds to support a national clinical trials program.** These high-level boards should not be involved in the oversight of individual trials or in concept review, which would further slow the process, but rather, they should have a greater influence on how much funding is allocated to the overall Cooperative Group Program.

Given the limits of the NCI budget, **the total number of NCI-funded trials undertaken by the Cooperative Groups should be reduced to a quantity that can be adequately supported, to ensure sufficient funding for high-priority trials.** Compromising the science to launch more trials than the available funding can support is detrimental to progress. However, even in the absence of a substantial increase in the overall funding of the Program, the funds saved by launching fewer but higher-priority trials could be allocated for increased per case reimbursement rates to trial sites, which has been set at $2,000 since 1999, well below the estimated median costs per patient. The many duties required of clinicians and other key research staff to participate in clinical trials are costly in terms of both time and resources. These voluntary contributions constitute a substantial value and strength of the Program. However, when the discrepancy between the per case reimbursement and the actual cost of participation is excessive, as it is now, it becomes a major disincentive to participation. The existing system also often does not provide the resources required to thoroughly characterize each patient's tumor and carefully match that profile to targeted therapeutics. Biomedical imaging and other biomarker tests are commonly becoming integral components of modern cancer clinical trials, but supplemental funding for these tests must be obtained by the Cooperative Groups through other support mechanisms. Thus, **NCI should increase the per case reimbursement and adequately fund highly ranked trials to cover the costs**

of the trial, including the costs of biomedical imaging and other biomarker tests that are integral to the trial design.

Given the limited funding capacity of NCI, it would also be beneficial to leverage the resources of industry to support the work of the Cooperative Groups in a transparent way to benefit patients, for example, in comparison trials or for secondary indications. Two recent reports from PCAST acknowledge the importance and value of strengthening public-private collaborations to enhance innovation, particularly for discovery and translational research in personalized medicine. However, industry funding for Cooperative Group trials has been limited for a variety of reasons, including concern about the inherent inefficiencies in the Program and the groups' concern about maintaining independence in study design and execution. These concerns may contribute to the increasing tendency of pharmaceutical companies to conduct trials in other countries.

Thus, NCI should facilitate the creation of more public-private partnerships and precompetitive consortia, guided in part by successful models. NCI should also facilitate the development of appropriate hybrid funding models, in which NCI and industry support clearly defined components of trials that are of mutual interest. Commercial firms might be more interested in collaborations with the Cooperative Groups if the review and operational procedures of the Program were streamlined, as recommended in this report. However, novel hybrid funding mechanisms, as well as new efforts to establish public-private partnerships and precompetitive consortia would further aid progress toward effective collaboration, to the benefit of patients, who desire access to new and promising cancer therapies. Maintaining a critical mass of clinical trials in the United States via appropriate collaborations is important to ensure that patients in this country gain access to promising therapies as they develop, that trials address questions and generate data that are relevant and meaningful to patients in the United States, and that the nation retains a sufficient number of properly trained clinical trial specialists.

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4

Physician and Patient Participation in Cancer Clinical Trials

The ability to translate scientific discoveries into clinical advances relies on a robust clinical trials infrastructure, which is largely dependent on a critical mass of patients and physicians willing to participate in clinical trials. However, current indications suggest that participation in clinical trials is the exception rather than the rule both for patients and for physicians. It is estimated that only 3 percent of adults with cancer participate in clinical trials, and people who are members of racial and ethnic minorities, elderly and low-income individuals, and people who live in rural areas remain underrepresented (EDICT, 2008). Without adequate rates of participation by patients and physicians, it is unlikely that important research questions with the potential to improve patient outcomes will be answered efficiently and effectively. Furthermore, the trend toward targeted therapy and personalized medicine necessitates larger numbers of patients willing to participate in clinical trials, since these trials are increasingly reliant on stratified populations. According to the National Cancer Institute (NCI), the true effectiveness of cancer therapies will not be known unless more people are involved in clinical trials (NCI, 2001).

The committee concluded that the value of clinical trials in advancing patient care necessitates a paradigm change in the current approach to clinical trials. Building on discussions at a prior Institute of Medicine (IOM) workshop (IOM, 2009b), the committee emphasized that the therapies offered through clinical trials should ideally be considered the preferred treatment choice for physicians and patients, if they are available. Broad participation in a publicly sponsored clinical trials system—by investigators, community physicians, cancer centers, and patients—will enhance the system's impact by efficiently providing practice-changing evidence.

Although many important clinical trials are undertaken by the pharmaceutical industry, relying solely on pharmaceutical companies and contract research organizations to maintain a clinical trials infrastructure would be detrimental for a variety of reasons. First, companies are primarily responsible to their shareholders and have less incentive to conduct certain types of clinical trials that are in the best interests of society. An industry-only clinical trials infrastructure may neglect important areas of research, including research on the comparative effectiveness of different therapeutics, research on novel indications for older drugs, determination of dose intensity, the development of combination products from multiple companies, research on the development of drugs for the treatment of rare diseases, evaluation of different surgical and radiation treatment methods, research on screening and prevention strategies, and research on rehabilitation and quality of life following therapy. In addition, industry trials are increasingly moving away from the United States (Agres, 2005; Glickman et al., 2009; IOM, 2009b; Normile, 2008), which could lower U.S. patient access to clinical trials and, in some instances, lower the applicability of the findings of clinical trials to the U.S. population. This movement of clinical trials overseas threatens the capacity of the United States to maintain a clinical trials infrastructure and workforce. Academic centers and community practices play a crucial role in training and mentoring the next generation of clinical investigators, but recent evidence suggests that the number of U.S.-based principal investigators is declining (Getz, 2007), potentially shrinking the training pipeline for new clinical investigators and negatively affecting the U.S. economy.

Rather than rely on a pharmaceutical industry-centered clinical trials infrastructure, the committee concluded that incentives must be realigned so that clinical investigators and patients will choose to participate in a publicly sponsored clinical trials system. The committee took a broad view of the disincentives preventing high rates of participation. For clinical investigators, the committee emphasized issues related to reimbursement, extensive regulatory burdens, and academic procedures related to tenure, promotion, and career development. For patients, the committee discussed third-party coverage for participation in clinical trials and patient and physician attitudes about participation in clinical trials, including knowledge of the availability of clinical trials. Many of these issues have been addressed in prior evaluations of the Clinical Trials Cooperative Group Program (NCI, 1997, 2005b), but low rates of participation in cancer clinical trials remains a significant barrier to the efficient translation of scientific discoveries into advances in patient care.

CLINICAL INVESTIGATOR PARTICIPATION

Retaining a workforce competent in conducting clinical trials is essential to maintaining a strong publicly funded clinical trials infrastructure.

However, the current system does not foster clinical investigator participation in publicly sponsored clinical trials. Misaligned incentives, both in academia and in physician practices, inhibit robust participation. Realigning incentives for clinical investigators so that they may participate in clinical trials is essential to increasing patient accrual.

Physicians who participate in Cooperative Group trials do so despite significant barriers and disincentives and have been referred to as an "all-volunteer army" because the costs of conducting trials outstrip the reimbursements provided by the NCI (IOM, 2009b; see also Chapter 3). Many of the reasons that investigators continue to participate in trials include the desire to advance cancer research and improve future patient care, to be involved in the design and conduct of clinical trials, and to offer patients access to state-of-the-art care, including access to investigational compounds.

Despite the importance of cancer clinical trials, the disincentives limiting provider participation are numerous. The American Cancer Society Cancer Action Network (ACS CAN) breaks down the disincentives into financial barriers, regulatory burdens, awareness of clinical trial options, and physician perceptions of clinical trials (ACS CAN, 2009). In addition to the barriers that are common to all investigators, academic physicians and community physicians confront somewhat unique barriers. Clinical trial involvement is not well rewarded in tenure and promotion processes in academia and is not aligned with the time investment required for conducting large, multi-institutional trials. Community practitioners lack the needed infrastructure and support to actively participate in clinical trials.

Financial and Regulatory Barriers

Participating Sites

In 2009, the American Society of Clinical Oncology (ASCO) conducted an Internet poll of Cooperative Group sites seeking to understand whether financial or other barriers are preventing participation in Cooperative Group clinical trials. The survey found that 32 percent of respondents (155 of 478 sites)[1] indicated that they plan on limiting participation[2] in the Cooperative Group Program (Blayney, 2009). Seventy-five percent of survey respondents who indicated that they were limiting participation cited

[1] A limitation of the interpretation of these findings is that the number of sites that received the poll is unknown, and it is unclear whether the 478 respondents are representative of the estimated 1,800 sites involved in Cooperative Group research.

[2] The survey defined limited participation as (1) a cap on the number of patients to be accrued, (2) a limit on the number of trials offered, or (3) a limit to the number of Cooperative Group affiliations.

inadequate per case reimbursement as an important factor in this decision. An additional 38 sites (or 8 percent or those surveyed) were considering these limitations. Although many respondents indicated a preference for participation in Cooperative Group trials, 49 respondents indicated that their sites were increasing their rate of participation in industry trials. Jeffrey Abrams, associate director of the Cancer Therapy Evaluation Program, has also noted that cancer centers are curtailing their participation in Cooperative Group trials. In a recent IOM workshop, Abrams said some cancer centers have capped the number of accruals that can go to Cooperative Group trials, because they believe that it is too much of an economic burden (IOM, 2009b).

As the findings of the survey suggest, cancer centers and other sites enrolling patients in Cooperative Group clinical trials may be limiting participation because of inadequate reimbursement. Although Cooperative Group trials are recognized for their fundamental importance in setting the standard of care, institutions are faced with increasing cost restraints, making it difficult to participate in inadequately reimbursed activities, such as Cooperative Group trials. Despite the resource-intensive nature of clinical trials, the per patient reimbursement of $2,000 has remained the same since 1999 (IOM, 2009b). In June 2008, the NCI began using a complexity rating scheme to increase the rate of reimbursement for complex clinical trials, with the maximum reimbursement of $3,000 (Mooney, 2008). However, the extra $1,000 of reimbursement for complex clinical trials is still far below estimated costs required to conduct clinical trials, which in 2004 were estimated to be a median cost of $3,500 and $6,000 per patient for Phase III and Phase II trials, respectively (C-Change, 2005). For many cancer clinical trials, this amount appears to be inadequate to cover most labor costs, per subject enrollment costs, and additional research-related paperwork and reporting requirements (ACS CAN, 2009). If an academic medical center or a physician practice stands to lose thousands of dollars per patient by participating in the current publicly sponsored clinical trials system, it is not surprising that physician preferences are to treat patients with the standard of care or with a therapeutic agent off protocol, rather than being involved in a significantly more costly and more burdensome clinical trial.

Individual Physicians

According to one survey, only 13 percent of physicians are clinical investigators (Taylor, 2004). Aside from the lack of opportunity to participate as a clinical investigator, that survey found that the primary reasons for not acting as a clinical investigator include the time commitment involved (32 percent), a lack of personal support (30 percent), not having

the resources to run a successful trial (26 percent), and the paperwork burden (24 percent). However, only 17 percent of physicians surveyed said that they had no interest in becoming a clinical investigator (Taylor, 2004).

Physicians who enroll patients in Cooperative Group clinical trials face increased time and effort not reflected in current reimbursement policies. To participate in clinical trials, physicians must find applicable trials for their patients, explain these trials to their patients, and obtain informed consent, which can add significant time and effort to a physician's workload (Comis et al., 2003). On average, 4 hours of a physician's time is required before a patient can be enrolled in a trial, and some of that time is devoted to patients who ultimately choose not to participate in the clinical trial (Mansour, 1994). If a patient enrolls in a trial, the data collection and documentation requirements are substantially more onerous for patients in a trial than for patients receiving standard therapy outside of a trial (Comis et al., 2003). The complexity of the protocol, the recruitment and selection of study participants, high-intensity visit schedules, protocols that deviate from the standard of care, and the complexity and acuity of the patient population all add to the costs of treating patients within a clinical trial setting (ACS CAN, 2009). At an IOM workshop, one community physician noted that he gives double bookings for patients participating in complex clinical trials (for example, one with two targeted molecules) to have time to sort through all of the toxicities and to adjust the doses for each drug (IOM, 2009b). In addition, radiologists and pathologists must spend additional time conducting tests and analyses for clinical trials and resist doing so because they are not compensated for the extra work and time required.

As discussed in Chapter 3, the regulatory requirements for clinical trials are highly complex. These requirements can also prevent robust provider participation. Clinical investigators must contend with ambiguous and complex regulations in clinical trials, including the reporting requirements of the Food and Drug Administration (FDA), in addition to those of the National Institutes of Health (NIH), such as requirements for proof of adherence to good clinical practice guidelines and human subject protections; reporting of adverse events; and adherence to data monitoring, audits, and quality control requirements (ACS CAN, 2009). Oncologists are less likely to refer patients for participation in a clinical trial if they perceive the paperwork to be onerous and trial entry requirements to be too stringent (Siminoff et al., 2000). Given the low reimbursement levels and the voluntary nature of the Cooperative Group Program, the added burden of the regulatory requirements on clinical investigators is a major disincentive to participation.

In light of the additional time and resources required for physician participation in a clinical trial, the committee recognized the importance

of establishing a mechanism to reimburse physicians for their time commensurate with the level of work involved with participation in a trial. **Specifically, the committee recommends that NCI increase the per case reimbursement rate. The committee also recommends that the American Medical Association establish new *Current Procedural Terminology* codes (CPT codes), reimbursed by the Centers for Medicare & Medicaid Services (CMS), private insurers, and other third-party payors, to pay an enhanced reimbursement for offering, enrolling, managing, and following a patient in a clinical trial.** New CPT codes, with a higher reimbursement rate, that acknowledge the additional time and resources needed to counsel and care for a patient in a clinical trial would address an important deterrent to physician participation in clinical trials. With a proper definition of eligible trials, use of such a code could be easily audited.

The committee also discussed the importance of funding principal investigators who participate in Cooperative Group research. The committee distinguished two types of principal investigators: first, principal investigators who develop and oversee a Cooperative Group clinical trial, and second, principal investigators who oversee all Cooperative Group trials at a participating institution. Both of these types of principal investigators are important to the design, implementation, and monitoring of Cooperative Group trials. **Therefore, the committee recommends that NCI provide funding to site and trial principal investigators to cover the time they need to develop and oversee approved clinical trials.** In a similar step, the Operational Efficiency Working Group recommended that NCI officially recognize investigators for leadership in the design and conduct of Cooperative Group trials (Doroshow and Hortobagyi, 2009).

Participation by Community Physicians

The majority of cancer patients are treated in community settings, whereas the majority of cancer patients who enroll in clinical trials are treated within academic settings (Cox and McGarry, 2003; Somkin et al., 2005). However, community physicians also play a vital role in recruiting patients into clinical trials, especially large-scale trials of methods for cancer screening, adjuvant therapies, and first-line therapies for metastatic disease. One of the strengths of the Cooperative Group Program is the extensive involvement of physicians and patients in community practices. Participation by physicians and patients within community settings helps to ensure that the results of clinical trials are meaningful to a broad segment of the U.S. population and provides the patients with access to promising, innovative therapies as they are developed. NCI's Cooperative Group Program is responsible for enrolling 85 percent of patients who enter NCI-sponsored trials, and about 65 percent of these patients enter from community-based

practices that include Community Clinical Oncology Program and academic medical center affiliates (C-Change and Coalition of Cancer Cooperative Groups, 2006). Despite the importance of enrolling community-based patients into clinical trials, a number of barriers prevent more community physicians from participating in clinical trials. During the IOM workshop on multicenter clinical trials, one speaker noted that doctors have virtually no incentives to enroll patients in a clinical trial but have many disincentives (IOM, 2009b). As with all physicians, financial burdens, regulatory complexity, awareness of trial availability, and attitudes about participation are barriers to clinical trial participation for community physicians. However, physicians in community practices may have fewer resources to support participation in a clinical trial, including a lack of logistical support and a lack of clinical research nurses. Some modest resources are available to support community practitioners, such as the Community Oncology Research grant, which gives up to $30,000 to support three community-based practices that enhance their clinical trials programs (ASCO, 2008). Despite the availability of these support mechanisms, a large discrepancy between the per case reimbursement and the actual cost of participation remains, and this is a major disincentive to participation. As mentioned above, a primary mechanism for improving community physician involvement in clinical trials includes better reimbursement for physicians enrolling patients in clinical trials.

In addition, the committee emphasized the importance of recognizing the research staff who participate in cancer clinical trials, including physicians, nurses, clinical research associates, pharmacists, and others who conduct clinical trials. **The committee recommends that NCI work with a nonprofit foundation to develop a certification program, as recommended by the Clinical Trials Working Group (CTWG).** Such a program could be one component of site credentialing for participation in Cooperative Group trials (see also the section on participation patterns). A certification program could distinguish investigators who actively participate in clinical trials and have met other metrics of high-quality care. Patients may seek out certified physicians, encouraging physicians to become certified and become more involved in clinical trials.

Singling out investigators who participate in clinical trials is consistent with the perspective that well-designed, properly implemented clinical trials are the optimal treatment option. In well-designed trials, patients randomized to the control group typically receive the current standard of care, whereas those allocated to the new treatment receive a treatment hypothesized to be similar to or better than the standard of care (Ellis, 2000). In one survey of oncology leaders at community integrated health centers, eight leaders agreed that trial participation is imperative to high-quality care, whereas only one leader did not support that assessment (Somkin et al., 2005).

Several analyses have attempted to assess whether clinical trial participants have better outcomes than nonparticipants, with mixed results (Braunholtz et al., 2001; Davis et al., 1985; Peppercorn et al., 2004; Robinson et al., 2009; Roy et al., 2000; Stiller, 1994). Although some studies suggest that individuals who participate in clinical trials have better outcomes than nonparticipants in specific medical areas, systematic reviews looking at clinical trials overall have not found such an effect. But these reviews did show that patients participating in a randomized controlled trial did not have worse outcomes than those receiving a similar treatment outside the trial (Vist et al., 2005, 2008). The National Comprehensive Cancer Network (NCCN) guidelines also state that "NCCN believes that the best management of any cancer patient is in a clinical trial" (NCCN, 2009).

Quality improvement programs, such as the ASCO Quality Oncology Practice Initiative (QOPI), may also single out high-performing practicing oncologists to patients and other stakeholders. QOPI is a voluntary self-assessment program that certifies oncology practices for high-quality care. ASCO analyzes practice data for evidence-based quality measures and provides feedback to practices to identify areas of improvement (ASCO certification program emphasizes quality of care, 2009). For example, QOPI could use a metric to assess how many of a physician's patients are enrolled in clinical trials. Currently, Kaiser Permanente uses trial enrollment as a quality metric as part of its practice-based accountabilities (Wallace, 2009).

Participation by Academic Clinicians

Tenure and promotion policies and declining numbers of clinical investigators may prevent higher levels of involvement by academic investigators in clinical research. Tenure and promotion policies tend to value individual investigator-initiated, basic research more than multi-institutional, team-oriented clinical research. In addition, the shrinking physician scientist pipeline suggests that additional efforts may be needed to encourage, train, and retain clinical investigators.

Recognizing and Rewarding Clinical and Team Research

Clinical investigators require a specialized skills set, training, and orientation to be successful. They must be able to navigate the complex regulatory environment, work in teams, share the rewards of their work, and defer financial compensation while spending years in training (Andrews et al., 2009). Despite these unique skills and orientation, physician scientists focused on clinical research may not receive academic recognition and advancement commensurate with the value of their work. This may be due

to a number of factors, including a lack of awareness by promotions committees of what such research entails; the collaborative nature of research, which makes it difficult to mark individual accomplishments; the time span needed to obtain results from clinical research; and the underfunding of the Cooperative Groups (IOM, 2009b). Because Cooperative Group research is primarily accomplished in multi-institutional settings, promotion committees may be unaware of the intellectual rigor and complexity involved in trial design and protocol implementation. Likewise, promotion committees may not have a sense of the time commitment required for clinical trial research or the importance of Cooperative Group research in advancing the field of oncology research and patient care. In addition, physician scientists are less likely than basic scientists to have protected paid time to perform their research (NCI, 2005a).

In particular, clinical research—such as involvement in the Cooperative Group Program—requires a team orientation. According to the President's Cancer Panel, team approaches are the paradigm for achieving progress in translating basic science discoveries into applications that improve clinical practice (NCI, 2005a). However, traditional academic metrics and incentives structures tend to reward individuals rather than teams (Altshuler and Altshuler, 2004). For example, current scientific journal authorship guidelines allow for singling out only first and last authors as leaders in publication. Altshuler and Altshuler called for a deconstruction of the author list so that the particular contributions of each author may be indicated. It is also possible to list all investigators instead of just the principal investigator in the Computer Retrieval of Information on Scientific Projects database[3] (IOM, 2009b).

Because traditional academic metrics focus on individual accomplishments, investigators may participate minimally in team-oriented research activities. For example, investigators may limit participation in multi-institutional, late-phase clinical trials, such as those conducted through the Cooperative Group Program, so that they can dedicate more time to activities that are viewed as having higher value within their institution in terms of both funding and recognition. Academic clinicians are incentivized to conduct smaller, individual investigator-initiated studies that lead to R01 grants, the primary mechanism of support for NIH-funded cancer research (NCI, 2005a). The inadequate value given to team-based, clinical research in academic tenure and promotion decisions prevents more robust participation in Cooperative Group trials. Therefore, **the committee recommends that academic medical centers develop policies and evaluation**

[3]The Computer Retrieval of Information on Scientific Projects is a biomedical database that contains information on U.S. Department of Health and Human Services-supported research projects and programs.

metrics that recognize and reward clinical/team research in promotion and tenure decisions. Similar to the committee's recommendation, the Operational Efficiency Working Group of the Clinical Trials Advisory Committee recommended that NCI create incentives for institutions to include accrual in Cooperative Group clinical trials as a service criterion for tenure and promotion.

Although there are mechanisms to support team-oriented research (such as NIH P01 Program Project, P30 Center, P50 SPORE grants, and U54 Cooperative Agreements[4]), they are a small fraction of the funding for individual project grants (NCI, 2005a). Without incentives to support team-oriented clinical research, the translation of discoveries in basic science into clinical knowledge and care will be slowed (Schrier, 1997). Recognizing the impact of this dilemma on the Cooperative Group Program, the CTWG recommended that NCI and academic incentives be realigned so that they promote collaborative team science (NCI, 2005b).

The Cooperative Group Program relies on clinical, team-oriented research. However, the committee found that cancer center Support Grants (CCSGs), which support the research capacities of cancer centers, do not adequately incentivize participation in multi-institutional Cooperative Group trials. Rather, CCSG review criteria favor investigator-initiated trials emerging from basic discoveries within a cancer center's own institution. To fulfill current CCSG review guidelines, cancer centers that have a clinical component are expected to provide leadership for and participate in Cooperative Group trials.[5] Part of the CCSG review is the assessment of a cancer center's funding base. The U10 award that supports a Cooperative Group's operations and statistical offices is considered equivalently with other peer-reviewed funding. However, the per case reimbursements that the Cooperative Groups provide to cancer centers are not counted in the CCSG review's benchmark ratio,[6] part of the funding base assessment that helps to determine the CCSG award amount. Because per case reimbursements are not adequately rewarded in CCSG reviews and do not fully cover the costs

[4]The P01 Research Program Project supports integrated, multi-project research projects involving a number of independent investigators who share knowledge and common resources. The P30 Center Core Grants supports shared resources and facilities for categorical research using a multidisciplinary approach, or for investigators from the same discipline who focus on a common research problem. The P50 Specialized Center supports basic and clinical research and development, with a multidisciplinary focus on a specific disease entity or biomedical problem area. Like the P50 award, the U54 cooperative agreement supports basic and clinical research and development, with a multidisciplinary focus on a specific disease entity or biomedical problem area (HHS, 2010).

[5]Personal communication, Linda Weiss, National Cancer Institute, November 2, 2009.

[6]The Cancer Centers Program is currently reviewing the CCSG guidelines and may not include a benchmark ratio in the next version, but it is not clear what it will be replaced with. Personal communication, Linda Weiss, National Cancer Institute, November 5, 2009.

of participation in a clinical trial, cancer center directors may discourage their investigators from actively participating in Cooperative Group trials. **To improve participation in Cooperative Group trials, the committee recommends that NCI recognize and reward Cooperative Group efforts in Cancer Center Support Grant (CCSG; P30) site visits, and allow the CCSG research base to include the federal per case funding received by cancer centers that participate in Cooperative Group trials.**

Ensuring the Clinical Investigator Pipeline

The pipeline of physician scientists is decreasing. In the United States, the physician scientist population is smaller now than it was 25 years ago (Ley and Rosenberg, 2005). In 1983, there were 18,535 physician scientists in the United States; by 1998, that number had fallen to 14,479, a 22 percent decline (Varki and Rosenberg, 2003). Reasons for the shrinking pipeline include the changing health care environment, the complexity of rapid advances in biomedical science and the consequent retooling necessary after clinical training, the length and rigor of research training required, the scarcity of funding for subspecialty training positions, competition for research funding, the perception that successful clinician scientists are those who focus on basic research and not clinical research, and senior faculty pessimism over the survival of physician scientists (Schrier, 1997).

Some progress toward reversing the trend has occurred. In 1998, NIH established career development rewards (the K23 and K24 grant programs) for young and established physicians undertaking clinical research. In 2002, NIH offered competitive loan repayment programs that offered at least 2 years of tax-free debt relief for young scientists with commitments to clinically oriented research training (Ley and Rosenberg, 2005). Several awards specifically focus on strengthening the physician scientist pipeline for oncology. For example, through the Damon Runyon Clinical Investigator Award, early career physician scientists receive $450,000 to support the development of their cancer research program to conduct patient-oriented cancer research under the mentorship of leading scientists (Damon Runyon Cancer Research Foundation, 2009). In addition, The ASCO Cancer Foundation (TACF) and NCI partnered to provide funding and recognition of clinical investigators leading cancer research programs at academic cancer centers through the NCI-TACF clinical investigator award. The award provides 2 years of salary support (10 to 15 percent) for up to 10 clinical investigators who play leadership roles in clinical trials at NCI-designated cancer centers. The intention of the award is to recognize clinical investigators who are not principal investigators on an NIH grant but who are actively involved in NCI-funded collaborative clinical trials, promoting collaborative team science and the retention of clinical investigators (NCI-TACF

clinical investigator award, 2009). In terms of mentorship, the American Association for the Advancement of Science and the journal *Science* recently launched CTScieNet, the Clinical and Translational Science Network. This site is both a career development portal and an evolving communications infrastructure whose goal is to educate trainees and new investigators in translational research skills and to link scientists by connecting communities of scientists through professional networks (Andrews et al., 2009).

The Cooperative Group infrastructure is recognized for its importance in mentoring and training young investigators because it brings together senior clinical investigators, experienced biostatisticians, data management experts, clinicians, and laboratory and population scientists (Mauer et al., 2007). According to Gregory Reaman, past chair of the Children's Oncology Group, young investigators are taking the lead in some pediatric trials and more experienced investigators are stepping back and acting as mentors (Reaman, 2009).

Although career development awards and mentorship activities are encouraging, the committee found that these actions do not appear to be resulting in robust improvements in ensuring a pipeline of well-trained, motivated investigators willing to make career commitments to clinical research. **The committee recommends that all stakeholders, including academic medical centers, community practices, professional societies, and NCI, work to ensure that clinical investigators have adequate training and mentoring, paid protected research time, the necessary resources, and recognition.**

Physician Awareness of Clinical Trials

A lack of physician awareness of clinical trials also limits trial participation. According to one survey, the most common reason cited for physician nonparticipation in clinical trials was a lack of knowledge about clinical trials (Taylor, 2004). Primary care and specialty physicians who are not affiliated with research institutions may be even less aware of patient eligibility for clinical trials (EDICT, 2008). Because physicians are the primary conduit to patient entry into clinical trials, physician knowledge and endorsement of clinical trials are essential to enrolling patients in clinical trials (Schain, 1994). Comis and colleagues (2009) found that patient participation in a clinical trial was directly related to the level of physician involvement reported by the patient. Although there are clinical trial registries, the committee found that these registries were inadequate for broadly informing physicians of clinical trial availability at the point of care. The committee concluded that user-friendly electronic tools could be valuable for better informing physicians of relevant clinical trials at the point of care, potentially leading to increased physician and patient participation in

clinical trials. A further discussion of current clinical trial registries and the potential impact of electronic medical record (EMR) systems that quickly alert physicians about relevant clinical trials can be found in the section on ensuring adequate patient accrual at participating sites.

Physician Perspectives on Clinical Trials

Although physicians' lack of knowledge about clinical trials is a documented barrier to participation in clinical trials, changing physicians' perspectives may be equally important in increasing rates of participation in the publicly sponsored clinical trials system. Some physicians may be reluctant to refer patients to clinical trials because they believe that their involvement in a clinical trial will be an excessive administrative or financial burden to their practice (EDICT, 2008). In addition to perspectives about uncompensated time and effort associated with participation in a clinical trial, physicians may limit patient participation because of their own beliefs and assumptions about patient eligibility related to factors of age, comorbidities, cost, and adherence (EDICT, 2008). Physicians may also feel more comfortable presenting a single therapeutic approach to a patient rather than discussing different treatment options—including clinical trials—for fear that they may lose contact with and control over a patient's follow-up if the patient participates in a clinical trial (Mansour, 1994). The committee noted the importance of changing physicians' perspectives so that they will be more likely to encourage their patients to participate in clinical trials. **The committee recommends that physicians strive to make participation in clinical trials a key component of clinical practice.** Emphasizing that evidence-based care requires participation in clinical research, the committee calls on physicians to take part in the accumulation of evidence by enrolling patients on clinical trials (see also the section on participation patterns).

ENSURING ADEQUATE PATIENT ACCRUAL AT PARTICIPATING SITES

Ensuring the rapid accrual of patients into available clinical trials is essential for the efficient translation of research advances into clinical practice. Without a high level of accrual of patients into trials, it is unlikely that important research questions with the potential to improve patient outcomes will be answered efficiently and effectively. However, many trials never reach their accrual goals and thus generate no meaningful results to be published or disseminated. To ensure the rapid conduct and completion of clinical trials, the enrollment of patients on to clinical trials must be improved. At the same time, it is essential that clinical trials conducted by the Cooperative Groups maintain high-quality standards. **Therefore, the**

committee recommends that NCI, Cooperative Groups, and physicians take steps to increase the speed, volume, and diversity of patient accrual and ensure high-quality performance at all sites participating in Cooperative Group trials. In addition, NCI, Cooperative Groups, and physicians should encourage greater enrollment in high-priority trials, regardless of where the trial originates.

Several opportunities to facilitate patient accrual exist. As noted earlier, patients and physicians often lack awareness of clinical trial availability. Encouraging the development of a user-friendly, transparent, up-to-date, and easily accessible centralized registry could improve both physician and patient awareness of the available trials. In combination with electronic tools, such as clinical decision support software, a centralized registry could cue physicians to important, applicable clinical trials at the point of care.

In addition to facilitating access to quality information about available clinical trials, it is also possible to limit overly stringent eligibility requirements for clinical trial participation. Participants in previous IOM workshop discussions suggested that overly stringent eligibility criteria unnecessarily inhibit patient accrual and may limit the applicability of the findings of clinical trials to the general population (IOM, 2009b). Programmatic changes to the Cooperative Group Program could also facilitate patient accrual. Sites participating in Cooperative Group trials overseen by multiple groups must currently be separately credentialed and audited by each group. The establishment of a centralized credentialing body could ease administrative burdens and encourage more sites to actively accrue patients to high-priority, applicable trials.

Information on Clinical Trial Availability

Registries of clinical trials are primary resources that patients and their providers use to locate information about clinical trials (IOM, 2006). A number of registries exist, and the goals of these databases vary by user. The most comprehensive registry to date is ClinicalTrials.gov. Since February 2000, all entities conducting clinical trials of experimental treatments for serious or life-threatening diseases and conditions have been required to submit specific information to this public clinical trial registry, which was established by the National Library of Medicine of the U.S. Department of Health and Human Services as a result of Section 113 of the FDA Modernization Act of 1997. The FDA Amendments Act of 2007 (FDAAA) expanded the scope of clinical trials required to be registered with ClinicalTrials.gov to include all controlled clinical investigations (except Phase I trials) of drugs, biologics, and devices subject to FDA regulation. The law applies to research for all conditions and to research conducted by all sponsor types (e.g., industry, government, and academia) (reviewed by Zarin and Tse, 2008). About

80,551 trials sponsored by NIH, other federal agencies, and private industry are registered with ClinicalTrials.gov (NIH, 2008). However, FDAAA does not mandate the public reporting of trials with investigational interventions not regulated by FDA, such as surgical therapies (Zarin and Tse, 2008), which may be relevant to cancer patients.

In 2004, the International Committee of Medical Journal Editors announced that beginning on July 1, 2005, member journals would require as a precondition for publication registration of the clinical trials described in the journal articles (De Angelis et al., 2004). This policy led to a 73 percent worldwide increase in the number of trial registrations of all intervention types (Zarin et al., 2005).

Other registries with information on clinical trials are also available. TrialCheck.org is a cancer clinical trials registry supported by the Coalition of Cancer Cooperative Groups. TrialCheck is updated daily and is the only clinical trials database integrated into an EMR system (Comis, 2007). In addition, companies such as EmergingMed provide web-based tools to help match patients' personal profiles to the enrollment criteria of available clinical trials, including both private and public trials (EmergingMed, 2009). NCI also has a clinical trials registry that contains information on more than 8,000 active clinical trials and 19,000 closed trials (NCI, 2009b). Georgia and North Carolina are trying to regionalize their clinical trials search engines and make the information more accurate and up-to-date to facilitate patient and physician access (IOM, 2009b).

Despite these encouraging steps, patients and physicians have difficulty navigating the available clinical trials registries. No centralized system currently exists to disseminate clinical trial information to patients and providers, making it difficult for patients with cancer and their providers to find appropriate trials of treatments for their particular disease and in their geographic location (IOM, 2009a). In addition, it has been reported that information on multiple trial search sites is often inaccurate, outdated, incomplete, or not regionalized (IOM, 2009b; Mathieu et al., 2009). Although the development of ClinicalTrials.gov, TrialCheck, EmergingMed and other registries are important first steps to providing the public with information on ongoing trials, they are not sufficient. A more comprehensive and transparent registry of clinical trials for drugs, biologics, and other therapeutic modalities is needed to enable patients and their providers to locate applicable, reliable clinical trial information. Better, user-friendly electronic tools that include information on high-priority trials, that are up-to-date, and that are easily, widely accessible by both patients and physicians could increase the level of awareness of trials and make it easier for physicians and patients to enroll in the most appropriate studies. **Therefore, the committee recommends that NCI and Cooperative Groups develop electronic tools that cue physicians practic-**

ing oncology via EMR systems about trials for which a particular patient is eligible.

For electronic tools to be highly successful, clinical research studies need automated connections to and interoperability with EMR systems, in addition to the seamless import and integration of protocol-directed assessments and interventions into existing clinical decision support systems (Masys, 2009). Such electronic tools with the right features for physician work flow could increase physician awareness about applicable clinical trials in real time. As mentioned above, TrialCheck is the only clinical trials database integrated into an EMR system (Comis, 2007). However, some impediments prevent the adoption and dissemination of user-friendly tools to notify physicians and their patients about applicable clinical trials. Current infrastructure limitations include the absence of interoperable EMRs and very low rates of adoption of clinical decision support tools (less than 10 percent of U.S. health care institutions have adopted these tools) (reviewed by Jha et al., 2006). However, the health information provisions of the American Recovery and Reinvestment Act of 2009 (ARRA) provided $19 billion to stimulate the meaningful use of EMR systems. The Office of the National Coordinator for Health Information Technology notes that the "focus on meaningful use is a recognition that better health care does not come solely from the adoption of technology itself, but through the exchange and use of health information to best inform clinical decisions at the point of care" (HHS, 2009), suggesting that meaningful use will include provisions for interoperability and the inclusion of tools such as decision support. In addition to the funding provided through ARRA, rapidly advancing information technologies[7] (Masys, 2009) could facilitate the development of tools to inform physicians and patients of clinical trial availability. Patients could also benefit from education about participating in a clinical trial (see the section on expanding patient access to clinical trials).

Eligibility Requirements

Patients must meet certain eligibility criteria for entry into clinical trials. Historically, stringent eligibility criteria have excluded many patients, including, for example, those with prior cancers or certain prior treatments. However, there are some indications that the current eligibility criteria are unnecessarily stringent; from 1999 to 2005, the median number of eligibility criteria increased from 31 to 49 (Malakoff, 2008). It is estimated

[7]These include patient portals, personal health records, machine-interpretable paper forms, smart pens, natural language processing to extract structured data from clinical narratives, wireless physiologic-monitoring systems, and telemedicine via bidirectional video and audio.

that in current cancer clinical trials, only 20 to 40 percent of patients presenting at community or academic centers are eligible for participation in clinical trials. Those who are excluded include patients who have previously received multiple treatments, as well as those who have no sites of measurable disease, have poor performance status, or have advanced age (Melisko et al., 2005). During the IOM workshop on multicenter trials, there was general agreement that overly stringent eligibility criteria, such as previous treatment or previous cancer, unnecessarily prevented high rates of participation by patients (IOM, 2009b). The argument against relaxing the eligibility criteria is the potential to complicate trial data. Using less restrictive eligibility criteria may make it more difficult to interpret clinical trial findings, attribute adverse events, and may require the collection of additional safety data. However, the adoption of less restrictive eligibility criteria for most studies would permit more rapid accrual and also allow broader generalizations to be made, could better mimic the conditions encountered in medical practice, and could reduce the complexity and costs of clinical trials without compromising patient safety or requiring major increases in sample size (George, 1996). **The committee recommends that NCI, Cooperative Groups, and physicians encourage the development of patient eligibility criteria that allow the broadest participation possible.** Eliminating needless patient eligibility criteria would allow more flexibility and increase the rates of accrual. More patients could potentially benefit from enrollment in clinical trials, which could increase accrual and facilitate the timely completion of clinical trials.

Patient Advocate Involvement

Cancer patient advocates have been working with the Cooperative Groups since the early 1990s, and approximately 120 patient advocates currently serve as members of the 10 Cooperative Groups (Collyar, 2008). Examples of patient advocacy activities within Cooperative Group operations include incorporation of the patient or family perspective in the design and implementation of trials, patient education and communication, and patient recruitment, among other activities (Table 4-1). Patient advocates can provide feedback in areas such as eligibility criteria, study design and procedures, safety and confidentiality issues, feasibility, informed-consent processes, and other factors important to potential research participants that can help facilitate the development, implementation, and recruitment processes (Demmy et al., 2004). The involvement of patient advocates in the design and conduct of clinical trials has the potential to hasten accrual because trials that appeal to a broader population of patients may be designed (ENACCT-CCPH, 2008). **Therefore, the committee recommends that NCI, Cooperative Groups, and physicians**

TABLE 4-1 Cooperative Group Patient Advocate Teams

Cooperative Group	Examples of Activities
ACOSOG Patient Advocacy Committee	Dissemination of trial results to advocate community
ACRIN Patient Advocacy Committee	Project IMPACT (Improving Patient Accrual to Clinical Trials); descriptions of imaging procedures
CALGB Patient Advocacy Sub-Committee	Committee participation; concept and protocol review; accrual plan; survivor survey; mentor and orientation program; training sessions
COG Patient Advocacy Committee	Patient/family perspective in design, implementation of research studies; resource for other COG communities
ECOG Representative Community	Full participation in executive and core committees; protocol videos; thank you letters; public research results on ECOG website
GOG Patient Advocate Committee	Planned: "Ask the Advocates" webpage; equal access for all patients
NCCTG Patient Advocate Committee	Protocol review; annual patient advocate symposium and community advocacy initiative
NSABP Patient Advocacy Working Group	Patient education and communications; accrual materials
RTOG Patient Advocacy Committee	Advocate community alerted to open clinical trials; recruitment plans; resources on website
SWOG Lay Advocates	SWOG IRB participation; patient information sheets; serve on Committee for Special Populations

NOTE: ACOSOG = American College of Surgery Oncology Group; ACRIN = American College of Radiology Imaging Network; CALGB = Cancer and Leukemia Group B; COG = Children's Oncology Group; ECOG = Eastern Cooperative Oncology Group; GOG = Gynecological Oncology Group; IRB = Institutional Review Board; NCCTG = North Central Cancer Treatment Group; NSABP = National Surgical Adjuvant Breast and Bowel Project; RTOG = Radiation Therapy Oncology Group; SWOG = Southwest Oncology Group.
SOURCE: Collyar, 2008. Reprinted from *Seminars in Oncology*, 35(5), D. Collyar, An essential partnership: Patient advocates and cooperative groups, 553–555, Copyright 2008, with permission from Elsevier.

encourage greater participation by patient advocates in the design of clinical trials and in patient recruitment for trials.

One potential way to achieve greater participation by patients in the design of clinical trials is via community-based participatory research, in which community-based organizations or groups bring community members into the research process as partners to help design studies and disseminate the knowledge gained.[8] Using their knowledge of the community to understand health problems and design trials that the community is likely

[8] See http://www.ahrq.gov/about/cpbr/cbpr/cbpr1.htm.

to value and participate in, these groups help recruit research participants. Additionally, community-based participatory research activities help to inform community members about how research is done and what comes out of it, with the goal of providing immediate benefits to the community from the results, when possible (ENACCT-CCPH, 2008).

Participation Patterns

A small percentage of physicians and sites enroll the majority of patients who participate in clinical trials. Many sites enroll only a few patients in trials to maintain their status in the program. Each Cooperative Group has specific criteria for accruing a certain number of patients to Cooperative Group trials. For example, Cancer and Leukemia Group B (CALGB) has three types of memberships with different thresholds for accrual: main member institutions are expected to have at least 50 registrations annually to CALGB trials, whereas at-large members are expected to have 30 registrations, and affiliates are expected to accrue at least 6 patients into CALGB trials (CALGB, 2009). However, discussions at an IOM workshop noted that it is difficult to encourage physicians and sites to participate more actively because there are few incentives to encourage greater involvement. Likewise, keeping sites open with very few accruals to Cooperative Group trials is usually not financially feasible. According to Laurence Baker, chair of the Southwest Oncology Group, the group "spends a lot of time talking about reducing the number of institutions and how we should police ourselves and reduce institutions that insufficiently participate" (IOM, 2009b).

Exacerbating the low rates of participation by sites and investigators is the amount of resources dedicated to credentialing and auditing the individual sites that participate in Cooperative Group research. Each Cooperative Group has its own rules and procedures for credentialing participating sites as part of its fulfillment of Cooperative Group Program guidelines. Both the operations centers and the statistics and data management centers of the Cooperative Groups have on-site auditing responsibilities (CTEP, 2006). In addition, the NCI Clinical Trials Monitoring Branch provides direct oversight of each Group's monitoring program, which requires on-site auditing as well. Cooperative Group audits document the accuracy of the data submitted to the groups, verify investigator compliance with protocol and regulatory requirements, and provide an opportunity for the auditing team to discuss concerns about data quality and data management with sites. Cooperative Group guidelines require all institutions to be audited once every 36 months. To be in compliance with this requirement, each Group must conduct a comprehensive review of its membership and provide an annual accounting to NCI's Cancer Therapy Evaluation Program of audit activities (CTEP, 2006).

With institutions participating in multiple Cooperative Group trials overseen by different groups, the various credentialing processes pose significant burdens to the participating site, the Cooperative Groups, and NCI. Having a single process for credentialing sites and investigators, with a corresponding registry, could ease administrative burdens. **The committee recommends that NCI establish a centralized credentialing system for sites that participate in Cooperative Group trials. Additionally, the committee recommends that the Cooperative Groups eliminate investigators and sites with low rates of accrual or inadequate data management skills or quality.** Centralized credentialing, in concert with the elimination of investigators or sites with low rates of accrual and inadequate data management capacity, could improve the efficiency of accrual while maintaining high standards for the participating sites. In addition to easing administrative burdens, centralized credentialing could also facilitate enrollment of patients in high-priority trials, as recommended earlier.

ASCO's recent policy statement on clinical trial sites is useful for establishing centralized credentialing criteria. The statement outlined ASCO's perspective on minimum site requirements and attributes that single out high-performing clinical trial sites (Zon et al., 2008) (Box 4-1). Among the attributes of exemplary sites are high rates of accrual, quality assurance, and promotion of clinical trials awareness programs. The Joint Commission, which accredits and certifies health care organizations and programs in the United States, may be another resource. As outlined earlier, the committee emphasizes the important role of physicians in the accumulation of data to support evidence-based care by offering high-quality clinical trials to their patients. **Therefore, the committee recommends that physicians strive to achieve the ASCO exemplary attributes for academic and community clinical trial sites, including high accrual rates of 10 percent or more.**

EXPANDING PATIENT ACCESS TO CLINICAL TRIALS

Ensuring patient access to clinical trials is essential to improving and advancing high-quality, evidence-based care. Without clinical trials that accrue patients in a timely manner, the rapid diffusion of clinical advances into practice is hampered and interventions of questionable benefit may remain part of clinical practice without adequate evidence supporting their use. For example, in 1999, evidence for the lack of benefit of bone marrow transplantation for breast cancer was found, after several years of delay because of poor trial accrual (Bennett et al., 2001). While the trial was ongoing, many women received this treatment outside of the clinical trial, enduring the severe adverse effects of this therapy, including treatment-related deaths, without evidence to guide the treatment decision.

BOX 4-1
American Society of Clinical Oncology
Exemplary Attributes for Clinical Trial Sites

Exemplary attributes:

- Diversification of the clinical trials offered to patients
- High accrual activity (patient accrual rate of at least 10 percent)
- Participation in the clinical trial development process
- Maintenance of high educational standards
- Quality assurance
- Multidisciplinary involvement in the clinical trial process
- Promotion of clinical trials awareness programs

NOTE: Accrual rate is defined as number of patients enrolled annually/number of new patients seen annually.
SOURCE: Zon et al., 2008.

Only 2 to 3 percent of adults with cancer participate in oncology clinical trials. Furthermore, elderly individuals, people who are members of racial and ethnic minority groups, low-income individuals, and people who reside in rural areas remain underrepresented in clinical trials (EDICT, 2008). This minimal participation has been attributed to a number of factors, including stringent eligibility criteria and physicians' perspectives and awareness of clinical trials (as described in the preceding sections), as well as inadequate and uncertain insurance coverage and patient attitudes about and knowledge of clinical trials (as further delineated below) and complex social and institutional barriers delaying the implementation of clinical trials (see Chapter 3).

Patient Participation in Clinical Trials

A variety of factors prevent robust patient participation in clinical trials (see Table 4-2). One survey demonstrated that a majority of cancer patients either are unaware of the possibility of participation in clinical trials or are unsure that participation in clinical trials is an option for them (HarrisInteractive, 2001). However, surveys indicate that once they are informed about clinical trials and their eligibility for participation, people are interested in participating in clinical trials. Of the 85 percent of cancer patients who were unaware or unsure that participation in clinical trials was an option, about 75 percent said that they would have been willing

TABLE 4-2 Why Cancer Patients Who Are Aware of Clinical Trials Do Not Participate

Percent Who Responded "Major Reason"	"Aware" But Did Not Participate Percent
Belief that they would be better off taking "the standard treatment"	37
Fear that they might get a placebo rather than actual treatment	31
Belief that "the standard treatment" would be more effective	30
Fear of being treated "like a guinea pig"	22
Distance they would have to travel to obtain treatment	21
Belief that the cost of treatment would not be covered by insurance	20
Amount they would have to pay out-of-pocket	18
Fear that their doctor would not be able to choose best treatment	18
The effort involved in the informed consent process	6

SOURCE: HarrisInteractive, 2001. Reprinted, with permission, from HarrisInteractive, 2001. Copyright 2001 by Harris Interactive Inc.

to enroll (HarrisInteractive, 2001). A patient advocate has noted that the general population is not usually aware of and does not pay attention to clinical trial awareness campaigns until they are afflicted with a condition with inadequate treatment options (IOM, 2009b). Other surveys also suggest that if they are asked to participate, adults are willing to participate in clinical trials. In a survey of American adults, 32 percent indicated that they would be very willing to participate in cancer clinical trials if they were asked to do so, and 38 percent of adults said that they are inclined to participate if they were asked but have some questions or reservations about participating (Comis, 2003). One study determined that a lack of awareness and low prioritization of clinical trials by physicians, policy makers, and patients remain significant challenges to advancing effective clinical trials (C-Change and Coalition of Cancer Cooperative Groups, 2006).

People who do enroll in clinical trials do so for different reasons. According to a review of the literature by Comis and colleagues (Comis et al., 2003), a combination of altruism and hope for better treatment motivates patients to enroll in clinical trials. These decisions are complex and multifaceted and involve a weighing of beliefs for and against the trial by using a "personal balance account" (Verheggen et al., 1998). Factors that influence participation include patient and physician attitudes about clinical trials, the informed-consent process, an unwillingness to receive a placebo treatment, and a perception of personal benefit (reviewed by Comis et al. [2003] and Cox and McGarry [2003]). The geographic distance from a site offering a clinical trial, concerns over toxicity, time constraints, eligibility requirements, and inconvenience to the patient may also contribute to decisions over clinical trial participation (Melisko et al., 2005). The majority of

TABLE 4-3 Positive Experiences with Clinical Trials

Percent Who	Clinical Trials Participants Percentage
Say they were treated with dignity and respect	97
Rate the quality of care received "excellent" or "good"	97
Describe their overall experience as positive	93
Do not feel that they were treated like a "guinea pig"	82
Believe they were not subjected to more tests and procedures than they thought necessary	81
Would recommend participation to someone else with cancer	76

SOURCE: HarrisInteractive, 2001. Reprinted, with permission, from HarrisInteractive, 2001. Copyright 2001 by Harris Interactive Inc.

clinical trial participants indicate that they viewed their experience in the trial positively (HarrisInteractive, 2001) (Table 4-3).

In addition to a low general rate of participation in clinical trials, individuals who are members of racial and ethnic minority groups are underrepresented in clinical trials (Figure 4-1), which may be related to historical, educational, cultural, linguistic, economic, geographic, social, and health system barriers (Colon-Otero et al., 2007; IOM, 1999, 2009a; Underwood, 2000). This low rate of participation may prevent segments of the population from benefiting from advances in cancer research and creating uncertainties over the applicability of research findings to diverse populations (Colon-Otero et al., 2007). According to an IOM report:

> The inclusion of ethnic minority and medically underserved individuals in clinical trials and the dissemination of information to their community and health care providers are critical links connecting scientific innovation with improvements in health and health care delivery. Enhancement of these links is clearly within the purview of NCI and NIH. Although many factors pose challenges to such improvements (e.g., mistrust of the scientific establishment among many members of ethnic minority communities), without a concerted effort to enhance this process, ethnic minority and medically underserved communities will continue to lag behind the American majority in benefiting from the tremendous recent scientific achievements and medical breakthroughs in cancer prevention, treatment, and control. (IOM, 1999)

Physician-patient communication is critical to improving clinical trial participation. To communicate effectively with their patients, physicians must meet ethical mandates, convey medical knowledge, and demonstrate credibility, without creating misunderstandings or overwhelming their

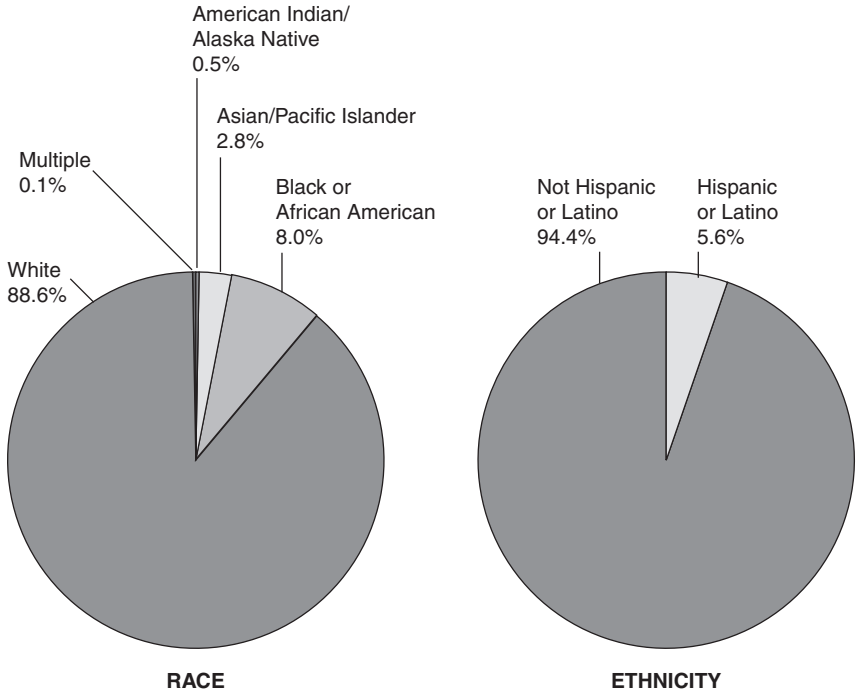

FIGURE 4-1 Enrollment by race and ethnicity for publicly funded NCI clinical trials.
SOURCE: Coalition of Cancer Cooperative Groups, 2006.

patients (Albrecht et al., 2008). A physician's decision to not offer a patient the possibility of participation in a clinical trial is a significant reason for low rates of patient accrual (reviewed by Ellis, 2000). One study found that in two urban NCI-designated comprehensive cancer centers, patients were offered clinical trials in only 20 percent of the interactions, but when the patients perceived that they were offered a trial, 75 percent of patients assented to trial participation (Albrecht et al., 2008).

Researchers, physicians, patient advocates, and policy makers have emphasized the importance of patient participation in clinical trials. However, among the general public, few people are aware of clinical trials. It is thus important that patients have access to information about clinical trials and the importance of participation. Educational initiatives about clinical trials may facilitate understanding about clinical research and dispel misconceptions. For example, patients may incorrectly assume that cancer clinical trials often use placebos as a comparator, but the comparator is usu-

ally the current standard of care. With education initiatives that promote clinical trials as a treatment option, it is important that clinical trials actually be available and accessible. For instance, it may be an insurmountable burden, in terms of both time and cost, for a patient to travel to a cancer center for participation in a clinical trial. Trial sites in community settings, such as through the Community Clinical Oncology Program, could ensure higher rates of access. As indicated earlier in this chapter, a centralized, accessible, up-to-date registry could improve patient access to information about clinical trials and help patients locate the trials being conducted in their area. **In addition, the committee recommends that CMS, federal and state health benefits plans, and private health insurers work with health care providers to educate patients more effectively about the availability, payment coverage, and value of clinical trials.**

Insurance Coverage

A lack of insurance coverage for participation in clinical trials is also a barrier preventing robust provider and patient participation. Compared with the rate of insurance among the general U.S. population, patients enrolled in Cooperative Group clinical trials are significantly less likely to be uninsured (Table 4-4) (Sateren et al., 2002). Those who are insured may also face barriers because coverage of care in clinical trials is variable and may be uncertain. Patients who are interested and willing to enroll in a trial may decline because of an inability to pay for care that is not or that may not be covered. Others may still enroll, but they then might experience significant financial hardship as a result.

A large proportion of the care provided to cancer patients enrolled in clinical trials is considered routine and would be eligible for reimbursement outside of a trial (IOM, 2000). However, it may be problematic to deter-

TABLE 4-4 Participation in Cooperative Group Clinical Trials by Type of Insurance Coverage (Percent)

Insurance Type	U.S. Population	Clinical Trial Population
Private	70.2	71.6
All government	24.3	32.5
Medicare	13.2	20.8
Medicaid	10.3	9.5
Military	3.2	3.2
Total covered	83.7	94.6
Not covered	16.3	5.4

SOURCE: Sateren et al., 2002. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved. Sateren, W. et al: *Journal of Clinical Oncology* Vol. 20(8), 2002:2109–2017.

mine the costs of routine care associated with clinical trials because there may be uncertainty about what items and services will be covered. According to ACS CAN, "one of the fundamental challenges arises from the fact that routine care may be difficult to define precisely and may vary substantially by geographic region and type of provider" (ACS CAN, 2009).

Many health insurance policies generally exclude coverage for participation in clinical trials. Additionally, the Federal Employees Health Benefit Program does not require participating insurers to cover the costs of routine care incurred during participation in a clinical trial (ACS CAN, 2009). Insurers may deny coverage associated with clinical trial participation because they consider clinical trials to be experimental and want to limit coverage of therapies with little experimental evidence of effectiveness (GAO, 1999; IOM, 2009b). Insurers may also be reluctant to cover the costs of routine care related to clinical trial participation because they believe that clinical trial participants incur substantially higher costs than those receiving the standard-of-care therapy (Goldman et al., 2003). However, several studies have suggested that clinical trial participation is associated with only modest increases in costs (Bennett et al., 2000, 2001; Goldman et al., 2001, 2003).

Some insurers have altered policies to cover care related to participation in clinical trials (Bennett et al., 2001; Kolata and Eichenwald, 1999). In a recent IOM workshop, one insurer noted the value of clinical trial participation because it provides a standardized protocol and defined treatment plan for patients, whereas the treatment received through usual clinical practice may be highly variable (IOM, 2009b). In January 2010, the major insurers of Florida, representing about 90 percent of Florida's group health insurance market, signed the Florida Clinical Trial Compact, agreeing to cover the costs of routine care for those participating in Phase II to IV cancer clinical trials that are approved by NIH, NCI, FDA, the Department of Defense, or accredited Florida medical schools and specialty hospitals (Colavecchio, 2010; Florida Clinical Trial Compact, 2010). Likewise, four other states, Georgia, Michigan, New Jersey, and Ohio, have special agreements to voluntarily provide coverage for clinical trials (see Table 4-5).

In addition, some insurers acknowledge that they pay for care related to participation in a clinical trial by unknowingly authorizing services that are part of a clinical research protocol (IOM, 2000; Mechanic and Dobson, 1996). Participants in an IOM workshop suggested that payment for care related to clinical trial participation without prior authorization by the insurance plan carries risks. If the insurer were to discover that the person was participating in a clinical trial, the potentially denied care costs could be significant (IOM, 2009b).

TABLE 4-5 States with Special Agreements to Cover Routine Care Costs Associated with Clinical Trial Participation

State (Year Became Effective)	Who Is Required to Pay?	What Services or Benefits Are Covered?	Other Criteria
Florida (2010)	All major insurers	Routine patient care costs associated with Phase II through IV clinical trials.	Trials include those that involve a drug that is exempt under federal regulations from a new drug application or those that are approved by one of the following bodies: a Cooperative Group of the National Institutes of Health, the Food and Drug Administration (in the form of an investigational new drug application), the U.S. Department of Defense, the U.S. Department of Veterans Affairs, or the National Cancer Institute.
Georgia (2002)	All major insurers	Routine patient care costs associated with Phase I through IV cancer clinical trials.	Trials include those that involve a drug that is currently exempt under federal regulations from a new drug application or those that are approved by specified federal agencies or a local institutional review board. Provides for the coverage of cancer screens and examinations in accordance with the most recently published guidelines and recommendations established by any nationally recognized health care organization.
Michigan (2002)	Private insurance plans, health maintenance organizations, and Medicaid	Routine patient care costs associated with Phase II and III cancer clinical trials.	Coverage for Phase I trials is under consideration.
New Jersey (1999)	All insurers	Routine patient care costs associated with all phases of cancer clinical trials.	
Ohio (1999)	State employees on Ohio Med Plan	Routine patient care costs associated with Phase II and III cancer treatment clinical trials.	Preauthorization is required for clinical trial participation.

SOURCES: Colavecchio, 2010; Florida Clinical Trial Compact, 2010; NCSL, 2009.

Employer-Sponsored Plans Subject to ERISA

Laws in 23 states have mandated coverage of routine care costs related to participation in a clinical trial (NCSL, 2009). However, state laws do not affect the majority of individuals covered by employer-sponsored health plans. Plans affecting about 131 million individuals are primarily regulated by federal law through the provisions of the Employee Retirement Income Security Act of 1974 (ERISA) (Chaikind, 2003). ERISA provides federal jurisdiction over the regulation of employee benefits plans (such as private-sector, employer-sponsored health plans) and preempts state laws mandating expanded access to health care through workplace coverage for some plans (Butler, 2000). ERISA plans are not required to cover the costs of routine care for patients on clinical trials.

The interpretation of ERISA has generally divided employer-sponsored health plans into two different types: self-insured plans, in which the employer rather than the insurer assumes the risk for paying for covered services, and insured employer plans, or purchased insurance. About 67 million people are covered by self-insured plans, which are preempted from state law and are covered only by ERISA. For the 64 million people who are covered by insured employer plans, federal law preempts state laws that "relate to" employee benefits plans but state laws apply for issues involving the business of insurance. Various interpretations of insured employee plans have blurred what issues are applicable to state laws. Traditionally, the courts have favored preempting state law for most employee benefits situations, but this may be changing (Chaikind, 2003). Because state laws mandating routine coverage for the care associated with participation in a clinical trial will not result in universal coverage, federal law is needed. In March 2009, Senator Edward Kennedy and 21 cosponsors introduced the 21st Century Cancer Access to Life-Saving Early Detection, Research, and Treatment (ALERT) Act.[9] Among other actions, the bill would amend ERISA to expand access to cancer clinical trials by requiring health plans governed by the requirements of ERISA to continue providing coverage for routine care, regardless of enrollment in a clinical trial. Likewise, an amendment to the U.S. Senate version of the health care reform bill would require insurers to cover routine costs of care for approved clinical trials for patients with cancer or other life-threatening diseases.[10] The Access to Cancer Clinical Trials Act of 2009 (H.R. 716/S. 488) would amend ERISA to prohibit a group health plan from (1) denying eligible participant or beneficiary participation in cancer clinical trials that are federally funded or

[9]The 21st Century Cancer ALERT Act, S.B. 717, 111th Cong., 1st Sess. (March 26, 2009).

[10]Patient Protection and Affordable Care Act, H.R. 3590, 111th Cong., 1st Sess. (December 24, 2009).

conducted under an investigational new drug application reviewed by FDA; (2) denying, limiting, or imposing additional conditions on the coverage of routine patient costs related to participation in a clinical trial; and (3) discriminating against an individual on the basis of participation in a clinical trial.[11] This legislation has also been introduced in previous legislative sessions, including those in 2008, 2007, 2006, 2003, 2001, and 1999.[12] **Reflecting the language of these bills, the committee recommends that the U.S. Congress amend ERISA to prohibit health plans from denying (or from limiting or imposing additional conditions on) coverage for routine care associated with clinical trial participation.[13]**

Medicare and Medicaid Coverage

Before 2000, Medicare and Medicaid beneficiaries were not reimbursed for expenses related to their participation in a clinical trial because the Health Care Financing Administration (the prior name of CMS) believed that the original Medicare legislation did not give the Health Care Financing Administration the authority to provide reimbursement for costs associated with clinical trials (Arnold and Vastag, 2000; IOM, 2009b). In 2000,

[11] Access to Cancer Clinical Trials Act of 2009, H.R. 716, 111th Cong., 1st Sess. (January 27, 2009). Access to Cancer Clinical Trials Act of 2009, S. 488, 111th Cong., 1st Sess. (February 26, 2009).

[12] Access to Cancer Clinical Trials Act of 2008, S. 2999, 110th Cong., 2nd Sess. (May 8, 2008). Access to Cancer Clinical Trials Act of 2007, H.R. 2676, 110th Cong., 1st. Sess. (July 24, 2007). Access to Cancer Clinical Trials Act of 2006, H.R. 6247, 109th Cong., 2nd Sess. (September 28, 2006). Access to Cancer Clinical Trials Act of 2003, H.R. 2021, 108th Cong., 1st Sess. (May 7, 2003). Access to Cancer Clinical Trials Act of 2001, H.R. 967, 107th Cong., 1st Sess. (March 8, 2001). Dr. Sydney E. Salmon Access to Cancer Clinical Trials Act of 1999, H.R. 3110, 106th Cong., 1st Sess. (October 19, 1999).

[13] After the committee had completed its report, the Patient Protection and Affordable Care Act (H.R. 3590) was signed into law by President Barack Obama on March 23, 2010, which provides coverage of routine care costs for individuals participating in approved clinical trials. According to this Act, a group health plan or a health insurance issuer "may not deny (or limit or impose additional conditions on) the coverage of routine patient costs for items and services furnished in connection with participation in the trial." As stipulated by the legislation, routine patient care costs include all items and services consistent with the coverage provided in the plan (or coverage) that is typically covered for a qualified individual who is not enrolled in a clinical trial. Approved clinical trials include Phase I–IV studies relating to the prevention, detection, or treatment of cancer or other life-threatening diseases or conditions that are either (a) federally funded; (b) a study or investigation conducted under an investigational new drug application reviewed by FDA; or (c) a drug trial that is exempt from having such an investigational new drug application. This provision will go into effect in 2014 and is intended to apply to both types of ERISA plans as well as plans offered by the Federal Employees Health Benefits Program. The Patient Protection and Affordable Care Act, H.R. 3590, 111th Cong., 2nd sess., Coverage for Individuals Participating in Approved Clinical Trials, § 2709 (March 23, 2010).

an IOM committee recommended that Medicare provide reimbursement for the costs of routine care for patients in clinical trials (IOM, 2000), and President Bill Clinton signed an executive order directing the Medicare program to provide reimbursement for the costs of routine care associated with participation in a clinical trial (Arnold and Vastag, 2000). Medicare began reimbursing routine care costs for beneficiaries enrolled in qualified clinical trials through a National Coverage Decision (NCD). In 2007, CMS reconsidered the 2000 NCD, clarified the policy, and also introduced the Coverage with Evidence Development program, which enables CMS to cover a medical intervention with the condition that the agency may concurrently collect data on the intervention while reimbursing it (CMS, 2009).

In an effort to extend reimbursement for cancer therapy, in 2005 Medicare made an NCD that covered the off-label use of four anticancer drugs, but coverage was restricted to nine trials sponsored by NCI (NCI, 2009a). To reduce the uncertainty over what Medicare would cover, NCI and CMS developed billing instructions and explicit information about what costs Medicare would cover and what costs the sponsor of the clinical trial would cover (Table 4-6) (IOM, 2009b). An initial analysis of individuals enrolled in these nine trials found that Medicare-eligible subjects comprised between one-fifth and one-third of the participants currently enrolled, whereas traditionally, only about 13 percent of people enrolled in clinical trials are aged 65 years and older (IOM, 2009b).

However, beyond those nine trials, inconsistencies in Medicare coverage continue because each CMS contractor is allowed to determine whether a particular item of service is considered standard of care, or if procedures in a clinical trial fall within the "reasonable and necessary" standard (IOM, 2009b). Likewise, beneficiaries who participate in Medicare Advantage

TABLE 4-6 Comparison of Medicare Policies

Question	2000 Clinical Trials Policy	2005 Anticancer Drug National Coverage Decision
What kind of costs are covered?	Routine costs associated with the patient's medical care in the clinical trial would be covered.	Both routine and nonroutine costs associated with the patient's care in any of nine designated trials are covered. An example would be an additional laboratory or imaging test required by the study protocol for data analysis.
Does the policy pay for off-label use of anticancer drugs?	Coverage for off-label use varies depending on whether the trial in question meets the policy's requirements.	Yes. In the nine designated trials, off-label use is covered of anticancer drugs.

SOURCE: NCI, 2009a.

plans[14] face 20 percent coinsurance for drugs and may be unable to afford the expensive new drugs often used in clinical trials.[15] Because of the high rate of coinsurance, Medicare Advantage beneficiaries are underrepresented in clinical trials (Fitterman, 2008; Lin et al., 2008). In addition, Medicare Advantage copayments make it difficult to mask participants and providers to their treatment if the copayments differ between the investigational items and services.

Medicare Part D plans may also be limiting access to cancer therapeutics. According to Avalere Health and the American Cancer Society, cancer patients enrolled in Medicare Part D plans spend more on copayments and face increased restrictions on access to orally administered cancer drugs. From 2006 to 2009, Medicare stand-alone prescription drug plans have been shifting name-brand orally administered cancer drugs to higher formulary tiers, requiring beneficiaries to pay from 26 to 35 percent of the cost (Murphy et al., 2008). Plans are also increasing the number of drugs requiring prior authorization for coverage to control access to orally administered cancer therapeutics. Geography and the prescription drug plan that a person chooses can influence how much a beneficiary will pay out of pocket for orally administered cancer therapeutics. According to modeling simulations conducted by Avalere Health and ACS CAN, hypothetical drug regimens for a woman with breast cancer could vary from $1,985 for the American Association of Retired Persons MedicareRX Saver in Florida to $2,551 for the Humana Part D Plans Standard in California (Co-payments to rise as access to drugs tightens for patients on Medicare Part D, 2008; Murphy et al., 2008).

Third-Party Payment Policies and Clinical Trial Participation

In 2009, the Agency for Healthcare Research and Quality (AHRQ) issued a technology assessment report that examined the impact that third-party payment policies have on clinical trials and evidence-based medicine. Overall, the AHRQ report found that the lack of a national consensus regarding the financial responsibility for clinical trial-related health care

[14] The Balanced Budget Act of 1997 expanded private plan options for Medicare beneficiaries instead of the traditional Medicare fee-for-service plans (Parts A and B). Initially known as Medicare+Choice, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 added prescription drug coverage to these plans and renamed them Medicare Advantage (Part C). Although the majority of the 45 million Medicare beneficiaries are enrolled in the fee-for-service program, 22 percent of beneficiaries (about 10.2 million individuals) are enrolled in a private Medicare Advantage plans (KFF, 2009).

[15] Coinsurance is a provision of some insurance policies requiring an insured individual to share in the cost of certain expenses. Coinsurance is usually expressed as a percentage of the cost, whereas a copayment (a form of coinsurance) is usually expressed as a fixed amount.

costs results in uneven reimbursement policies, which may hamper patient recruitment and negatively affect evidence-based medicine (AHRQ, 2009). Specifically, the report found, "[v]arious plausible scenarios are supported by anecdotal evidence, though data do not exist to describe and quantify the actual impact of payment policy on clinical trial participation" (AHRQ, 2009). These scenarios include the following:

- when third-party payors provide reimbursement for a diagnostic or therapeutic treatment outside a clinical trial setting, patients may be less likely to participate in a trial assessing that intervention;
- if third-party payors initiate coverage for an intervention under study while clinical trials are still accruing patients, enrollment may slow down or stop because patients may lose the financial incentive to participate and may opt to avoid the extra time or demands of clinical trial participation (such as filling out questionnaires);
- if an intervention becomes covered outside of a trial but is not reimbursed for patients enrolled in the trial, patients may be less willing to enroll or continue participation;
- when two arms of a trial with two different interventions have distinct payment structures, patients may take financial factors into account in their decisions to participate or not; and
- third-party payment structures may contribute or may be perceived to contribute additional financial and time burdens to people who participate in trials (AHRQ, 2009).

Uncertainty over insurance coverage has the potential to decrease provider and patient participation in clinical trials. However, third-party payment policies aligned with participation in high-quality clinical trials have the potential to improve treatment and sometimes reduce the costs of care associated with less-effective treatments: "A paradox exists in reimbursement policies in which insurers may refuse to cover a promising new therapy because it is available only through clinical trials while covering what is considered standard treatment even though it may often be ineffective and sometimes more expensive" (Bennett et al., 2001).

If cancer care is to be evidence based and relevant to the diverse cancer patient population, it is important for coverage policies to encourage rather than deter patient enrollment in clinical trials. **In recognition of these issues, the committee recommends that health care payment policies value the care provided to patients in clinical trials and adequately compensate that care. For example, CMS (via a national coverage decision), federal and state health benefits plans, and private health insurers should establish consistent payment policies to cover all patient care costs (except for study-related costs, such as study drugs, devices, and tests, which should be paid for by**

the manufacturer) in clinical trials approved through the NCI prioritization mechanism, without having to pay for experimental therapies administered to patients outside of a clinical trial. Any such limitation in coverage should not affect off-label use that is backed by evidence from clinical trials published in the scientific literature, as evidence-based off-label use constitutes standard of care for many cancer therapies and is therefore not experimental.

As a quid pro quo for improved coverage of the care received as a part of participation in clinical trials, insurers should be able to eliminate coverage of experimental therapies delivered outside of the clinical trial setting. Currently, many patients who are not enrolled in trials receive experimental therapy and expect coverage for it. The committee's approach is analogous to the "coverage with evidence development" mechanism that CMS has occasionally used, in which coverage is provided only within the context of a clinical trial. However, any such limitation in coverage should not affect off-label indications backed by evidence from clinical trials published in the scientific literature, as off-label use constitutes the standard of care for many cancer therapies and is therefore not experimental.

SUMMARY

The recommendations in this chapter support two of the committee's goals: (1) incentivize participation of patients and physicians in clinical trials, and (2) improve the prioritization, selection, support, and completion of cancer clinical trials. On the basis of the review of the information described in this chapter, the committee agreed that incentives must be realigned to increase participation by clinical investigators and community physicians in publicly sponsored clinical trials and to increase access to clinical trials by patients. Likewise, the committee recognized that additional steps need to be taken to facilitate the implementation, conduct, and completion of the very best clinical trials.

A robust clinical trials infrastructure is largely dependent on a critical mass of patients and physicians willing to participate in clinical trials. However, current indications suggest that participation in clinical trials is the exception rather than the rule, both for patients and physicians. For clinical investigators, concerns about reimbursement, extensive regulatory burdens, and academic procedures regarding tenure, promotion, and career development can all deter participation in trials. Patient access to clinical trials is also an import issue to consider. Even if patients are eligible for trials and are informed about the option by their physicians, they may decline due to financial concerns, as coverage of patient care costs in clinical trials by health insurers is not consistent.

In terms of physicians, multiple stakeholders need to take steps to support the recruitment and retention of clinical investigators in both com-

munity practices and academia. An important first step is ensuring that physicians receive reimbursement commensurate with the level of time and resources involved in conducting clinical trial research. The many duties required of physicians and other key research staff, such as research nurses and clinical research associates, to participate in clinical trials are costly in terms of both time and resources. Even in cases where routine patient care in a clinical trial is covered by health insurers, the current payment policies do not reflect the additional time needed to enroll and follow patients in a trial. Before a trial can be opened at a particular site, much work must be done to ensure compliance with federal regulations governing human subjects research. Once a trial is opened, a significant amount of time is spent discussing potential trial options with patients. If a patient enrolls, the data collection and documentation requirements are substantially more onerous than for patients receiving standard therapy outside of a trial.

Therefore, NCI should increase the per case reimbursement rate. A substantial increase in the NCI per case reimbursement would constitute a major step toward aligning the incentives of physicians with those of their patients who wish to participate in clinical trials. The per case reimbursement has been set at $2,000 since 1999, even though the median costs are estimated at $3,500 to $6,000 per patient. When the discrepancy between the per case reimbursement and the actual cost of participation is excessive, as it is now, it becomes a major disincentive to participation. **NCI should also provide funding to site and trial principal investigators to cover the time they need to develop and oversee approved clinical trials.** The provision of funds for principal investigators to cover the time needed to develop and oversee approved trials could improve the speed and quality of trials and encourage greater participation. **In addition, the American Medical Association should establish new CPT codes, reimbursed by CMS, private insurers, and other third-party payors, to pay an enhanced reimbursement for offering, enrolling, managing, and following a patient in a clinical trial.** New CPT codes, with a higher reimbursement rate that acknowledges the additional time and resources needed to counsel and care for a patient in a clinical trial, would address an important deterrent to physician participation in clinical trials. With a proper definition of eligible trials, use of such a code could be easily audited.

Ensuring that physicians are recognized, rewarded, and appropriately trained in clinical trial research is also essential to encouraging participation. **All stakeholders, including academic medical centers, community practices, professional societies, and NCI, should work to ensure that clinical investigators have adequate training and mentoring, paid protected research time, the necessary resources, and recognition.** Ultimately, the inability to recruit, train, and retain a sufficient number of talented clinical investigators will compromise the ability to conduct clinical trials in the

United States, to the detriment of the U.S. biomedical research enterprise and to patients, those who participate in clinical trials as well as those who do not. Clinical trials help to raise the standard of care in the community by setting examples, and they have educational and training value for the oncologists involved, as physicians gain early knowledge of new drugs and gain experience with delivering complex therapies. One way to recognize investigators is through a certification program. **NCI should work with a nonprofit foundation to develop a certification program and registry, as recommended by the CTWG.** A certification program for all research staff (including physicians, nurses, clinical research associates, pharmacists, etc.) would recognize the valuable contributions these professionals make to improving patient care.

In addition, academic medical centers should develop policies and evaluation metrics that recognize and reward clinical and team research in promotion and tenure decisions. The large-scale, multi-institutional trials that are the hallmark of the Cooperative Group Program require a team approach to research. However, career advancement in the field has traditionally focused on individual accomplishment. Collaborative work is not adequately recognized, rewarded, or supported in the current system. Furthermore, clinical investigation is often accorded less value than either basic research or patient care. This must change if we wish to have talented individuals embark on a career that entails active participation in clinical investigation, in cancer as well as other diseases. **NCI should recognize and reward Cooperative Group efforts in Cancer Center Support Grant (CCSG; P30) site visits, and allow the CCSG research base to include the federal per case funding required by cancer centers that participate in support of Cooperative Group trials.** CCSG review criteria do not adequately incentivize participation in multi-institutional Cooperative Group trials, and instead favor individual investigator-initiated trials emerging from basic discoveries within a cancer center's own institution. Recognizing the per case reimbursements for Cooperative Group Trials in the CCSG assessment of a cancer center's funding base would acknowledge the importance of patient accrual in these trials and encourage broader participation at those centers. Clinical research is a complex endeavor that requires training, mentoring, and paid time set aside for research to master and apply the skills needed to undertake innovative trials.

If cancer care is to be evidence-based and relevant to the diverse patient population, it is important for coverage policies to encourage rather than deter patient enrollment in trials. **Therefore, the committee recommends that health care payment policies value the care provided to patients in clinical trials and adequately compensate that care.** Inadequate health care coverage is a major deterrent to participation in trials, for patients as well as physicians. Health care insurers traditionally have not paid for "experi-

mental therapy." However, much of the care provided to cancer patients is similar regardless of whether the patient is receiving a standard or experimental drug. Some insurers and states acknowledge this and reimburse the routine clinical care of patients enrolled in trials, while others do not. Policies at CMS regarding coverage of care in clinical trials have been in flux recently, and, absent National Coverage Decisions, may not be nationally uniform because fiscal intermediaries and carriers have some discretion on coverage, which can cause regional variation and inconsistency. Furthermore, the provisions of the ERISA, which places the regulation of employee benefit plans (including health plans) primarily under federal jurisdiction for about 131 million people, preempts state laws governing such things as access to care and mandated coverage.

Thus, coverage of care in clinical trials is variable and may be uncertain. Patients who are interested and willing to enroll in a trial may decline due to an inability to pay for care that is not, or may not be, covered. Others might still enroll, but then may experience significant financial hardship as a result. If such patients drop out of the trial, the scientific integrity of the trial can be compromised due to inferential problems that result from missing data. In order to facilitate patient and physician participation in clinical trials, more consistent policies regarding patient care costs are needed. **The committee recommends that CMS (via a national coverage decision), federal and state health benefits plans, and private health insurers establish consistent payment policies to cover all patient care costs (except for study-related costs, such as study drugs, devices, and tests, which should be paid for by the manufacturer) in clinical trials approved through the NCI prioritization mechanism, without having to pay for experimental therapies administered to patients outside of a clinical trial.** Currently, many patients who are not enrolled in trials receive experimental therapy and expect coverage for it. **Any such limitation in coverage should not affect off-label use that is backed by evidence from clinical trials published in the scientific literature, as evidence-based off-label use constitutes standard of care for many cancer therapies and is therefore not experimental.**

In addition, the U.S. Congress should amend ERISA to prohibit health plans from denying (or from limiting or imposing additional conditions on) coverage for routine care associated with clinical trial participation. The committee's recommended approach is analogous to the "coverage with evidence development" mechanism that has occasionally been used by CMS, in which coverage is only provided within the context of a trial.

However, taking steps to align the incentives of patients and providers to participate in clinical trials may not be effective unless more is done to educate patients about the availability and value of clinical trials. **The committee recommends that CMS, federal and state health benefit plans, and private health insurers work with health care providers to educate patients**

more effectively about the availability, payment coverage, and value of clinical trials. Educational efforts should focus on making the general population more aware of clinical trials. One reason is that it can be difficult for patients to sort through a large volume of new information and make complex decisions having just received a diagnosis of a life-threatening illness. Patients often lack comprehensive and reliable information about clinical trials and may not be able to identify trials they might be eligible for. Patients value reliable information from trusted sources, including family members, so appropriate education efforts could provide useful information that would allow patients to make informed choices about trial participation. In addition, as noted in more detail below, user-friendly electronic tools would increase awareness of trials and make it easier for physicians and patients to enroll in the most appropriate studies.

To ensure the rapid conduct and completion of clinical trials, the enrollment of patients onto clinical trials must be improved. At the same time, it is essential that clinical trials conducted by the Cooperative Groups maintain high quality standards. **Thus, NCI, Cooperative Groups, and physicians should take steps to increase the speed, volume, and diversity of patient accrual and to ensure high-quality performance at all sites participating in Cooperative Group trials. In addition, they should encourage greater enrollment in high-priority trials, regardless of where the trial originated.** Currently, the majority of patients who participate in clinical trials are enrolled by a small percentage of participating sites. Many sites enroll only a few patients in Cooperative Group clinical trials—enough to maintain their status as investigators. These circumstances can contribute to the underrepresentation in clinical trials of minority and underserved populations. Given the importance of trials in generating the evidence needed for making the best treatment decisions, more physicians should be encouraged to include trial participation in their clinical practice. As mentioned previously, providing adequate case reimbursement would help to align physician and patient incentives and facilitate higher accrual at participating sites. However, another obstacle to increasing patient enrollment is that physicians may lack timely and easy-to-access information about clinical trials that would be appropriate for their patients. Some public databases with information about clinical trials exist, but in current form, may not adequately serve the information needs of physicians and patients as they are not in the normal workflow of a busy clinical practice. **Therefore, the committee recommends that NCI, Cooperative Groups, and physicians develop electronic tools that cue physicians practicing oncology via EMR systems about trials for which a particular patient is eligible.** User-friendly electronic tools, available with the right features for physician workflow, would increase awareness of trials and make it easier for physicians and patients to enroll in the most appropriate studies. Complementing increased

awareness, the committee encourages physicians to incorporate clinical trial involvement into their practices. **Physicians should strive to make participation in clinical trials a key component of clinical practice and to achieve the ASCO exemplary attributes for academic and community clinical trial sites, including high accrual rates of 10 percent or more.**

Eligibility criteria present another challenge to increasing enrollment. Historically, stringent eligibility criteria have excluded many patients, including, for example, those with prior cancers or certain prior treatments. However, it has been argued that adoption of less-restrictive eligibility criteria for most studies would permit more rapid accrual and also allow broader generalizations, better mimic medical practice, and reduce complexity and costs, without compromising patient safety or requiring major increases in sample size. **To facilitate accrual speed, volume, and diversity, NCI, Cooperative Groups, and physicians should encourage the development of patient eligibility criteria that allow the broadest participation possible.** Greater involvement by patient advocates could help to facilitate this change. **Thus, the committee encourages greater participation of patient advocates in trial concept development and accrual planning, and partnerships with patient advocacy organizations to support accrual efforts.** Advocates also provide valuable input to study design and procedures, safety and confidentiality issues, feasibility, informed consent processes, and other factors important to potential research participants to help facilitate the development, implementation, and recruitment processes.

Ensuring consistent quality at participating trial sites is also important. Site credentialing requirements vary among the Cooperative Groups, making it difficult for sites that wish to engage with multiple groups. **Therefore, the committee recommends that NCI, Cooperative Groups, and physicians establish a centralized credentialing system for participating sites and eliminate investigators and sites with low rates of accrual or inadequate data management skills or quality.** A centralized credentialing system, perhaps outsourced to an independent entity, would increase consistency and quality across sites, and eliminate the burden of re-credentialing. Such a system would also facilitate greater enrollment in high-priority trials, regardless of where the trial originated, because sites would be credentialed to participate in any Cooperative Group Trial. Moreover, elimination of low accruing sites would reduce costs and improve the efficiency of the trials system.

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Appendix A

Previous and Ongoing Analyses Undertaken by NCI

In the 50 years of its existence, the Cooperative Group Program has advanced the treatment of cancer and the conduct of clinical research. Despite these successes, the Cooperative Group Program has continued to face a number of challenges that threaten its effectiveness. To further explore the challenges and opportunities confronting the Cooperative Groups, multiple evaluations of the Program have been conducted. Two of the most recent reviews of the Cooperative Group Program include the Armitage report (1997) and a review by the Clinical Trials Working Group (CTWG) in 2005. As a result of the CTWG report, the National Cancer Institute (NCI) established the Operational Efficiency Working Group (OEWG) to provide recommendations for improving the time from concept approval to enrolling patients on a clinical trial. In addition to these specific recommendations aimed at the Cooperative Group Program, the Program has also been influenced by other working group recommendations, including the Translational Research Working Group (TRWG) report recommendations.

REVIEWS OF THE COOPERATIVE GROUP PROGRAM

Armitage Report

In 1996, the NCI director and the chair of the Extramural Board of Scientific Advisors commissioned an external review of the Cooperative Group Program in response to concerns that the clinical trials portfolio had become increasingly inefficient and unresponsive to evolving needs.

The Clinical Trials Review Group was asked to recommend changes to the current system that would (1) take advantage of the most promising opportunities in therapy and diagnosis; (2) prioritize the most important research questions so that they can be explored in the fastest possible time; (3) improve the organization, funding, review, and cooperation in the Cooperative Group Program; and (4) attract both patients and researchers to participate in clinical trials.

The review committee met six times over an 11-month period and included experts from academic research institutions, cancer centers, community oncology practices, cancer patient advocacy groups, and the National Institutes of Health. The committee released its findings, known as the Armitage report, after its chair, James Armitage, in 1997 (NCI, 1997). The report made the recommendations regarding review, funding, design, oversight, and administration of the NCI clinical trials system. A subsequent implementation committee report was completed in 1998.

Clinical Trials Working Group Report

In 2004, the NCI director established the CTWG to advise the National Cancer Advisory Board on the development, conduct, infrastructure, support, and coordination of cancer clinical trials across NCI. The CTWG was asked to develop recommendations to (1) optimize the NCI-supported clinical trials system by improving coordination and research infrastructure, (2) remove institutional and regulatory barriers that inhibit collaboration in clinical trials research, and (3) envision how clinical trials should use the tools of contemporary bioinformatics and molecular medicine.

The review committee conducted 7 face-to-face meetings and 10 group conference calls over a 16-month period and included experts from academic research institutions, community oncology practices, the pharmaceutical and biotechnology industries, cancer patient advocacy groups, NCI, the Food and Drug Administration (FDA), and the Centers for Medicare & Medicaid Services (CMS). The committee released its findings in 2005 (NCI, 2005b).

The committee proposed 22 recommendations to achieve four major goals for designing a more efficient national system for clinical trials conducted or supported by NCI, as follows: (1) better coordination, (2) prioritization based on solid science and the needs of patients, (3) standardized tools and procedures, and (4) improved operational efficiency (NCI, 2005b).

Recommendations

While the Armitage report had a broader focus than the CTWG report, including a focus on issues such as organization, prioritization,

participation, and funding, the CTWG report was more narrowly focused and emphasized coordination, collaboration, and the adoption of new technologies (Box A-1). Table A-1 lists the recommendations of both the Armitage and the CTWG reports, divided into several categories: data collection, standardization, and management; cooperation; process improvement; organizational and structural improvement; accrual; funding; and

BOX A-1
Comparison of the Armitage and Clinical Trials Working Group Committee Charges

- Armitage Report (1997)
  - Is the organization of the Cooperative Group Program (number, membership, trials portfolio) best serving the needs of the field?
  - How can the program ensure that the most promising clinical research opportunities and therapeutic questions are identified and addressed in the fastest possible time?
  - How can the program be organized to
    - effectively deal with increasing pressures to steer patients away from academic medical centers,
    - enhance laboratory-to-clinic and clinic-to-laboratory information,
    - ensure optimal peer review of Cooperative Group trials,
    - optimize links between industry and the Cooperative Group Program to maximize program productivity, and
    - effectively oversee and support the clinical trials program?
  - What funding mechanisms would provide the most research progress in the clinical trials program?
  - What is the best relationship between the clinical trials program and other research programs of NCI?
  - What options exist to ensure the continued training of clinical researchers?
  - What are the incentives/disincentives for participating in clinical trials and how can NCI ensure that clinical trials are available to all segments of the population?

- Clinical Trials Working Group (2005)
  - The CTWG was charged with developing recommendations and an implementation plan to optimize the NCI-supported clinical trials system by
    - improving coordination and research infrastructure,
    - removing institutional and regulatory barriers that inhibit collaboration in clinical trials research, and
    - envisioning how clinical trials should be conducted by using the tools of contemporary bioinformatics and molecular medicine.

SOURCES: NCI, 1997, 2005b.

TABLE A-1 Comparison of Prior Recommendations for the NCI Cooperative Group Program

	Armitage Report	Clinical Trials Working Group
Data collection, standardization, and management	• Cooperative Groups and cancer centers should have access to all relevant electronic databases and should be primary participants in the development and testing of the new NCI informatics system. • Data collection should be uniform among the groups: o Use the same protocol guidelines, o Simplify the eligibility criteria, o Standardize study endpoints, o Develop a common algorithm for protocol development, o Use the same common data collection forms, o Develop common toxicity criteria, o Develop common biostatistical principles, o Create a simplified common adverse drug reaction and adverse event reaction reporting system, and o Simplify informed-consent documents. • NCI should enlist industry and the clinical trial and patient communities to work with FDA to develop uniform standards and reporting requirements for clinical trials. • Entry criteria for all studies need to be simplified and broadened: a range, rather than absolute, set of parameters should be considered. • Data collection should be reduced to only data pertinent to study endpoints and patient safety. • Large, uncomplicated trials of common cancers with minimal data requirements and accrual goals large enough to see definitive treatment differences should be part of the Program's portfolio. • Tissue samples and other clinical data from intergroup trials should be stored and maintained.	• Create a comprehensive database that contains regularly updated information on all NCI-funded clinical trials. • Create a national cancer clinical trials information technology infrastructure, fully interoperable with NCI's Cancer Bioinformatics Grid, to improve the cost-effectiveness and comparability of results across trials and sites. • Develop a standards-setting process for measurement, analysis, and reporting of biomarker data in association with clinical trials to enhance data comparisons, reduce duplication, and facilitate data submission for regulatory approval. • In consult with industry and FDA, develop standard case report forms incorporating common data elements to improve information sharing among cancer researchers and to optimize data requirements.

Cooperation	• NCI should appoint a group to develop legal templates for interactions between universities, Cooperative Groups, and industry for material transfer agreements, clinical cooperative agreements, and Cooperative Research and Development Agreements (CRADAs).	• Develop commonly accepted clauses for clinical trial contracts with industry to reduce the lead time needed to open trials. • Realign NCI and academic incentives to promote collaborative team science.
Process improvement	• Cooperative Groups and the Cancer Therapy Evaluation Program (CTEP) need well-defined timelines for protocol development, approval, and activation and need to have clearly stated positive and negative consequences of meeting or not meeting timelines. • All groups participating in an inter-Group trial should be able to conduct direct registration and submit forms directly to the coordinating Group. • Amendments and addenda to trials should become the full responsibility of the Group conducting the study and should not require the approval of NCI (although they should be filed with NCI). • The interval for Cooperative Group renewal should be lengthened to 8 to 10 years for established Groups. • The separate protocol review processes of the Division of Cancer Treatment, Diagnosis and Centers (DCTDC) and the Division of Cancer Prevention and Control (DCPC) should be combined. • Cooperative Groups should be engaged as soon as possible in CTEP CRADA negotiations that require Group participation.	• Reduce institutional barriers to timely trial initiation. • Expand awareness of NCI-FDA expedited approval process to speed trial initiation. • Investigate integration of Phase II trials into the overall prioritization process to further coordinate the national clinical trials system. • Develop a funding prioritization process that ensures that critical correlative science and quality-of-life studies can be conducted in a timely manner. • Build a credentialing system for investigators and sites recognized by NCI and industry to allow faster trial initiation and to keep the investigative community abreast of legal, safety, and regulatory changes. • Promote the adoption of an NCI central institutional review board-facilitated review process to reduce the time and resources needed to open trials at individual sites.

continued

TABLE A-1 Continued

	Armitage Report	Clinical Trials Working Group
Organizational and structural improvement	• NCI should urge FDA to form a single oncology advisory committee with provision for obtaining the necessary expertise for ad hoc review. • Inter-Group trials should be harmonized and simplified. • The Decision Network needs to be publicized and would benefit from external input. CTEP must clarify its role in reviewing novel drugs with questionable patent status to better move agents toward clinical trials. • CTEP's role should depend on the type of agent studied: o For Phase II and III studies not involving new agents, CTEP should approve study concepts and collaboratively establish research priorities; CTEP's authority should otherwise be limited to regulatory and safety issues and prevention of unnecessary duplication. o For studies with investigational new agents, CTEP should retain its current legislated authority and responsibility, in partnership with industry and the Cooperative Groups. • For most prevention and control studies, the Groups should be provided with the authority to establish priorities and conduct studies. For large-scale cancer prevention and controlled Phase III studies, the DCPC or a combined DCTDC and DCPC review process should actively participate in concept approval and priority setting. • Treatment trials conducted through the Community Clinical Oncology Program (CCOP) mechanism should be transferred to DCTDC; cancer prevention studies conducted across the NCI clinical trials system should be the responsibility of the newly configured DCPC.	• Create an Investigative Drug Steering Committee to work with the NCI to enhance design and prioritization of early-phase drug development trials. • Create a network of scientific steering committees leveraging inter-Group, Cooperative Group, Specialized Programs of Research Excellence (SPOREs), and cancer center structures to work with NCI in the design and prioritization of Phase III trials to better allocate resources, increase scientific quality, and reduce duplication. • Create a clinical trials oversight subcommittee of the National Cancer Advisory Board to advise the NCI director on the conduct of clinical trials across the Institute. • Develop a coordinated NCI organizational structure to manage the entire clinical trials enterprise supported by the NCI.
Accrual	• High-quality patient-oriented public awareness campaigns presenting the value of clinical trials should be a priority.	• Increase patient and public awareness and understanding of clinical trials.

	• The public should have access to all information about ongoing clinical trials. • NCI should continue to improve efforts to recruit and retain members of minority groups, medically underserved populations, and elderly individuals in clinical trials and to tailor recruitment and retention approaches to address linguistic and cultural differences. • Representatives of patient and high-risk communities need to be integrated into the clinical trials decision-making process. • NCI-designated cancer centers should be encouraged to participate in Cooperative Group research and participation should be reviewed favorably in the cancer center review process. • NCI should develop strategies to convince payors that clinical trials are the preferred way to manage patients. • The informed-consent process must be modified and simplified, and NCI should work with the Office for Protection from Research Risks (now the Office for Human Research Protection) to develop a template for informed-consent forms for distribution to clinical scientists and the patient community.	• Increase minority patient access to clinical trials to improve the participation of underserved and underrepresented populations. • Increase community oncologist and patient advocate involvement in clinical trial design and prioritization, which will increase patient accrual and better address the practical and quality-of-life concerns in clinical trials.
Funding	• NCI should work with other governmental agencies and private organizations, including third-party payors, to determine costs associated with Phase I to IV clinical trials and should develop a plan for funding the research required to determine these costs. • NCI should increase funding to Cooperative Groups to fully recommended levels. • NCI should provide extra funds to the coordinating Group of an intergroup trial to cover additional expenses. • Funding should be based on costs of performing as a headquarters office, proportional to CCOP membership. • Systems for awarding credit and funding to institutions participating in intergroup studies must be developed.	• NCI should work with CMS to identify clinical studies that address the objectives of both the NCI and CMS for which CMS may provide reimbursement for routine costs in investigational trials. • Restructure Phase III funding model to promote rapid patient accrual rates and cost-effectiveness.

continued

TABLE A-1 Continued

	Armitage Report	Clinical Trials Working Group
Investigator recruitment	• Awards to midcareer and senior scientists should emphasize salary to ensure protected time for clinical investigation. • Clinical investigator salary lines should be available on cancer center's core grants and should be for a 3- to 5-year duration. • K12 and T32 awards should be expanded, and K08 awards should be directed to patient-oriented research.[a] NCI should create new awards and salary support for junior faculty. • NCI should fund at least 10 fellowship programs that provide a formalized academic degree program for clinical scientists. • Cooperative Group grants should include a salary commitment to responsible committee chairs to ensure that time and effort are matched by salary support in planning, implementation, and review of trials.	• No recommendations on investigator recruitment.

[a]K12 awards support newly trained clinicians appointed by an institution for development of independent research skills and experience in a fundamental science within the framework of an interdisciplinary research and development program. T32 awards enable institutions to make National Research Service Awards to individuals selected by them for predoctoral and postdoctoral research training in specified shortage areas. K08 awards provide the opportunity for promising medical scientists with demonstrated aptitude to develop into independent investigators, or for faculty members to pursue research aspects of categorical areas applicable to the awarding unit, and aid in filling the academic faculty gap in these shortage areas.

SOURCES: NCI, 1997, 2005b.

investigator recruitment. Interestingly, the Armitage report gave several recommendations on the retention and recruitment of clinical scientists, whereas the CTWG report's 22 recommendations did not address recruitment and retention issues. Despite the time lapse between the release of the two reports, several themes emerged from both reports, including the importance of data standardization, the need for a comprehensive database of NCI trials, improved public awareness of clinical trials, and the need to reduce the time it takes to initiate a clinical trial.

RESPONSE TO THE CTWG REPORT

NCI has launched several initiatives in response to the CTWG report, as delineated in Box A-2. In addition, NCI has launched an evaluation plan in response to the CTWG recommendation for a quantitative and qualitative, evidence-based evaluation to assess measures of the program management process, the system performance process, and system outcomes.[1] The evaluation plan consists of a baseline feasibility analysis, an interim evaluation of specific initiatives related to these measures, and final evaluations at specified intervals after implementation of the initiatives. A goal is to develop a structured framework for continuous monitoring and feedback to accommodate midcourse corrections.

The evaluation aims to compare the baseline to the future on the basis of system outcome measures (overall output) and system performance measures (performance of individual CTWG initiatives). The system outcome measures are intended to gauge the quality and impact of clinical trials and the efficiency of both trial development and initiation and trial conduct. NCI has engaged evaluation specialists to assist with development of the definitions, survey instruments, statistical adjustments, and other tools; to conduct the evaluations; and to determine the appropriate timing for examining the various measures in the context of the implementation timelines and the nature of the impacts envisioned.

The baseline evaluation of the current system was completed in 2008 to provide a basis for ascertaining the value of the restructuring effort. The results of that baseline evaluation are being analyzed by a Working Group of the Clinical Trials and Translational Research Advisory Committee (formerly the Clinical Trials Advisory Committee [CTAC]), which will propose which elements of the recommended evaluation system should be implemented and establish a timeline for follow-up evaluations.

[1] See http://restructuringtrials.cancer.gov/initiatives/evaluation.

BOX A-2
NCI Initiatives in Response to the CTWG Report

NCI has launched initiatives in six categories in response to the CTWG report. The objectives and current status of those initiatives are briefly described below. Many of these activities are also described in Chapter 3.

Enterprise-wide initiatives aim to enhance coordinated leadership of the clinical trials enterprise by addressing ongoing National Cancer Advisory Board oversight of clinical trials and an integrated NCI organizational structure for clinical trials management. NCI established the Clinical Trials Advisory Committee (CTAC; since renamed the Clinical Trials and Translational Research Advisory Committee) so that a broad range of stakeholders could provide advice on NCI-supported national clinical trials (both extramural and intramural) to the NCI director, deputy directors, and division directors. NCI also established the Clinical Trials and Translational Research Operations Committee (CTROC) as an internal NCI advisory committee responsible for review of ongoing clinical trials and prioritization of proposed NCI-supported clinical trials, correlative science programs, and translational research. CTROC members include the directors of all NCI divisions, offices, and centers that have clinical trials or translational science portfolios. The Coordinating Center for Clinical Trials was established to oversee implementation of the 22 initiatives recommended by the CTWG in 2005, as well as 15 initiatives recommended by the TRWG in 2007. The center, which resides within the NCI's Office of the Director, facilitates and manages the operations of CTAC and CTROC in conjunction with all NCI divisions, offices, and centers.

Coordination initiatives aim to improve coordination and cooperation among the functionally diverse components of the current system, including industry and federal regulatory agencies. Currently, NCI is working to establish a comprehensive database containing regularly updated information on all NCI-funded interventional clinical trials. Grantees will be requested to enter specific information about each clinical trial into the database.

Prioritization and scientific initiatives aim to improve prioritization and scientific quality by developing a more open and transparent process for the design and prioritization of clinical trials that are science driven and that meet the needs of patient care. NCI has established an Investigational Drug Steering Committee and several disease-specific steering committees, as described in Chapter 3.

Standardization initiatives aim to improve standardization of the tools and procedures used for trial design, data capture, data sharing, and administrative functions to minimize duplication of effort and to facilitate the development of a shared infrastructure to support an integrated national cancer clinical trials network. Working with the CEO Roundtable on Cancer, NCI developed the Standard Terms of Agreement for Research Trials clauses to help cut the time spent on contract negotiations between pharmaceutical or biotechnology companies and academic medical centers.

BOX A-2 Continued

Operational efficiency initiatives aim to improve operational efficiency by increasing the rate of patient accrual and reducing operational barriers so that trials can be initiated and executed in a timely, cost-effective manner. NCI funded a study to identify institutional barriers to the initiation of clinical trials by documenting and analyzing the steps needed to activate clinical trials (Dilts and Sandler, 2006; Dilts et al., 2006, 2008). In addition, since 2006, selected grantees have received administrative supplements to increase funding for the recruitment of minority and medically underserved patients to NCI clinical trials. In 2008, nine continuation supplements totaling $830,000 and four new supplements totaling $399,000 were awarded.

Informatics initiatives aim to define, design, build, and deliver a comprehensive clinical trials informatics infrastructure that will serve all of the critical stakeholders. NCI plans to rely on the NCI Center for Bioinformatics to provide program management and infrastructure through caBIG to achieve these aims.

SOURCE: See http://restructuringtrials.cancer.gov/initiatives/overview.

Results of the Baseline Feasibility Study

The baseline measures of system performance for the CTWG initiatives included incentives for collaboration among investigators, the extent of multisite Phase II and multi-Cooperative Group Phase III trials, the extent of collaboration between industry and NCI, the nature and quality of clinical trial prioritization processes, and the distribution and cost-effectiveness of accrual across sites (Doroshow, 2008). The baseline measures did not consider initiatives in which there was little or no activity ongoing prior to the CTWG report, such as a comprehensive clinical trials database, the level of caBIG (cancer Biomedical Informatics Grid)-compatible clinical information technology, the value added by the Investigational Disease Steering Committee and Scientific Steering Committee processes, the impact of correlative science funding and standardization, the value and use of standardized clinical trial tools, and the cost savings achieved by shifting patient accrual to highly accruing, more efficient sites.

Multiple sources of data were used for the baseline feasibility analysis, including interviews, database analyses, and reviews of factual information in documents. Baseline interviews were held in 2007 with 81 stakeholders (investigators conducting Phase I, II, and III trials; principal investigators of the Community Clinical Oncology Program, investigators conducting

industry trials, and NCI staff). The questions were mostly open-ended, and some questions were designed to elicit perceptions of specific facts or events. Two CTEP databases (the Clinical Data Update System and the Division of Cancer Prevention Enterprise System Knowledgebase) have been analyzed, and the analysis includes all clinical trials, letters of intent (LOIs) for the conduct of clinical trials, and clinical trial concepts that were active between January 1, 2000, and December 31, 2005. However, no current database captures all clinical trials performed at the cancer centers.

The baseline document review covers NCI program guidelines, cancer treatment guidelines, and academic medical center tenure and promotion guidelines. An expert panel, composed of nine individuals who conduct NCI-funded clinical trials, an individual from industry who conducts clinical trials, and a patient advocate, participated in the development of measures and interview guides and reviewed the key findings at the end. Plans for future evaluations include the refinement of baseline measures and the development of new measures; incorporation of additional information into clinical trials databases to strengthen future evaluation efforts; and the development of an initiative-specific timeline.

For the system outcome measures, the analysis of the quality of trials focused on early closure and publications. Recommendations were made to include fields in clinical trials databases to indicate early closure and the reason for closure, as well as to report the publications that resulted from the clinical trial. Suggestions were also made to include Phase II and III linkages in clinical trials databases, as well as measures to evaluate the strength of evidence for dose and toxicity criteria in Phase I trials and outcome in Phase II and III trials. In addition, the group recommended that the databases include earlier time points in concept development, as well as fields for trial complexity and patient eligibility criteria to facilitate the interpretation of the accrual data.

To assess the impact of the changes on fostering collaboration, the group suggested that future interviews examine collaboration in trial design and that NCI develop a way to track collaborative trial efforts in the clinical trials databases. Collaboration in accrual and accrual through the Cancer Trials Support Unit (CTSU) also was considered, and repeat analyses at regular intervals were suggested (Doroshow, 2008).

Operational Efficiency Working Group

As discussed in Box A-2, the CTWG report called for an analysis of the institutional barriers that prolong the time from concept approval to accrual of the first patient onto a trial. In response, CTAC established the OEWG to recommend strategies and implementation plans based on the findings of its analysis. Sixty-three clinical trial stakeholders participated in the OEWG, including 10 Cooperative Group chairs, 8 cancer center

directors, clinical investigators, statisticians, protocol and trial specialists, a community oncologist, NCI clinical trials leadership and staff, representatives of the pharmaceutical and biotechnology industries, patient advocates, representatives of the FDA, CMS, and the CTSU.

OEWG deliberations focused on identification of the key barriers to the timely activation of clinical trials and a commitment to achieve new target timelines for the steps in trial activation. In these discussions, the OEWG developed new process maps for trial activation and established firm dates to terminate the development of a trial protocol if all issues were not resolved. To achieve the targeted timelines, the OEWG developed recommendations and associated implementation plans (Box A-3). The OEWG target timeline for Phase III Cooperative Group trials is 300 days to complete steps under CTEP and Cooperative Group control (including concept review, protocol development, protocol review, and forms development). The 300-day timeline excludes contract and drug supply negotiations with industry partners as well as institutional review board (IRB) approval; however, if the protocol is not activated in 2 years, it will be terminated. For cancer center investigator-initiated trials, the target timeline is 90 days to complete protocol review and revision, forms development, IRB review, and ancillary committee review, and 180 days to complete all steps from protocol submission to trial activation. The Investigational Drug Branch (IDB) early drug development Phase II target timeline is 210 days to complete steps under CTEP/IDB and extramural control, including letter of intent review, protocol development, protocol review, and forms development. This timeline excludes industry negotiations, arranging drug supply, and IRB and FDA approval; however, if the protocol is not activated within 18 months, it will be terminated.

TRANSLATIONAL RESEARCH WORKING GROUP REPORT

The TRWG was established in June 2005 under the auspices of the National Cancer Advisory Board and was charged with evaluating the current status of the NCI's investment in translational research, envisioning its future, and developing recommendations and implementation plans to realize that vision. The work of the TRWG was intended to complement and extend the work of the CTWG. While the CTWG report primarily focused on late translation (Phase III trials), the TRWG's focus was on early translation activities, including partnerships and collaborations among government, academia, and industry; intervention development; and early-stage trials.[2]

[2] The TRWG used the definitions of early- and late-stage translation of the President's Cancer Panel (NCI, 2005a).

BOX A-3
Operational Efficiency Working Group Recommendations

Cooperative Group Process Improvement

- **Recommendation 1: Group-specific action plan to achieve OEWG target timeline**
  - Potential staffing changes
    - Physician senior protocol officers
    - Nonphysician trial development managers
    - Specialist medical writers
  - Performance of trial development steps in parallel
  - Direct, coordinated interactions to resolve issues
  - Project management and protocol tracking tools
- **Recommendation 2: CTEP action plan to achieve OEWG target timeline**
  - Project managers
    - Manage overall protocol review, revision, and approval process
    - Facilitate interactions between CTEP and the Cooperative Groups
  - Coordinated NCI scientific review to identify all issues at time of initial concept review
  - Prompt communication of critical issues in advance of formal written reviews
  - Streamlined methods for communicating comments
  - Differentiation of advisory comments from those requiring a response
  - Project management and protocol tracking tool
- **Recommendation 3: Collaborative Group-CTEP process for concept and protocol revision**
  - Direct, coordinated interactions to resolve issues
  - High priority for devotion of time to issue resolution
  - Resolution of fundamental aspects of study design at concept stage
  - Focus of interactions at protocol stage on mechanics of completion of protocol embodying an agreed-upon concept
    - Prompt communication and resolution of major differences
    - Minimization of time discussing noncritical differences of opinion
    - Minimization of time and effort for routine or pro forma revisions
  - Rapid arbitration for any issues not resolved quickly
- **Recommendation 4: Development of approaches to reward performance against timelines**
  - Establish a comprehensive, reliable system for reporting timeline performance for each step in trial activation process
  - Collect timeline performance data for at least 1 year and assess accuracy and value of the data and reports
  - Analyze performance data by individual Cooperative Groups and across the Group system in comparison with target timelines
  - Joint Cooperative Group-NCI deliberations concerning
    - Linking incentives to Group-specific timeline performance
    - Incorporating performance against timeline targets
  - CTEP inclusion of timeline performance in its annual staff performance evaluations

Early Drug Development Phase II Trial Activation Process Improvement

- **Recommendation 5: CTEP action plan to achieve OEWG target timeline**
  - Project managers
    - Management of overall protocol review, revision, and approval process
    - Facilitation of interactions among CTEP, principal investigators, and industry
  - Teleconferences to resolve issues for LOIs on hold
  - Prompt communication of disapprovals in advance of review letter
  - Streamlined methods for communicating comments
  - Differentiation of advisory comments from those requiring response
  - Project management and protocol tracking tools
- **Recommendation 6: Collaborative Group, N01 research and development contracts, CTEP process for LOI and protocol revision**
  - Direct, coordinated interactions to resolve issues (within 14 days of LOI review)
  - High priority on devoting time to issue resolution
  - Resolution of fundamental aspects of study design at LOI stage
  - Focus of interactions at protocol stage on mechanics of completing a protocol embodying an agreed-upon LOI
    - Prompt communication and resolution of major differences
    - Minimization of time spent discussing noncritical differences of opinion
    - Minimization of time and effort for routine or pro forma revisions
  - Rapid arbitration for any issues not resolved quickly

Cancer Center Process Improvement

- **Recommendation 7: Cancer center-specific action plan to achieve OEWG target timeline**
  - Potential action plan elements
    - Specialist medical writers
    - Direct, coordinated interactions to resolve differences
    - Project management and protocol tracking tool
  - Center-specific timeline targets
    - Modification of OEWG target to reflect specific cancer center environment
    - Analysis of targets for reasonableness by cancer center directors and NCI
    - Reporting of timeline data against target on an annual basis
    - Annual report on actions taken against centers performing below expectations
  - Funding sources
    - Allowance for explicit use of Cancer Center Support Grant (CCSG) funds for protocol development
    - Provision of supplemental funds to implement action plan
- **Recommendation 8: Streamline university contracting and financial review processes**
  - System-level activities

continued

BOX A-3 Continued

- Education of universities on NCI Standardized Clauses for Clinical Trial Agreements
- Development of standardized clauses for other types of agreements
- Collaboration with Clinical and Translational Science Awards program to streamline processes

- Institution-level activities
  - Education of stakeholders on NCI Standardized Clauses for Clinical Trial Agreements
  - Establishment of master agreements with individual companies
  - Consideration of use of nonfederal funds for university legal and contracting staff devoted to cancer center trials
  - Direct interactions among cancer center, university, and hospital staff to resolve issues

Standardization of Tools and Templates

- **Recommendation 9: Form a working group involving the NCI, Cooperative Group, and cancer center staff to coordinate standardization efforts**
  - Compilation of inventory of protocol templates, data elements, case report form modules, etc., from Cooperative Groups, cancer centers, and the NCI
  - Analysis of inventory to identify current standards, best-in-class products, redundant development efforts, and unmet needs
  - Analysis of status and output of existing standardization efforts
  - Identification of tools and templates for which standardization is mandatory versus recommended or optional
  - Identification of standards needed for interoperability
  - Development of a coordinated process for implementing standards

Recommendations

In developing its recommendations, the TRWG outlined the current challenges confronting early translational research at the NCI (Box A-4). To address these challenges, the TRWG developed 15 recommendations in three categories: coordinated management, tailored funding programs, and operational effectiveness (Table A-2). In addition, the TRWG constructed six developmental pathways to describe the decision-making points and processes along which translational research occurs for six domains: biospecimen-based risk assessment devices, image-based risk assessment agents

Enhanced Biomarker Funding and Capabilities

- **Recommendation 10: Enhancement of funding and capabilities for use of biomarkers in NCI-funded clinical trials**
  - Expansion of the Biomarker, Imaging, and Quality of Life Studies Funding Program to large randomized Phase II trials
  - Support biomarker studies for early-phase trials
  - Requirement for clinical trial concepts and LOIs to describe proposed integral or integrated biomarker studies
  - Provision of funding for development, validation, and conduct of clinical-grade assays
  - Development of standards for qualifying sites to conduct imaging studies associated with clinical trials

Cancer Center Trial Prioritization

- **Recommendation 11: Performance of rigorous review of clinical trial concepts in advance of protocol development**
  - Specification of concept review process in CCSG guidelines
    - Approval or disapproval by disease group or throughout the cancer center
    - Uniformity of reviews across diseases
    - Content of a concept document
    - Criteria by which concepts are reviewed
  - NCI should mandate the specific process or criteria
  - Applicable to all trials: investigator-initiated, Cooperative Group, and N01 trials

SOURCE: Doroshow and Hortobagyi, 2010.

and techniques, anticancer agents (drugs or biologics), immune response modifiers, interventive devices, and lifestyle alterations (Cheever et al., 2008; Dorfman et al., 2008a,b; Hawk et al., 2008a,b; Schilsky et al., 2008; Srivastava et al., 2008).

Some TRWG recommendations are outgrowths of the CTWG initiatives, such as the Clinical and Translational Advisory Committee (CTAC; previously the Clinical Trials Advisory Committee, created in response to the CTWG recommendations). The TRWG report expanded the scope of the CTAC committee to include translational research, noting that CTAC

BOX A-4
Translational Research Working Group Assessment of Current Challenges in Translational Research

- Insufficient coordination and integration results in a fragmented translational research effort that risks duplication and missed opportunities.
- The absence of clearly designated funding and adequate incentives for researchers threatens the perceived importance of translational research within the NCI enterprise.
- The absence of structured, consistent review and prioritization processes tailored to the characteristics and goals of translational research makes it difficult to direct resources to critical needs and opportunities.
- The multidisciplinary nature of translational research and the need to integrate sequential steps in complex developmental pathways warrant dedicated project management resources.
- Translational research core services can be duplicative and inconsistently standardized, with capacity being poorly matched to the need.
- Collaboration with industry delays appropriate developmental handoffs.
- Extended negotiation on intellectual property issues delays or prevents potentially productive collaborations.
- Insufficient collaboration and communication between basic and clinical scientists and the paucity of effective training opportunities limit the supply of experienced translational researchers.

SOURCE: NCI, 2007.

was already responsible for early-stage trials and correlative science studies. The TRWG report also indicated that integrated oversight would facilitate the coordination and prioritization process for both early- and late-stage translational research. Other report recommendations focused on prioritizing translational research activities at NCI, providing better project management of translational research activities, establishing enhanced biospecimen repositories and analytical methods, and ensuring the provision of training and career incentives for early translational research.

TABLE A-2 Summary of TRWG Recommendations and Implementation Status

Category	Specific Recommendations	Implementation Status
Coordinated management	• Establish a flexible, integrated organizational approach that coordinates early translational research across NCI.	• Expansion of CTAC to include translational research expertise; expansion of the Clinical Trials Operations Committee (and name change to Clinical Trials and Translational Research Operations Committee) to include translational research responsibilities; expansion of Coordinating Center for Clinical Trials to include Translational Research Support Team
	• Designate a specific portion of the NCI budget for early translational research.	
	• Develop a set of award codes that accurately capture the nature and scope of the early translational research portfolio.	• Pilot project with NCI's Division of Extramural Activities to code grants for translational research on the basis of the TRWG pathways; comparison with principal investigator's assessment of projects to look for consistency and interpretation of pathways
	• Establish a distinctive prioritization process for early translational research.	• Two-day NCI translational science meeting (NCI Translates) held in November 2008 and 2009 to explore potential of translational research prioritization and acceleration, as recommended by the TRWG report • Pilot project to prioritize cancer antigens within the immune response modifier pathway; project expanded to prioritize translational research opportunities within the immune response modifier pathway

continued

TABLE A-2 Continued

Category	Specific Recommendations	Implementation Status
Tailored funding programs	• Modify multiproject collaborative award guidelines, as appropriate, to facilitate early translational research.	• CTAC Coordination Subcommittee Guideline Harmonization Working Group mission: promote collaborative team science and ensure that guidelines for different clinical trials funding mechanisms are aligned, eliminate redundancy and duplication while proactively encouraging collaboration, harmonize program guidelines and develop incentives to foster collaboration among all components of the clinical trials infrastructure, including cancer centers, Specialized Programs of Research Excellence, and Cooperative Groups
	• Improve processes and mechanisms for funding investigator-initiated early translational research. • Establish a special translational research acceleration project (STRAP) to advance prioritized early translational research opportunities. • Establish a funding program for early translational research that requires academia and industry collaboration involving resource sharing or cofunding.	• Pilot project to establish a STRAP for the immune response modifier pathway
	• Integrate access to manufacturing and other preclinical development services according to good manufacturing practices and good laboratory practices more effectively with milestone-driven early translational research projects.	• Development of the NCI Experimental Therapeutics Program, a new drug discovery and development pipeline that can partner with researchers to bring new cancer treatments to patients

Operational effectiveness	• Establish a formal project management system for early translational research. • Establish a system to coordinate core services essential for early translational research. • Enhance quality and accessibility of annotated biospecimen repositories and associated analytical methods. • Develop enhanced approaches for negotiation of intellectual property agreements and agent access. • Enhance interactions and collaborations with foundations and advocacy groups to advance early translational research. • Enhance training and career incentives for early translational research.	• New Project Management Office established within the NCI Division of Cancer Treatment and Diagnosis • CTAC Coordination Subcommittee is developing criteria for regional cores and guidelines to encourage sharing and reduce redundancy • Enhancement of NCI's Office of Biorepositories and Biospecimen Research • NCI and the Life Sciences Consortium of the CEO Roundtable on Cancer have jointly developed a set of common clauses, the Standard Terms of Agreement for Research Trial clauses, that are accessible for use by any party initiating a trial. These standard clauses provide common language for use as a starting point in the contract agreements that govern clinical trials.

SOURCES: Cheever et al., 2009; Clinical Trials Advisory Committee, 2008; Hawk et al., 2008b; NCI, 2007.

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Appendix B

Committee Member and Staff Biographies

COMMITTEE MEMBER BIOGRAPHIES

John Mendelsohn, M.D. (*Chair*), combines experience in clinical and laboratory research with administrative expertise in preparing the University of Texas M.D. Anderson Cancer Center for the next century. Since becoming president in 1996, he has recruited a visionary management team and implemented new priorities for integrated programs in patient care, research, education, and cancer prevention. For almost three decades, Dr. Mendelsohn has been at the forefront in understanding how growth factors regulate the proliferation of cancer cells by activating receptors on the surface of the cells. He developed cetuximab, a specific monoclonal antibody that blocks epidermal growth factor (EGF) and transforming growth factor-alpha binding to EGF receptors, thereby inhibiting activation of receptor tyrosine kinase and preventing the growth factors from stimulating cell growth and division. His research led to the first clinical trial with an antireceptor therapy and an anti-tyrosine kinase therapy. Dr. Mendelsohn was born in Cincinnati, Ohio, and earned a bachelor's degree in biochemical sciences magna cum laude from Harvard College in 1958. After spending a year in Scotland as a Fulbright Scholar, Dr. Mendelsohn received a medical degree cum laude from Harvard Medical School in 1963. Between 1963 and 1970, he took residency training in internal medicine and completed a research fellowship in oncology at Washington University Medical School in St. Louis, Missouri. From 1970 to 1985, he was on the University of California-San Diego (UCSD) faculty, rising from assistant professor to professor of medicine at UCSD in less than 9 years. He was instrumental in establishing and

funding a National Cancer Institute-designated Cancer Center at UCSD, which he directed from its inception in 1976 until he went to Memorial Sloan-Kettering Cancer Center in 1985. At Memorial Sloan-Kettering, Dr. Mendelsohn chaired, reorganized, and expanded its Department of Medicine. He also extended the landmark research that he began at UCSD to clarify at the molecular level how cetuximab alters growth-signaling pathways and cell functions. He also demonstrated the additive antitumor effects of EGF receptor inhibition plus chemotherapy or radiotherapy. As a result of successful clinical trials, the Food and Drug Administration approved cetuximab (Erbitux) for the treatment of colon cancer in 2004 and head and neck cancer in 2006. Dr. Mendelsohn served as the founding editor-in-chief of *Clinical Cancer Research*, a monthly translational research journal published by the American Association for Cancer Research, and he has been a member of the editorial boards of other leading scientific journals. He has authored more than 200 scientific papers and articles for journals and textbooks and is senior editor of *The Molecular Basis of Cancer*. His awards include the Joseph H. Burchenal and the Dorothy P. Landon awards from the American Association for Cancer Research and the David A. Karnofsky Prize from the American Society of Clinical Oncology. He is a member of the Institute of Medicine of the U.S. National Academies.

Harold L. Moses, M.D. (*Vice Chair*), is director emeritus of the Vanderbilt-Ingram Cancer Center; the Hortense B. Ingram Professor of Molecular Oncology; professor of cancer biology, medicine and pathology; and the founding and current director of the Frances Williams Preston Laboratories. Dr. Moses graduated from Berea College in 1958 and then obtained an M.D. degree from the Vanderbilt University School of Medicine in 1962. After residency training in pathology at Vanderbilt and postdoctoral research training at the National Institutes of Health, he spent 5 years as a faculty member in pathology at Vanderbilt and 12 years at the Mayo Clinic in Rochester, Minnesota, the last 6 of which were as chair of the Department of Cell Biology. He returned to Vanderbilt 23 years ago as professor and chair of the Department of Cell Biology in the School of Medicine. Fifteen years ago he became the founding director of the Vanderbilt Cancer Center and had a concurrent appointment as the B.F. Byrd, Jr. Professor of Clinical Oncology. He resigned as chair of the Department of Cell Biology in 1998 to devote more time to the cancer center, now named the E. Bronson Ingram Cancer Center. At the end of 2004, he became director emeritus of the Vanderbilt-Ingram Cancer Center and the Hortense B. Ingram Professor of Medical Oncology.

Susan G. Arbuck, M.D., M.Sc., F.A.C.P., is an independent consultant at Susan G. Arbuck MD LLC. Dr. Arbuck has been a a leader in medical oncol-

ogy in the pharmaceutical industry, from translational research to global drug registration. As vice-president, she led clinical development groups in the oncology therapeutic area of the research and development organizations of major drug companies, most recently at Schering-Plough. During her career, she contributed to the development and registration of many approved oncology products. Before she joined the pharmaceutical industry, Dr. Arbuck worked for 10 years at the National Cancer Institute (NCI), where she led the Developmental Chemotherapy Section, directing the development of a portfolio of approximately 75 drugs through NCI grantees, contractors, and national Cooperative Groups. She worked with pharmaceutical and biotechnology companies on strategies for the development of agents such as Taxol, Taxotere, Gleevec, Iressa, Velcade, Eloxatin, Camptosar, and Topotecan. She also provided leadership in the development of standardized criteria for adverse event and tumor response reporting, which are used internationally in oncology clinical trials. Throughout her career, she has contributed to the development of novel trial designs and strategies to increase the efficiency of cancer drug development and registration. Before joining NCI, at the Roswell Park Cancer Institute, she had primary responsibility for a pharmacology-based translational drug development research program in upper gastrointestinal malignancies and was a principal coinvestigator in Cooperative Group Phase III trials. She was an associate professor of medicine at the State University of New York at Buffalo. Dr. Arbuck is a board-certified medical oncologist who has served on various committees for the American Association for Cancer Research and the American Society of Clinical Oncology. She has written more than 100 peer-reviewed publications. She holds a B.Sc. from the University of Toronto, a M.Sc. in pharmacology from the State University of New York at Buffalo, and an M.D. from McMaster University Medical School in Hamilton, Ontario, Canada.

Donald A. Berry, Ph.D., is an international expert in the field of biostatistics. He holds the Frank T. McGraw Memorial Chair for Cancer Research at the University of Texas M.D. Anderson Cancer Center, where he is head of the Division of Quantitative Sciences and chair of the Department of Biostatistics. His primary interest is the prevention and treatment of breast cancer. He serves as the faculty statistician on the Breast Cancer Committee of the Cancer and Leukemia Group B (CALGB), a national oncology group. In this role, he designs and supervises the conduct and analysis of clinical trials of breast cancer treatments. A native of Massachusetts, Dr. Berry received a Ph.D. in statistics from Yale University and previously served on the faculty at the University of Minnesota and at Duke University, where he held the Edger Thompson Professorship in the College of Arts and Sciences. The author of more than 200 published articles as well as several books on biostatistics in medical research, Dr. Berry has been

the principal investigator for numerous medical research programs funded by the National Institutes of Health and the National Science Foundation. A current project funded by NCI describes the use and benefits of breast cancer treatment. He was also the principal investigator of an NCI project, CISNET: Cancer Intervention and Surveillance Network. That project focused on statistical modeling to assess the relative contribution of screening mammography, tamoxifen, and chemotherapy to the drop in breast cancer mortality observed in the United States since 1990. Another focus of Dr. Berry's statistical research is designing clinical trials that utilize patients more efficiently and that treat the patients in the trials more effectively. Dr. Berry is a statistics editor for the *Journal of the National Cancer Institute*, associate editor for *Breast Cancer Research and Treatment* and *Clinical Cancer Research*, and is a fellow of the American Statistical Association and of the Institute of Mathematical Statistics.

Michael A. Carducci, M.D., F.A.C.P., is AEGON Professor in Prostate Cancer Research, professor of oncology and urology at the Johns Hopkins University School of Medicine, Baltimore. He is co-leader of the Prostate Cancer/Genitourinary Oncology Program and co-leader of the Chemical Therapeutics Program at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University School of Medicine. A translational researcher, Dr. Carducci directs a laboratory program focused on the re-expression of epigenetically silenced genes in cancer cells via the use of small molecules targeting DNA methyltransferases and histone deacetylases, and manages a portfolio of clinical trials targeted at introducing these small molecules into cancer treatment. Overall, the focus of his laboratory and clinical research is on the development and evaluation of new therapies for urologic cancers. A fellow of the American College of Physicians, Dr. Carducci is a member of several professional organizations, including the American Association for Cancer Research, the American Society of Clinical Oncology (ASCO), and the American Urological Association. Dr. Carducci serves as the principal investigator of an NCI Phase I clinical trial grant titled Phase I Clinical Trials of Anti-Cancer Agents and of a major project in the Johns Hopkins Prostate Cancer Specialized Programs of Research Excellence titled Epigenetic Therapy: Advancing the Therapeutic Implications in Prostate Cancer. He also leads the Johns Hopkins site for the Prostate Cancer Foundation/U.S. Department of Defense Prostate Cancer Clinical Trials Consortium grant. In addition, he has received peer-reviewed funding for his laboratory and clinical research from the U.S. Department of Defense and the Prostate Cancer Foundation. He is the chair of the Prostate Cancer Subcommittee of the Genitourinary Oncology Committee of the Eastern Cooperative Oncology Group and serves as an alternate to the Genitourinary Steering Committee for NCI. Dr. Carducci is also a full member of the Investiga-

tional Drug Steering Committee for NCI. Within ASCO, he is immediate past chair of the Scientific Program Committee and has previously served on the Cancer Education, Scientific Program, and Grants Selection Committees. A graduate of Georgetown University, Dr. Carducci received a medical degree from Wayne State University School of Medicine. He completed an internal medicine internship, residency, and chief residency at the University of Colorado Health Sciences Center. He went on to complete medical oncology and research fellowships at the Johns Hopkins Oncology Center at Johns Hopkins Hospital.

David M. Dilts, Ph.D., M.B.A., is director of clinical research for the Knight Cancer Institute and professor of healthcare management at the Oregon Health & Science University. Formerly, he held the sole joint professorship between the Owen Graduate School of Management and the Vanderbilt University School of Engineering, where he was the founding director of the Engineering Management Program and co-director of the Center for Management Research in Healthcare (cMHRc.org). That center, supported by NCI, WebMD, and others, has as its mission the exchange of knowledge between management research and health care professionals to dramatically impact the practice of medicine. One research stream, funded by NCI, is to apply management principles to significantly reduce the time steps required to open oncology clinical trials. That research has completed in-depth examinations of four NCI-designated comprehensive Cancer Centers, two major oncology Cooperative Groups, and the NCI Cancer Therapy Evaluation Program and the NCI central institutional review board. Dr. Dilts's work has been published in nearly 200 articles, conference papers and presentations, book chapters, books, and monographs, including *Clinical Cancer Research*, *IEEE Transactions on Engineering Management*, *Journal of Clinical Oncology*, *Journal of the American Medical Informatics Association*, *Journal of Technology Transfer*, *Health Economics*, *Journal of Supply Chain Management*, *Management Accounting*, *Medical Decision Making*, and *Tissue & Cell*. Dr. Dilts has published on a range of topics, from complexity in supply chain networks to delays in opening oncology clinical trials and issues with business incuba-tion. Over the past 15 years, he has been a principal investigator or co-principal investigator on grants totaling over $18.5 million from sources such as NCI, the U.S. Department of Defense, and the Ontario Ministry of Health. He is a frequent speaker at national and international conferences.

Susan S. Ellenberg, Ph.D., is professor of biostatistics and associate dean for clinical research at the University of Pennsylvania School of Medicine. Her research interests have focused on issues in the design and analysis of clinical trials and assessment of medical product safety. Particular areas of

interest include efficient trial designs, interim monitoring and the operation of data-monitoring committees, evaluation of surrogate endpoints, ethical issues in clinical research, and special issues in trials of cancer and AIDS therapies and of vaccines. She serves as associate editor of *Clinical Trials* and of the *Journal of the National Cancer Institute*. Dr. Ellenberg is a fellow of the American Statistical Association, the Society for Clinical Trials, and the American Association for the Advancement of Science (AAAS) and is an elected member of the International Statistical Institute. She has served as president of the Society for Clinical Trials and the Eastern North American Region of the International Biometric Society, and has chaired the Statistics Section of AAAS. Her book on clinical trials data-monitoring committees, coauthored with Thomas Fleming (University of Washington) and David DeMets (University of Wisconsin), was named the WileyEurope Statistics Book of the Year for 2002. Before she joined the University of Pennsylvania, Dr. Ellenberg directed the Office of Biostatistics and Epidemiology at the Center for Biologics Evaluation and Research, Food and Drug Administration (1993 to 2004), served as chief of the Biostatistics Research Branch of the Division of AIDS, National Institute of Allergy and Infectious Diseases (1988 to 1992), and served as a mathematical statistician in the Biostatistics Research Branch, Cancer Therapy Evaluation Program, National Cancer Institute (1982 to 1988).

Gwen Fyfe, M.D., is an independent consultant in oncology clinical development. Until August 2009, she was a senior staff scientist in clinical hematology/oncology at Genentech. She attended Washington University Medical School and trained in pediatrics and pediatric oncology at Washington University and the University of California-San Francisco. Following a postgraduate fellowship in immunology, Dr. Fyfe joined Chiron Corporation, where she participated in the successful approval of high-dose interleukin-2 (IL-2; aldesleukin [Proleukin]) for the treatment of metastatic renal cell cancer and subsequently studied the role of intermittent IL-2 for the treatment of HIV disease. Dr. Fyfe joined Genentech in 1997. While at Genentech, her responsibilities included overseeing the Genentech oncology pipeline, including the clinical trials that led to the approvals of trastuzumab (Herceptin), a humanized antibody for the treatment of human epidermal growth factor receptor 2-positive metastatic breast cancer; rituximab (Rituxan), the first therapeutic antibody used for the treatment of non-Hodgkin's lymphoma in the United States; and bevacizumab (Avastin) for the treatment of metastatic colon cancer, breast cancer, renal cell carcinoma, and non-small cell lung cancer (NSCLC). In addition, she worked with OSI Pharmaceuticals and Roche in the development of erlotinib (Tarceva), culminating in its approval for the treatment of relapsed NSCLC and newly diagnosed pancreatic cancer. She was promoted to vice-

president of clinical hematology/oncology in 2002 and moved to a new role in oncology strategy in May 2007.

Stephen S. Grubbs, M.D., has for the past 24 years been a medical oncologist in private practice in Newark, Delaware, at the Helen F. Graham Cancer Center. He is a graduate of the Thomas Jefferson University Medical School and received postgraduate training in internal medicine at the Medical Center of Delaware and hematology and oncology at the Dartmouth Hitchcock Medical Center. He serves as principal investigator of the Delaware Christiana Care Community Clinical Oncology Program, board member of the Cancer and Leukemia Group B Cooperative Group, a member of the State of Delaware Cancer Consortium Council, and chair of Colorectal Cancer Screening. He also serves on the American Society of Clinical Oncology (ASCO) Clinical Trials Committee, Exemplary Trials Site Subcommittee, and is chair-elect of the Clinical Trials Workshop. He is an assistant professor of clinical medicine of the Thomas Jefferson Medical School faculty. Dr. Grubbs is a member of the National Cancer Institute (NCI) Clinical Trials Advisory Committee and is co-chair of the Clinical Trials Subcommittee of the NCI Community Cancer Centers Program. He is the recipient of the 2007 Association of Community Cancer Centers David King Community Clinical Scientist Award. His practice, Medical Oncology Hematology Consultants, P.A., is honored as a recipient of the 2008 ASCO Clinical Trials Participation Award.

Hedvig Hricak, M.D., Ph.D., is chair of the Department of Radiology at Memorial Sloan-Kettering Cancer Center. She holds a senior position within the Program of Molecular and Pharmacology Therapeutics at the Sloan-Kettering Institute and is professor of radiology at the Weill Medical College of Cornell University. Her research involves the use of a variety of imaging methods, including ultrasound, computed tomography, magnetic resonance imaging (MRI), and magnetic resonance spectroscopy, with the aim of improving cancer detection, treatment planning, and follow-up. She pioneered the use of ultrasound in kidney disease. In addition, through multidisciplinary collaborative research, she helped introduce MRI for the evaluation of prostate and gynecologic cancers and was involved in developing and validating the use of MR spectroscopy for prostate cancer. Dr. Hricak received an M.D. from the University of Zagreb and a Ph.D. in oncology from the Karolinska Institute. She has authored or coauthored 23 books, more than 300 peer-reviewed research papers, and 128 review/editorial papers. In recognition of her many accomplishments, she has received the Marie Curie Award from the Society of Women in Radiology, the gold medals of the International Society for Magnetic Resonance in Medicine and the Association of University Radiologists, the Beclere Medal

of the International Society of Radiology, and the Morocco Medal of Merit. She was named Honorary Professor, University of Zagreb, Zagreb, Croatia, and is an honorary member of the British Institute of Radiology, the German Radiological Society, the Austrian Roentgen Society, the Journées Françaises de Radiologie, and the Swedish Society of Medical Radiology. She is an honorary fellow of the Royal College of Radiologists as well as a member of the Croatian Academy of Science and Art, and she holds an honorary doctorate in medicine from the Ludwig Maximilian University of Munich.

Richard Kaplan, M.D., is associate director of the National Cancer Research Network and also serves as associate director for industry of the United Kingdom Clinical Research Network. He is professor of clinical cancer studies at the Leeds Institute of Molecular Medicine and senior scientist at the Medical Research Council Clinical Trials Unit. Dr. Kaplan is a medical oncologist with 30 years of experience in clinical research in the United States and was previously chief of the NCI Clinical Investigations Branch. He was program director for NCI's national program of Cooperative Group clinical trials of cancer treatments and program director for NCI's Brain Tumor Consortia. He has been responsible for the scientific coordination of NCI-funded or -sponsored treatment trials in brain, urological, and gastrointestinal malignancies and has served on advisory committees and panels for NCI, NIH, the Food and Drug Administration, and other governmental agencies and professional organizations, as well as for clinical trials networks in the United Kingdom, Ireland, and Europe. A major focus of Kaplan's effort at present is in improving the research environment in the United Kingdom for collaborative efforts between the National Health Service and companies in the pharmaceutical, biotechnology, and medical device industries.

Minetta C. Liu, M.D., is an associate professor of medicine and oncology and director of translational breast cancer research at Georgetown University Hospital's Lombardi Comprehensive Cancer Center. She also serves on the Breast Correlative Science Working Group and the Breast Committee of the Cancer and Leukemia Group B Cooperative Group. Dr. Liu is heavily involved in clinical and translational research and focuses on the use of tissue- and serum-based biomarkers in identifying the molecular mechanisms responsible for determining sensitivity versus resistance to chemotherapy. Her work is currently supported by research grants from the National Cancer Institute, the U.S. Department of Defense, the Susan G. Komen for the Cure Foundation, and industry sponsors. Most importantly, she is firmly dedicated to the care and education of women with breast cancer and uses an individualized, multidisciplinary approach to patient

management. Dr. Liu received an A.B. from the Department of Molecular Biology at Princeton University and an M.D. from Jefferson Medical College in Philadelphia, Pennsylvania. She completed residency training in internal medicine and fellowship training in hematology/oncology at Georgetown University Hospital in 1998.

Lee N. Newcomer, M.D., M.H.A., is senior vice-president of oncology for United HealthCare. His unit is responsible for improving the quality and affordability of care for the 111,000 cancer patients covered by United HealthCare. Before he rejoined United Health Group (UHG), Dr. Newcomer was a founding executive of Vivius, a consumer-directed venture that allowed customers to create their own personalized health plans. From 1991 to 2000, Dr. Newcomer held a number of positions at UHG, including chief medical officer. His work there emphasized the development of performance measures and incentives to improve clinical care. Before he joined UHG, he was medical director for CIGNA Health Care of Kansas City, Missouri. Dr. Newcomer is a board-certified medical oncologist; he practiced medical oncology for 9 years in Tulsa, Oklahoma, and Minneapolis, Minnesota (Park Nicollet Clinic). He is currently the chairman of Park Nicollet Health Services, an integrated system of more than 650 physicians and a 400-bed hospital. The group is nationally recognized for its leadership in quality, safety, and lean processes. Dr. Newcomer earned a bachelor of arts degree in biology from Nebraska Wesleyan University, an M.D. degree from the University of Nebraska College of Medicine, and an M.S. degree in health administration from the University of Wisconsin at Madison. He completed an internship and residency in internal medicine at the University of Nebraska Hospital and fellowships in medical oncology and administrative medicine at the Yale University School of Medicine and the University of Wisconsin at Madison, respectively.

Edith A. Perez, M.D., is the deputy director, Mayo Clinic Comprehensive Cancer Center for Florida, director of the Breast Program, and a professor of medicine at Mayo Medical School. She is a cancer specialist and an internationally known translational researcher at Mayo Clinic. Her roles extend nationally, including chairing the Breast Committee for the North Central Cancer Treatment Group, as well as other positions within the American Association for Cancer Research, the American Society of Clinical Oncology, and the National Cancer Institute. Dr. Perez has developed and is involved in a wide range of clinical trials exploring the use of new therapeutic agents for the treatment and prevention of breast cancer. She also developed studies to evaluate the role of genetic markers in the development and aggressiveness of breast cancer. Dr. Perez has authored more than 555 research articles in journals, books, and abstracts. Dr. Perez receives invitations to

lecture at national and international meetings frequently. She serves on the editorial boards of multiple academic journals. Dr. Perez is a recipient of the Breast Cancer Research Foundation Research Grant Award (1998–2010); the Horizon Achievement Award in Cancer Research (2002); the North Florida Hispanic of the Year Award (2003); the Mayo Clinic Outstanding Faculty Award (2002 and 2004); the Mayo Clinic Distinguished Educator Award (2003); the named Serene M. and Frances C. Durling Professorship of Medicine (2006); Honorary Doctorate of Letters, University of North Florida (2006); Mayo Clinic Distinguished Investigator (2007); the Florida State Biomedical Research Advisory Council (2009–2012) and is a member of the Alpha Omega Alpha Honor Medical Society (2009).

Charles L. Sawyers, M.D., is an investigator of the Howard Hughes Medical Institute and the inaugural director of the Human Oncology and Pathogenesis Program at Memorial Sloan-Kettering Cancer Center (MSKCC). He is building a program of laboratory-based translational researchers across various clinical disciplines as well as an institutional infrastructure to enhance the application of global genomics tools to clinical trials. Dr. Sawyers' laboratory is focused on characterizing signal transduction pathway abnormalities in various cancers, including chronic myeloid leukemia and prostate cancer, with an eye toward translational implications. His research is best demonstrated through his studies of BCR-ABL tyrosine kinase function in chronic myeloid leukemia, his work with Brian Druker and Novartis in the development of the kinase inhibitor imatinib (Gleevec) as primary therapy for chronic myelogenous leukemia, and his discovery that imatinib resistance is caused by BCR-ABL kinase domain mutations. This discovery led Dr. Sawyers to evaluate second-line Abl kinase inhibitors, such as the dual Src/Abl inhibitor dasatinib, which received fast-track approval by the Food and Drug Administration in June 2006. His group also found that dasatinib resistance can occur through additional, novel BCR-ABL mutations that remain sensitive to imatinib, making a strong case for combined Abl kinase inhibitor treatment to prevent the emergence of resistant subclones. Dr. Sawyers has also developed a leading laboratory-based program in prostate cancer. That work is currently focused on the role of the androgen receptor in disease progression, even when tumors progress to the hormone-refractory stage. After demonstrating that higher levels of androgen receptor are necessary and sufficient to confer resistance to current antiandrogens, he collaborated with chemist Michael Jung (of the University of California-Los Angeles) to discover a small-molecule inhibitor that targets the increased levels of androgen receptor found in hormone-refractory disease by a novel mechanism. A Phase I-II trial of this compound (MDV3100), now under way at MSKCC and other sites, has shown impressive clinical responses in men with castrate-resistant prostate

cancer, including those who have progressed on chemotherapy. Dr. Sawyers is past president of the American Society of Clinical Investigation and serves on the National Cancer Institute's Board of Scientific Councilors. He has won numerous honors and awards, including the Richard and Hinda Rosenthal Foundation Award from the American Association of Cancer Research and the David A. Karnofsky Award from the American Society of Clinical Oncology. He was recently elected to the Institute of Medicine of the National Academies.

Richard L. Schilsky, M.D., is professor of medicine, section chief of Hematology-Oncology, and Deputy Director of the Comprehensive Cancer Center at the University of Chicago at the University of Chicago Medical Center. He specializes in the treatment of gastrointestinal cancers and in the development of new cancer treatments for diseases such as colorectal and pancreatic cancers. Dr. Schilsky led a groundbreaking study, which found that aspirin reduces the incidence of precancerous polyps in patients at high risk for colorectal cancer. From 1995 to April 2010, Dr. Schilsky served as chair of the Cancer and Leukemia Group B, the largest and oldest cancer clinical trials group in the United States. He is the immediate past president of the American Society of Clinical Oncology.

Ellen V. Sigal, Ph.D., is chair and founder of Friends of Cancer Research (Friends), a nonprofit organization based in the Washington, DC, metropolitan area. Friends is dedicated to accelerating the nation's progress toward the prevention and treatment of cancer by mobilizing public support for cancer research funding and providing education on key public policy issues. Over the past 11 years, Friends has pioneered innovative public-private partnerships, organized critical policy forums, educated the public, and brought together key communities to develop collaborative strategies in the field of cancer research. Dr. Sigal is vice-chair of the inaugural board of directors of the Reagan-Udall Foundation, a partnership designed to modernize medical product development, accelerate innovation, and enhance product safety in collaboration with the Food and Drug Administration. She serves on the National Cancer Institute Board of Scientific Advisors; the National Institutes of Health Foundation Board, chairing its Public-Private Partnerships Committee; and the American Association for Cancer Research Foundation Board. Dr. Sigal was recently appointed to the Stand Up To Cancer (SU2C) Advocate Advisory Council, and she is one of two council members nominated to the SU2C Scientific Advisory Committee. She holds leadership positions with a broad range of cancer advocacy and public policy organizations and leadership positions with academic health centers, including the M.D. Anderson Cancer Center External Advisory Board and the Duke University Cancer Center Board of Overseers. She

serves on the C-Change Research Committee and is a member of the Entertainment Industry Foundation Oversight Committee for the Biomarker Discovery Project.

CONSULTANT BIOGRAPHY

Michaele Chamblee Christian, M.D., received an M.D. summa cum laude from Georgetown University School of Medicine, where she was first in her class. Among numerous awards, she received the Kober Award for highest academic achievement and was elected to the Alpha Omega Alpha honor medical society. She completed residency training in internal medicine and fellowships in hematology and oncology at Georgetown University. From 1997 until her retirement in 2007, she was director of the Cancer Therapy Evaluation Program (CTEP) of NCI, which maintains a major program in early drug development and collaborates with more than 50 pharmaceutical companies to develop new agents for cancer. CTEP is also responsible for coordinating NCI's extensive program of extramural cancer treatment clinical trials. Before that, she worked in the Investigational Drug Branch on the clinical development of new anticancer drugs. In 1995 she established NCI's Clinical Trials Monitoring Branch, which oversees quality assurance for hundreds of NCI clinical trials. Her personal research interests include early therapeutics development, ovarian cancer treatment, clinical trial design and methodology, and health disparities. She has authored numerous articles and chapters in these areas. She has been an active participant in professional societies, including the American Association of Cancer Research, where she served on the board of directors and was chair of Women in Cancer Research, and the American Society of Clinical Oncology. She has reviewed manuscripts for many medical journals and served as an associate editor of *Clinical Cancer Research*, *Journal of Clinical Oncology*, and *Molecular Cancer Therapeutics*. Medicine is her second career. She began in arts administration with Friends of the Kennedy Center and the Duke Ellington School of the Arts. She is active in community organizations, primarily in education and the arts, including the boards of the Black Student Fund and the Duke Ellington School of the Arts, which she chairs.

STAFF BIOGRAPHIES

Sharyl Nass, Ph.D., is the director of the National Cancer Policy Forum and study director at the Institute of Medicine (IOM). She has worked with the IOM Board on Health Sciences Policy, Board on Health Care Services, and National Cancer Policy Board and Forum. Her previous work at the IOM has focused on topics that include the development of cancer

biomarkers, strategies for large-scale biomedical science, the development of technologies for the early detection of breast cancer, improving breast imaging quality standards, the Health Insurance Portability and Accountability Act Privacy Rule, and contraceptive research and development. Her current position at the IOM combines her dual interests in biomedical research and health science policy. With a Ph.D. in cell and tumor biology from Georgetown University and postdoctoral training at the Johns Hopkins University School of Medicine, she has authored papers on the cell and molecular biology of breast cancer. She also earned a B.S. in genetics (with highest distinction) and an M.S. in endocrinology/reproductive physiology, both from the University of Wisconsin-Madison. In addition, she studied developmental genetics and molecular biology at the Max Planck Institute in Germany under a fellowship from Fulbright and the German Heinrich Hertz-Stiftung Foundation. Dr. Nass was the 2007 recipient of the Cecil Award for Excellence in Health Policy Research.

Erin Balogh, M.P.H., joined the Institute of Medicine in August 2008 as a research associate for the National Cancer Policy Forum and Board on Health Care Services. She has worked on two committee studies, the Qualification of Biomarkers and Surrogate Endpoints in Chronic Disease and Cancer Clinical Trials and the NCI Cooperative Group Program. She completed an M.P.H. in the Department of Health Management and Policy at the University of Michigan and before that graduated summa cum laude from Arizona State University with bachelor's degrees in microbiology and psychology. Ms. Balogh interned with AcademyHealth in Washington, DC, and worked as a research site coordinator for the Urban Institute in Topeka, Kansas. As an undergraduate, Ms. Balogh worked as a management intern with the Arizona State University Office of University Initiatives, a strategic planning group for the university.

Sally Cluchey (née Robinson), M.S., is currently a research associate with the Engelberg Center for Health Care Reform at the Brookings Institution. There she is responsible for working with multiple stakeholders to develop the infrastructure, methods, and governance structure necessary to conduct active medical product safety surveillance and comparative effectiveness research. Before she joined Brookings, she was a program officer with the Institute of Medicine (IOM). At the IOM, she staffed multiple projects, including the consensus study on Comparative Effectiveness Research Prioritization, where she helped to write the report *Initial Priorities for Comparative Effectiveness Research*, and served for 2 years as staff to the Forum on Drug Discovery, Development, and Translation. While working on the Forum, Ms. Cluchey was responsible for several key IOM initiatives involving the science of drug safety, Food and Drug

Administration policy, funding models for drug development, and improving the clinical research process. Before she joined the IOM in 2006, she worked for the Walter Reed Army Institute of Research's Malaria Vaccine Development Program, where she managed the manufacture, preclinical, and Phase I development of multiple vaccine candidates and coordinated regulatory submissions. Ms. Cluchey holds a master's of science in biomedical science and regulatory compliance from Hood College and a bachelor of arts from Kenyon College.

Lisa Boyette, M.D., completed an M.D. at the University of Virginia in 2007 and is now working on a Ph.D. in molecular physiology and biological physics at the National Institutes of Health (NIH). Her research at NIH focuses on stem cell reprogramming techniques and how reprogramming technology can be applied to cell-based therapies and tissue engineering. Dr. Boyette studied biomedical engineering and physics as an undergraduate at Virginia Commonwealth University and the Medical College of Virginia. After the completion of her Ph.D., she plans to complete residency training in neurosurgery.

Sharon Murphy, M.D., joined the Institute of Medicine (IOM) as a scholar-in-residence in October 2008, coming to Washington, DC, from Texas, where she was the inaugural director of the Greehey Children's Cancer Research Institute and professor of pediatrics at the University of Texas Health Science Center at San Antonio. Dr. Murphy brings more than 30 years of experience in academic medicine, pediatric oncology, and clinical research to the IOM. A graduate of Harvard Medical School, she has previously held positions at the Northwestern University Feinberg School of Medicine; Children's Memorial Hospital in Chicago, Illinois; and St. Jude Children's Research Hospital. She has served as an adviser to the National Cancer Institute and the Food and Drug Administration. At the IOM, she is working on projects relating to national cancer policy, cancer clinical trials, the oncology workforce, and the learning health care system for cancer.

Michael Park is a senior program assistant for the Board on Health Care Services and the National Cancer Policy Forum. Before arriving at the Institute of Medicine in September of 2007, Mr. Park worked for the National Academy of Education and the International Law Group in Washington, DC. He earned a bachelor's in German and Italian Studies from the University of Maryland at College Park. He is fluent in Spanish, Italian, and German and plans to pursue studies in environmental health and urban design at the University of Maryland.

Roger Herdman, M.D., received undergraduate and medical school degrees from Yale University. After an internship at the University of Minnesota and a stint in the U.S. Navy, he returned to Minnesota, where he completed a residency in pediatrics and a fellowship in immunology and nephrology and where he served on the faculty. He served as professor of pediatrics at Albany Medical College until 1979. In 1969, Dr. Herdman was appointed director of the New York State Kidney Disease Institute in Albany and shortly thereafter was appointed deputy commissioner of the New York State Department of Health (1969 to 1977). In 1977, he was named New York State's Director of Public Health. From 1979 until joining the U.S. Congress's Office of Technology Assessment (OTA), he served as a vice-president of the Memorial Sloan-Kettering Cancer Center in New York City. In December 1983, Dr. Herdman was named assistant director of OTA, where he subsequently served as director (1993 to 1996). He later joined the National Academies Institute of Medicine (IOM) as a senior scholar and directed studies on graduate medical education, organ transplantation, silicone breast implants, and the U.S. Department of Veterans Affairs national formulary. Dr. Herdman was appointed director of the IOM/NRC National Cancer Policy Board from August 2000 through April 2005. From May 2005 until September 2009, Dr. Herdman directed the IOM National Cancer Policy Forum, which includes federal and private-sector agencies or organizations relevant to cancer, in addition to academic/industry members. In October 2007, he was also appointed director of the IOM Board on Health Care Services. During his time at the IOM, Dr. Herdman has worked closely with the U.S. Congress on a wide variety of health care policy issues.

Acronyms

AACI	Association of American Cancer Institutes
AAMC	American Association of Medical Colleges
ACOSOG	American College of Surgeons Oncology Group
ACRIN	American College of Radiology Imaging Network
ACS CAN	American Cancer Society Cancer Action Network
AE	adverse event
AHRQ	Agency for Healthcare Research and Quality
AIPC	androgen-independent prostate cancer
ALERT Act	21st Century Cancer Access to Life-Saving Early Detection, Research, and Treatment Act
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ARRA	American Recovery and Reinvestment Act of 2009
ASCO	American Society of Clinical Oncology
BCG	bacillus Calmette-Guérin
BICR	blinded independent central review
BIG	Breast International Group
BRB	Biometric Research Branch
BSA	Board of Scientific Advisors (National Cancer Institute)
CALGB	Cancer and Leukemia Group B
CCG	Children's Cancer Group
CCOP	Community Clinical Oncology Program
CCSG	Cancer Center Support Grant

CER	comparative effectiveness research
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CIRB	central institutional review board
CLL	chronic lymphocytic leukemia
CMS	Centers for Medicare & Medicaid Services
COG	Children's Oncology Group
CRADA	Cooperative Research and Development Agreement
CRI	Clinical Research Initiative (Association of American Cancer Institutes)
CSDD	Center for the Study of Drug Development
CT	computed tomography
CTAC	Clinical Trials Advisory Committee
CTEP	Cancer Therapy Evaluation Program
CTMB	Clinical Trials Monitoring Branch
CTROC	Clinical Trials and Translational Research Operations Committee
CTSA	Clinical and Translational Science Awards
CTSU	Cancer Trials Support Unit
CTTI	Clinical Trials Transformation Initiative
CTU	Clinical Trials Unit
CTWG	Clinical Trials Working Group
CYP2D6	cytochrome P-450 2D6
DCE-MRI	dynamic contrast-enhanced magnetic resonance imaging
DCPC	Division of Cancer Prevention and Control
DCTD	Division of Cancer Treatment and Diagnosis
DCTDC	Division of Cancer Treatment, Diagnosis, and Centers
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMR	electronic medical record
EORTC	European Organisation for Research and Treatment of Cancer
ER	estrogen receptor
ERISA	Employee Retirement Income Security Act of 1974
5-FU	fluorouracil
^{18}F-FDG	fluorine-18 fluorodeoxyglucose
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FNIH	Foundation for the National Institutes of Health
FOLFOX4	oxaliplatin, 5-fluorouracil, and leucovorin

FTE	full-time equivalent
GIST	gastrointestinal stromal tumors
GOG	Gynecologic Oncology Group
HER-2	human epidermal growth factor receptor 2
HHS	U.S. Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed-consent form
IDB	Investigational Drug Branch
IDE	investigational device exemption
IND	investigational new drug
IOM	Institute of Medicine
IP	intellectual property
IRB	institutional review board
I-SPY TRIAL	Investigation of Serial studies to Predict Your Therapeutic Response with Imaging And moLecular analysis
KRAS	Kirsten *ras*
LOI	letter of intent
MAMS	multiarm, multistage (trial design)
MARVEL	Marker Validation for Erlotinib in Lung cancer
MINDACT	Microarray in Node-negative Disease may Avoid ChemoTherapy
MMRC	Multiple Myeloma Research Consortium
MRC	Medical Research Council
MRD	minimal residual disease
MRI	magnetic resonance imaging
NBL	neuroblastoma
NCAB	National Cancer Advisory Board
NCCF	National Children's Cancer Foundation
NCCN	National Comprehensive Cancer Network
NCCTG	North Central Cancer Treatment Group
NCD	National Coverage Decision
NCI	National Cancer Institute
NIH	National Institutes of Health
NNCO	National Nanotechnology Coordination Office
NSABP	National Surgical Adjuvant Breast and Bowel Project
NSCLC	non-small-cell lung cancer

NSET	Nanoscale Science, Engineering, and Technology Subcommittee
OCR	Office for Civil Rights (U.S. Department of Health and Human Services)
OEWG	Operational Efficiency Working Group
OHRP	Office for Human Research Protections (U.S. Department of Health and Human Services)
pCR	pathologic complete response
PERCIST	PET Response Criteria in Solid Tumors
PET	positron emission tomography
Ph+	Philadelphia chromosome positive
POG	Pediatric Oncology Group
QIBA	Quantitative Imaging Biomarkers Alliance
QOPI	Quality Oncology Practice Initiative
RECIST	Response Evaluation Criteria in Solid Tumors
RTOG	Radiation Therapy Oncology Group
SACHRP	Secretary's Advisory Committee on Human Research Protections
SPECT	single-photon emission computed tomography
SPORE	Specialized Programs of Research Excellence
STAMPEDE	Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy
STPI	Science and Technology Policy Institute
SWOG	Southwest Oncology Group
TAILORx	Trial Assigning IndividuaLized Options for Treatment
TRWG	Translational Research Working Group
Tufts CSDD	Tufts Center for the Study of Drug Development
US	ultrasound
VA	U.S. Department of Veterans Affairs
VEGF	vascular endothelial growth factor

Glossary

Accrual—the enrollment of qualified patients into clinical trials

Adaptive trial design—trials that incorporate one or more decision points into their design. How a trial proceeds following each decision point depends on the data observed up to that point

Adenoma—a tumor that is not cancer. It starts in gland-like cells of the epithelial tissue (thin layer of tissue that covers organs, glands, and other structures within the body)

Adjuvant therapy—additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy

Adverse event—an unexpected medical problem that happens during treatment with a drug or other therapy. Adverse events do not have to be caused by the drug or therapy, and they may be mild, moderate, or severe. Also called adverse effect

Alkylating agent—a type of drug that is used in the treatment of cancer. It interferes with the cell's DNA and inhibits cancer cell growth

All-trans retinoic acid—a nutrient that is used to treat acute promyelocytic leukemia (a fast-growing cancer in which there are too many immature

blood-forming cells in the blood and bone marrow). All-trans retinoic acid is being studied in the prevention and treatment of other types of cancer. Also called ATRA, retinoic acid, tretinoin, and vitamin A acid

Analytical validation—assessing an assay and its measurement performance characteristics, determining the range of conditions under which the assay will give reproducible and accurate data

Angiogenesis—blood vessel formation. Tumor angiogenesis is the growth of new blood vessels that tumors need to grow. This is caused by the release of chemicals by the tumor

Annotated specimens—samples of material, such as urine, blood, tissue, cells, DNA, RNA, and protein that are associated with clinical information

Antibody—a protein made by plasma cells (a type of white blood cell) in response to an antigen. Each antibody can bind to only one specific antigen

Antifolate—a substance that blocks the activity of folic acid. Antifolates are used to treat cancer. Also called folate antagonist

Antigen—any substance that causes the body to make a specific immune response

Apoptosis—a type of cell death in which a series of molecular steps in a cell leads to death. This is the body's normal way of getting rid of unneeded or abnormal cells. The process of apoptosis may be blocked in cancer cells. Also called programmed cell death

Assay—a laboratory test to find and measure the amount of a specific substance

Back office operations—also called back-end processes, those operations that rarely directly interface with a customer

Bayesian—a trial design that considers the treatment effect as a random variable with a probability distribution rather than as an unknown constant that the investigator wishes to estimate

Bevicizumab (Avastin)—a monoclonal antibody used to treat several types of cancer, including certain types of colorectal, lung, breast, and kidney cancers and glioblastoma. Bevacizumab binds to vascular endothelial growth

factor (VEGF) and may prevent the growth of new blood vessels that tumors need to grow

Bias—a systematic as opposed to random distortion of a statistic as a result of a sampling procedure

Biomarker—a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

Biomarker qualification—the evidentiary process of linking a biomarker with biological processes and clinical endpoints

Biomedical imaging—the technique and processes used to create images of the human body for clinical purposes or medical science

Biorepository—a facility that collects, catalogs, and stores samples of biological material, such as urine, blood, tissue, cells, DNA, RNA, and protein, from humans for laboratory research. Medical information may also be stored along with a written consent to use the samples in laboratory studies

Biospecimen—samples of material, such as urine, blood, tissue, cells, DNA, RNA, and protein

b-raf—a gene that makes a protein called B-RAF, which is involved in sending signals in cells and in cell growth. This gene may be mutated (changed) in many types of cancer, which causes a change in the B-RAF protein. This can increase the growth and spread of cancer cells

Cancer staging—describes the extent or severity of an individual's cancer

Case report form—a paper or electronic questionnaire used to collect data from trial sites participating in a clinical trial. Case report forms include data on each patient participating in a clinical trial, including adverse events.

Cervical cancer—cancer that forms in tissues of the cervix. It is usually a slow-growing cancer that may not have symptoms and is almost always caused by human papillomavirus infection

Cetuximab (Erbitux)—a monoclonal antibody used to treat certain types of cancer. Cetuximab binds to the epidermal growth factor receptor (EGFR), which is found on the surface of some types of cancer cells

Chemoprevention—the use of drugs, vitamins, or other agents to try to reduce the risk of, or delay the development or recurrence of, cancer

Chemoradiotherapy—treatment that combines chemotherapy with radiation therapy

Chemotherapy—treatment with drugs that kill cancer cells

Cisplatin (platinol)—a drug containing platinum used to treat many types of cancer. It kills cancer cells by damaging their DNA and stopping them from dividing.

c-kit—a gene that makes a protein found on the surface of some cells that binds to stem cell factor (a substance that causes certain types of cells to grow). Altered forms of this receptor may be associated with some types of cancer. Also called stem cell factor receptor

Clinical decision support—a clinical system, application, or process that helps health professionals make clinical decisions to enhance patient care

Coinsurance—describing the joint assumption of risk between the insurer and the insured that can be represented as a percentage or as a flat rate (copayment)

Colorectal cancer—cancer that develops in the colon (the longest part of the large intestine) and/or the rectum (the last several inches of the large intestine before the anus)

Combination products—multiple therapeutic agents that are used together in a treatment, or a therapeutic agent accompanied by a diagnostic test

Combination therapy—treatment using more than one anticancer drug

Common Rule—the term used by 18 federal agencies that have adopted the same regulation governing the protection of human subjects of research (Subpart A of 45 Code of Federal Regulations [C.F.R.] part 46)

Community-based participatory research—a collaborative approach to research, bringing community members into the research process as partners to develop studies and disseminate knowledge gained

Comorbidity—the condition of having two or more diseases at the same time

Comparative effectiveness research—the conduct and synthesis of systematic research comparing different interventions and strategies to prevent, diagnose, treat and monitor health conditions

Computed tomography (CT)—a series of detailed pictures of areas inside the body taken from different angles. The pictures are created by a computer linked to an x-ray machine

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 government 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 NCI

Correlative science—a general term referring to research done on biospecimens that are collected during clinical trials

Current Procedural Terminology (CPT)—a medical nomenclature used to report medical procedures and services under public and private health insurance programs

Cyclophosphamide—a synthetic alkylating agent chemically related to the nitrogen mustards with antineoplastic and immunosuppressive activities. In the liver, cyclophosphamide is converted to the active metabolites aldophosphamide and phosphoramide mustard, which bind to DNA, thereby inhibiting DNA replication and initiating cell death

Cytogenetic marker—chromosomal abnormalities that can be detected in cells microscopically

Cytostatic—stopping cells from multiplying

Cytotoxic—cell-killing

Dexamethasone—a synthetic steroid used to treat leukemia and lymphoma and may be used to treat some of the problems caused by other cancers and their treatment

Digital mammography—the use of a computer, rather than x-ray film, to create a picture of the breast

Dosimetry—measurement of radiation exposure from x-rays, gamma rays, or other types of radiation used in the treatment or detection of diseases, including cancer

Doxorubicin—an anthracycline antitumor antibiotic drug that is used to treat many types of cancer by damaging DNA and cancer cells

Efficacy—the ability of an intervention to produce the desired beneficial effect

Eligibility criteria—requirements that must be met for an individual to be included in a clinical trial. Examples of eligibility criteria include age, type and stage of cancer, general health, and previous treatment

Endometrial cancer—cancer that forms in the tissue lining of the uterus

Epidermal growth factor receptor (EGFR)—the protein found on the surface of some cells and to which epidermal growth factor binds, causing the cells to divide. It is found at abnormally high levels on the surface of many types of cancer cells, so these cells may divide excessively in the presence of epidermal growth factor

Estrogen receptor (ER)—a protein found inside the cells of the female reproductive tissue, some other types of tissue, and some cancer cells. The hormone estrogen will bind to the receptors inside the cells and may cause the cells to grow

Exogenous probes—targeted contrast agents used in molecular imaging

Finasteride—a drug used to reduce the amount of male hormone (testosterone) produced by the body

Flourine-18 fluorodeoxyglucose (^{18}F-FDG)—a marker for the elevated level of glucose metabolism that occurs in most cancers

Fluorouracil (5-FU)—an antimetabolite drug used in cancer treatment. The drug may kill cancer cells by stopping cells from making DNA

Formalin-fixed, paraffin-embedded tissue—a tissue sample that has been preserved to enable pathological or molecular analysis

Frequentist—an approach to statistical inference based on quantifying the frequency with which errors in rejecting or not rejecting a specific hypothesis would be made if an experiment were repeated many times

Front office operations—also called front-end processes in information systems, are those operations that interface directly with the customer (in this case, patients and physicians)

Gastrointestinal stromal tumor (GIST)—a type of tumor that usually begins in cells in the wall of the gastrointestinal tract

Gemtuzumab ozogamicin—a monoclonal antibody combined with a toxic substance that is used to treat certain types of acute myeloid leukemia in older patients and is being studied in the treatment of other types of cancer

Genome—an organism's entire complement of DNA, which determines its genetic makeup

Genomics—the study of the complete genetic material, including genes and their functions, of an organism

Germline DNA—the DNA in germ cells. Germline DNA is the source of DNA for all other cells in the body

Glioma—a cancer of the brain that begins in glial cells (cells that surround and support nerve cells)

Glycolysis—a process in which glucose is partially broken down by cells in enzyme reactions that do not need oxygen. Glycolysis is one method that cells use to produce energy. When glycolysis is linked with other enzyme reactions that use oxygen, more complete breakdown of glucose is possible and more energy is produced

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

Head and neck cancer—cancer that arises in the head or neck region (in the nasal cavity, sinuses, lips, mouth, salivary glands, throat, or larynx)

Health Insurance Portability and Accountability Act of 1996 (HIPAA)—an Act that requires, among other things, under the Administrative Simplification subtitle, the adoption of standards for protecting the privacy and security of personally identifiable health information

Hematologic malignancies—cancer of the blood or bone marrow, such as leukemia or lymphoma

Hepatocellular carcinoma—a primary cancer of the liver

Histologic subtypes—categories of cancer based on microscopic appearance of the tissue

Human epidermal growth factor receptor 2 (HER-2)—a tyrosine kinase receptor, found on some types of cancer cells, including breast and ovarian. Cancer cells removed from the body may be tested for the presence of HER-2 to help decide the best type of treatment

Hypoxia—a condition in which there is a decrease in the oxygen supply to a tissue. In cancer treatment, the level of hypoxia in a tumor may help predict the response of the tumor to the treatment

Imatinib mesylate (Gleevec)—a drug used to treat different types of leukemia and other cancers. Imatinib mesylate blocks the protein made by the bcr/abl oncogene. It is a type of tyrosine kinase inhibitor

Immunophenotyping—a process used to identify cells, based on the types of antigens or markers on the surface of the cell. This process is used to diagnose specific types of leukemia and lymphoma by comparing the cancer cells to normal cells of the immune system

Immunostaining—use of an antibody-based method of detection

Immunotherapy—treatment to boost or restore the ability of the immune system to fight cancer, infections, and other diseases. Also used to lessen certain side effects that may be caused by some cancer treatments. Agents used in immunotherapy include monoclonal antibodies, growth factors, and vaccines. These agents may also have a direct antitumor effect. Also called biological response modifier (BRM) therapy, biological therapy, and biotherapy

In vivo—in the body

Incidence—the number of new cases of a disease diagnosed each year

Indication—the use of a particular drug or diagnostic test for a specific disease or condition

Informed consent—a legal form required by the Common Rule that describes the potential risks and benefits of research and seeks permission to involve the subject

Institutional Review Board (IRB)—"An administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the institution with which it is affiliated. The IRB has the authority to approve, require modification in, or disapprove all research activities that fall within its jurisdiction as specified by both the federal regulations and local institutional policy" (Department of Health and Human Services IRB Guidebook)

Interoperability—the ability of two or more systems or components to exchange information and use the information that has been exchanged

Investigational device exemption (IDE)—an FDA designation that allows an investigational device to be used in a clinical study to collect safety and effectiveness data supporting a premarket approval application or a premarket notification submission

Investigational new drug application (IND)—a new molecular, antibiotic, or biological drug that is used in a clinical investigation. It also includes biological products used in vivo for diagnostic purposes

KRAS—the *Kras* gene makes the *KRAS* protein, which is involved in cell signaling pathways, cell growth, and cell death, and may cause cancer when mutated. Agents that block the activity of the mutated *Kras* gene or its protein may stop the growth of cancer.

Large-scale genomic profiling—a strategy that identifies nucleic acid sequences of interest in patient samples

Leukemia—cancer that starts in blood-forming tissue such as the bone marrow and causes large numbers of blood cells to be produced and enter the bloodstream

Levamisole—an antiparasitic drug that is also being studied in cancer therapy with fluorouracil

Ligand—a molecule that binds to another molecule (i.e., an antigen that binds to a specific antibody)

Lumpectomy—surgery to remove abnormal tissue or cancer from the breast and a small amount of normal tissue around it. It is a type of breast-sparing surgery

Lymph node negative (node negative)—cancer that has not spread to the lymph nodes

Lymphoma—cancer that begins in cells of the immune system

Macromolecule—a very large molecule consisting of many smaller structural units, such as nucleic acids, proteins, carbohydrates, or lipids

Magnetic resonance imaging (MRI)—a procedure in which radio waves and a powerful magnet linked to a computer are used to create detailed pictures of areas inside the body that can show the difference between normal and diseased tissue

Magnetic resonance spectroscopy—a noninvasive imaging method that provides information about cellular activity (metabolic information). It is used along with MRI, which provides information about the shape and size of the tumor (spatial information). Also called 1H-nuclear magnetic resonance spectroscopic imaging, MRSI, and proton magnetic resonance spectroscopic imaging.

Mastectomy—surgery to remove the breast (or as much of the breast tissue as possible)

Maximum tolerated dose—the highest dose of a drug or treatment that does not cause unacceptable side effects. The maximum tolerated dose is determined in clinical trials by testing increasing doses on different groups of people until the highest dose with acceptable side effects is found

Medulloblastoma—a malignant brain tumor that begins in the lower part of the brain and that can spread to the spine or to other parts of the body. Medulloblastomas are a type of primitive neuroectodermal tumor (PNET)

Melanoma—a form of cancer that begins in melanocytes (cells that make the pigment melanin). It may begin in a mole (skin melanoma), but can also begin in other pigmented tissues, such as in the eye or in the intestines

Mercaptopurine—a drug used to treat acute lymphocytic leukemia. It belongs to the family of drugs called antimetabolites. Also called Purinethol

Messenger RNA—single-stranded RNA molecule that is complementary to one of the DNA strands of a gene

Metabolomics—the systematic study of the unique chemical fingerprints that specific cellular processes leave behind; that is, small-molecule metabolites

Metastatic—having to do with metastasis, which is the spread of cancer from the primary site to other places in the body

Minimal residual disease—detection of small numbers of leukemia cells that are undetectable by conventional morphologic methods, using assays with greater sensitivity

Molecular biology—the branch of biology that deals with the formation, structure, and function of macromolecules essential to life, such as nucleic acids and proteins, and especially with their role in cell replication and the transmission of genetic information

Molecular genetic marker—biomarkers that are specific sequences of DNA

Molecular profiling—using genomics, proteomics, imaging, and bioinformatics to provide a molecular portrait of an individual patients' disease

Morbidity—a disease or the incidence of disease within a population. Morbidity also refers to adverse effects caused by a treatment

Mortality—refers to the death rate, or the number of deaths in a certain group of people in a certain period of time. Mortality may be reported for people who have a certain disease, live in one area of the country, or who are of a certain gender, age, or ethnic group

Multiarm, multistage (MAMS) trial design—a trial design testing a number of new agents (and combinations of agents) simultaneously against a single control arm

Multimodality—therapy that combines more than one method of treatment

Myelodysplastic syndromes—a group of diseases in which the bone marrow does not make enough healthy blood cells. Also called preleukemia

Myeloma—cancer that arises in plasma cells, a type of white blood cell

Nanoparticle—a particle of that is smaller than 100 nanometers (one-billionth of a meter). In medicine, nanoparticles can be used to carry antibodies, drugs, imaging agents, or other substances to certain parts of the body. Nanoparticles are being studied in the detection, diagnosis, and treatment of cancer

Nanotechnology—the field of research that deals with the engineering and creation of things from materials that are less than 100 nanometers (one-billionth of a meter) in size, especially single atoms or molecules. Nanotechnology is being studied in the detection, diagnosis, and treatment of cancer

Neoadjuvant therapy—treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy

Neovacularization—altered blood volume, permeability, perfusion, and vascularity of the tumor tissue

Neuroblastoma—cancer that arises in immature nerve cells and affects mostly infants and children

Non-Hodgkin's lymphoma—a large, diverse group of cancers of the immune system cells

Non-small cell lung cancer—a group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of non-small cell lung cancer are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. Non-small cell lung cancer is the most common kind of lung cancer

Oncogene—a gene that is a mutated (changed) form of a gene involved in normal cell growth. Oncogenes may cause the growth of cancer cells

Oncotype DX—assay that measures the expression of 21 genes to predict the likelihood of recurrence of ER-positive lymph node-negative breast cancer

Ovarian cancer—cancer that forms in the tissues of the ovary; most ovarian cancers are either ovarian epithelial carcinomas (cancer that begins in

the cells on the surface of the ovary) or malignant germ cell tumors (cancer that begins in egg cells)

P13K/Akt/mTOR (PAM)—a pathway that regulates several normal cellular functions that are important for tumorigenesis

Paclitaxel (Taxol)—an antimitotic drug used to treat several types of cancer by blocking cell growth by stopping cell division

Panitumumab (Vectibix)—a human monoclonal antibody that is being used to treat colorectal cancer that has spread to other parts of the body and is also being studied in the treatment of other types of cancer. Panitumumab binds to the epidermal growth factor receptor (EGFR) and may block tumor cell growth

Peptide—a molecule that contains two or more amino acids (molecules that join together to form proteins)

Performance status—a measure of how well a patient is able to perform ordinary tasks and carry out daily activities

Personalized medicine—leveraging scientific advances in fields such as genomics, proteomics, molecular biology, and metabolomics to improve the extent to which medical care is personalized to an individual patient and his or her cancer

Pharmacodynamics—the study of the biochemical and physiological effects of drugs and the mechanisms of their actions

Pharmacogenetics—the study of how a person's genes affect the way he or she responds to drugs. The goal of pharmacogenetics is to predict what the best drug or the best dose of a drug will be for a person. Also called pharmacogenomics

Pharmacology—the study of drug action

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

Placebo—an inactive substance or treatment that looks the same as, and is given the same way as, an active drug or treatment being tested. The effects of the active drug or treatment are compared to the effects of the placebo

Positron emission tomography (PET)—a nuclear imaging technique used in medicine in which a small amount of radioactive compound, such as glucose (sugar), is injected into a vein, and a scanner is used to make detailed, computerized pictures of areas inside the body where the glucose is used. Because cancer cells often use more glucose than normal cells, the pictures can be used to find cancer cells in the body. Also called positron emission tomography scan

Practice guidelines—evidence-based recommendations to guide patient treatment decisions

Preclinical study—research using animals to find out if a drug, procedure, or treatment is likely to be useful. Preclinical studies usually take place before clinical trials in humans are conducted

Precompetitive—collaboration among competitors to achieve goals that cannot be feasibly attained alone and have the potential to benefit everyone

Predictive biomarker—a biomarker that can identify populations that are likely to be sensitive or resistant to specific treatments

Prevalence (disease)—the number of existing cases of a disease in a given population at a specific time

Prevention—action taken to decrease the risk of getting a disease or condition

Principal investigator—a lead investigator for a research project, such as a clinical trial, who takes direct responsibility for the completion of a funded project

Privacy Rule—a federal regulation establishing national standards to protect individuals' medical records and other health information. The Rule requires appropriate safeguards to protect the privacy of personal health

information, and sets limits and conditions on the uses and disclosures that may be made of such information without patient authorization

Process map—a description of the organizations and decision-making steps involved in a process

Prognosis—the likely outcome or course of a disease; the chance of recovery or recurrence

Prognostic biomarker—a biomarker that can predict disease progression in the absence of treatment considerations

Progression free survival—the length of time during and after treatment in which a patient is living with a disease that does not get worse. Progression-free survival may be used in a clinical study or trial to help find out how well a new treatment works

Prospective biomarker-drug codevelopment studies—study designs that simultaneously evaluate the utility of predictive biomarkers and the effect of therapy on outcomes

Prospective biomarker validation studies—studies using a prospective design to test the validity of a predictive biomarker for selecting patient therapy

Prospective design—in medicine, a study or clinical trial in which participants are identified and then followed forward in time

Prostate cancer—cancer that grows in the tissues of the prostate

Protected health information—as defined in the Privacy Rule, protected health information is personally identifiable health information created or received by a covered entity

Proteomics—the study of the structure and function of proteins, including the way they work and interact with each other inside cells

Protocol—a detailed plan of a scientific or medical experiment, treatment, or procedure. In clinical trials, it states what the study will do, how it will be done, and why it is being done. It explains how many people will be in the study, who is eligible to take part in it, what study drugs or other interventions will be given, what tests will be done and how often, and what information will be collected

Radiation therapy—the use of high-energy radiation from x-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors

Radionuclide—an unstable form of a chemical element that releases radiation as it breaks down and becomes more stable. Radionuclides may occur in nature or be made in a laboratory. In medicine, they are used in imaging tests and in treatment

Radiopeptide—a compound consisting of two or more amino acids (the building blocks of proteins) that has been joined with a radioactive substance for use in biomedical imaging and/or therapy

Raloxifene—a selective estrogen receptor modulator drug used to reduce the risk of invasive breast cancer in postmenopausal women who are at high risk of the disease or who have osteoporosis. It is also being studied in the prevention of breast cancer in certain premenopausal women and in the prevention and treatment of other conditions. Raloxifene blocks the effects of the hormone estrogen in the breast and increases the amount of calcium in bone

Randomized controlled trial (RCT)—a study in which the participants are assigned by chance to separate groups that compare different treatments; neither the researchers nor the participants can choose which group. Using chance to assign people to groups means that the groups will be similar and that the treatments they receive can be compared objectively. At the time of the trial, it is not known which treatment is best

Randomized distribution trial design—a trial design that enriches the patient population with likely responders

RECIST (Response Evaluation Criteria in Solid Tumors) guidelines—a standard set of criteria to assess treatment response via biomedical imaging

Recurrence—cancer that has recurred (come back), usually after a period of time during which the cancer could not be detected. The cancer may come back to the same place as the original (primary) tumor or to another place in the body

Remission—a decrease in or disappearance of signs and symptoms of cancer. In partial remission, some, but not all, signs and symptoms of cancer have disappeared. In complete remission, all signs and symptoms of cancer have disappeared, although cancer still may be in the body

Repository—see Biorepository

Retrospective analysis—a study design that starts with the present condition of a population of individuals and collects data about their past history

Rhabdomyosarcoma—cancer that forms in the soft tissues in a type of muscle called striated muscle. Rhabdomyosarcoma can occur anywhere in the body

Routine care—care that would be received by a patient undergoing standard treatment, and would include such items as room and board for patients who are hospitalized, diagnostic and laboratory tests and monitoring appropriate to the patient's condition, post-surgical care when indicated, office visits, and so on

Screening—checking for disease when there are no symptoms

Selection bias—this phenomenon occurs when data are more likely to be collected from one subset of the population than from a representative sample of the entire population. This can cause systematic differences between the characteristics of the individuals included in a study and the individuals not included

Signal transduction—the process by which a cell responds to substances in its environment. The binding of a substance to a molecule on the surface of a cell causes signals to be passed from one molecule to another inside the cell. These signals can affect many functions of the cell, including cell division and cell death. Cells that have permanent changes in signal transduction molecules may develop into cancer

Single photon emission computed tomography (SPECT)—a special type of computed tomography (CT) scan in which a small amount of a radioactive drug is injected into a vein and a scanner is used to make detailed images of areas inside the body where the radioactive material is taken up by the cells. SPECT can give information about blood flow to tissues and chemical reactions (metabolism) in the body

Sorafenib (nexavar)—a kinase inhibitor that stops cells from dividing and may prevent the growth of new blood vessels that tumors need to grow. Sorafenib is used to treat advanced kidney cancer and a type of liver cancer that cannot be removed by surgery

Standard of care—in medicine, treatment that experts agree is appropriate, accepted, and widely used. Also called best practice and standard therapy

Standard operating procedures (SOPs)—instructions detailing steps and activities of a process or procedure

Tamoxifen—a drug that interferes with the activity of estrogen, a female hormone, and used to treat breast cancer

Targeted therapy—a type of treatment that uses drugs or other substances (such as monoclonal antibodies) to identify and attack cancer cells without harming normal cells. Targeted therapy may be less harmful to normal cells than other types of cancer treatments

Thalidomide—an angiogenesis inhibitor drug that is used to treat multiple myeloma in patients who have just been diagnosed

Thoracic—having to do with the chest

Time to progression—a measure of time after a disease is diagnosed (or treated) until the disease starts to get worse

Toxicity—the extent to which something is poisonous or harmful

Translational research—a term used to describe the process by which the results of research done in the laboratory are used to develop new ways to diagnose and treat disease

Trastuzumab—a monoclonal antibody that binds to HER-2 (human epidermal growth factor receptor 2), and can kill HER-2-positive cancer cells. Used to treat breast cancer that is HER-2 positive

Trial concept—an initial idea for a clinical trial

Tumor response—a change in tumor size, usually defined as tumor shrinkage by 50 percent bidimensionally or 30 percent unidimensionally

Type I error—also known as a "false positive," occurs when a difference is observed when in truth there is none

Type II error—also known as a "false negative," the error of failing to observe a difference when in truth there is one

Tyrosine kinase inhibitor—a drug that interferes with cell communication and growth and may prevent tumor growth

Ultrasound—a procedure in which high-energy sound waves are bounced off internal tissues or organs and make echoes. The echo patterns are shown on the screen of an ultrasound machine, forming a picture of body tissues

Vincristine (oncovin) sulfate—a drug used to treat acute leukemia that blocks cell growth by stopping cell division

Wilms' tumor—a disease in which malignant cells are found in the kidney, and may spread to the lungs, liver, or nearby lymph nodes. Wilms tumor usually occurs in children younger than 5 years old