CANCER CLINICAL TRIALS SYSTEM REFORM/REINVIGORATION


Coalition of Cancer Cooperative Groups: Guiding principles to ensure successful reconfiguration of the cancer cooperative groups, May 19, 2011.

Alliance for Clinical Trials in Oncology press release: Newly formed cancer cooperative group selects name, June 14, 2011.

ECOG-ACRIN Press release: Biomarker-drive science at the heart of the new ACRIN-ECOG structure, Mach 18, 2011.

Annual Plan and Budget Proposal for Fiscal Year 2012: Cancer; changing the conversation, excerpt on revitalizing the nation’s cancer clinical trials system, 2011.
A National Cancer Clinical Trials System for the 21st Century
Reinvigorating the NCI Cooperative Group Program

Advances in biomedical research continue to create significant opportunities for improving the detection, treatment, and prevention of cancer. But generating knowledge is only a start. Clinical trials that test the safety and therapeutic benefit of promising treatments are essential in translating new knowledge into tangible benefits for patients with cancer—the second leading cause of death in the United States, behind heart disease.

For the past 50 years, the National Cancer Institute’s (NCI) Clinical Trials Cooperative Group Program has played a key role in developing new and improved cancer therapies. The program’s 10 Cooperative Groups conduct clinical trials through networks of cancer centers and community oncology practices across the country. More than 25,000 patients and thousands of clinical investigators participate in the program’s clinical trials annually. Its efforts complement the clinical trials that pharmaceutical and biotechnology companies conduct, particularly by addressing questions that are less likely to be among industry’s top priorities. In recent years, however, many stakeholders—including clinical investigators, patient advocates, Cooperative Group leadership, industry participants, as well as the NCI—have expressed concerns that the program is falling short of its potential to conduct the timely, large-scale, innovative clinical trials needed to improve patient care. As a result, NCI asked the Institute of Medicine (IOM) to assess the state of cancer clinical trials, review the Cooperative Group Program, and provide advice on improvements.
Building on a Strong Foundation

The IOM’s report, *A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program*, reviews the roles of the various stakeholders involved in cancer clinical trials and recommends a series of changes across the board. The report’s authoring committee envisions a dynamic system that efficiently responds to emerging scientific knowledge; involves broad cooperation of stakeholders; and leverages evolving technologies to provide high-quality, practice-changing research. Clinical trial participation would be desirable for patients and physicians because it would provide access to innovative therapies that reflect patient preferences and are reimbursed. The report emphasizes the need to maintain a robust, standing cancer clinical trials network by preserving the historical strengths of the Cooperative Group Program while improving components that are not working well. The following overarching goals should guide improvement efforts:

- Improving the speed and efficiency of the design, launch, and conduct of clinical trials
- Making optimal use of scientific innovations
- Improving selection, prioritization, support, and completion of clinical trials
- Fostering expanded participation of both patients and physicians

Improving Speed and Efficiency

Clinical trials are complex endeavors that involve hundreds of steps and lengthy, iterative review processes by multiple oversight bodies with varying objectives and responsibilities. Inefficiencies in the processes used to develop, launch, and conduct clinical trials often lead to long delays. The average time required to design, approve, and activate a cancer clinical trial is two years. Given the pace at which new scientific findings are emerging, a trial concept may become outdated in that period. The committee recommends that protocol development be coordinated and streamlined by implementing the processes proposed by the Operational Efficiency Working Group.

The committee stresses the need to move beyond cooperation to integration by reorganizing clinical trial structures and operations into a truly national trials network. Among its recommended actions for improving overall operations, the report calls for consolidating many of the administrative functions and processes within the Cooperative Group Program, streamlining government oversight of trials, and enhancing collaboration among stakeholders. NCI should lead in instituting the necessary changes, but other federal agencies such as the Food and Drug Administration, as well as academic centers, community practices, and the pharmaceutical industry, will need to be involved in improving the system. NCI also should expand drug distribution and implement standardized case report forms and remote data capture systems to aid trial efficiency.

Incorporating Innovative Science

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, biomarkers (predictors of a response to a particular therapeutic intervention) increasingly are being used to select which treatment strategy is most likely to benefit individual patients. To advance this field, NCI should, among other actions, mandate that biospecimens collected from patients in the course of Cooperative Group trials be submitted to standardized central biorepositories supported by a national inventory and a defined peer-review process for accessing specimens for study.

The Cooperative Groups should lead in developing and testing innovative designs for clinical trials that evaluate multiple therapies, combinations of therapies, and biomarkers. The National Institutes of Health, including NCI, should take a
more systematic, multidisciplinary, and dynamic approach when developing standards for new scientific methods and technologies used in trials, to ensure appropriate and consistent use.

Prioritizing and Supporting Trials
The increasingly complex environment in which cancer clinical trials are conducted has created considerable challenges for the Cooperative Group Program. Inefficient interactions among the various stakeholders are contributing to delays in the system. To increase the speed of advances in oncology care, NCI should shift its primary focus from oversight to the facilitation of Cooperative Group trials. As part of this effort, NCI should streamline processes for prioritizing, selecting, and supporting clinical trials and for enrolling patients quickly after a trial is launched. Participating sites should be credentialed to enroll patients in any high-priority trial, and sites with low patient accrual should be eliminated.

NCI should allocate a larger portion of its research portfolio to the Cooperative Group Program. However, the trial prioritization and selection process should be strengthened so that only well-designed clinical trials that have the greatest possibility of improving survival and quality of life for cancer patients are undertaken. 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.

Patient and Physician Participation
A robust clinical trials infrastructure depends on a critical mass of physicians and patients willing to participate. But participation is not the norm today. Participation in clinical trials requires substantial resources and support staff. Clinical investigators and sites are not adequately reimbursed for the costs of participating in Cooperative Group trials. Moreover, the current system does not adequately reward collaborative work, and at academic medical centers, clinical investigation often is accorded less value than either basic research or patient care. 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. NCI and other stakeholders should explore and expand approaches for reducing career and financial concerns, such as providing salary support for protected research time.

Even if patients are eligible for trials and are informed about the option by their physicians, they may decline participation because of financial concerns, as coverage of patient care costs in clinical trials by health insurers is inconsistent. Among other actions, federal and state health benefits plans, private health insurers, and the Centers for Medicare and Medicaid Services should establish consistent payment policies to cover patient care costs (except for specific study-related costs that should be paid for by the drug or device manufacturer) in clinical trials approved through the NCI prioritization mechanism. As a quid pro quo, pri-
private insurers should be able to eliminate coverage of experimental therapies delivered outside of the clinical trial setting, but 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.

Conclusion

Improved treatments for cancer will be delayed and patient lives will be lost unnecessarily unless the efficiency and effectiveness of the clinical trials system improves. The implementation of the report’s collective recommendations will reinvigorate the NCI Clinical Trials Cooperative Group Program 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 single element of the Program or the clinical trials process will not suffice; changes across the board are urgently needed. All stakeholders, including physicians, patients, and health care insurers, as well as NCI, other federal agencies, academia, foundations, and industry, must reevaluate their roles and responsibilities in cancer clinical trials and work together to develop an improved, efficient multidisciplinary trials system. The health of nearly 1.5 million patients diagnosed with cancer in the U.S. each year depends on these efforts.
Implementing a National Cancer Clinical Trials System
for the 21st Century

An American Society of Clinical Oncology and Institute of Medicine
Workshop

INTRODUCTION

Clinical trials enable scientific discoveries to advance patient care, and they also inform
and guide subsequent research. The National Cancer Institute (NCI) supports the largest U.S.
network of clinical trials of any type, of which the largest component is the Clinical Trials
Cooperative Group Program (informally known as the Cooperative Group Program). It currently
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. Since its inception in the 1950s, the
Cooperative Group Program has been instrumental in establishing the standards for cancer
patient care and clinical research methods. Research performed by the Cooperative Groups has
significantly advanced cancer treatment and prevention (IOM, 2010).

However, despite its many and important accomplishments, the Cooperative Group
Program faces several challenges that threaten its ongoing productivity. Stagnant and declining
funding, inefficient processes, extensive and complex government oversight, and a lack of
resources to pursue cutting-edge research hinder the Cooperative Group Program’s ability to
translate research discoveries into timely clinical applications (IOM, 2010).

Recognizing the importance of maintaining an effective publicly funded clinical trials
system, the director of NCI at the time, John Niederhuber, requested that the Institute of
Medicine (IOM) conduct a consensus study of cancer clinical trials and the Cooperative Group
Program and develop recommendations as to how to improve the current system. In April 2010,
the consensus committee’s report, entitled A National Cancer Clinical Trials System for the 21st
Century: Reinvigorating the NCI Cooperative Group Program (IOM, 2010) was released to the
public.1 The report’s recommendations are summarized in Box 1.

The authoring committee of the report concluded (IOM, 2010):
“Collectively, the implementation of [the committee’s] 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”.

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1 The Executive Summary from the IOM consensus report appears in Appendix B of this workshop summary.

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**BOX 1**

**Summary of the IOM Consensus 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\(^6\) of the Cooperative Groups on the basis of peer review
2. Consolidate back office operations of the Cooperative Groups and improve processes\(^6\)
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

\(^6\)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.

\(^6\)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.


To discuss how best to achieve the aims underlying the recommendations in the IOM consensus report and to summarize progress to date toward addressing these recommendations, the IOM’s National Cancer Policy Forum and the American Society of Clinical Oncology convened a workshop on March 21, 2011, in Washington, D.C.. The goals of the workshops were to

1. Establish a venue to promote a collaborative approach by all stakeholders to implement recommended changes;
2. Provide a forum to ensure public involvement;
3. Document changes that take place; and
4. Facilitate progress toward the IOM committee’s goal of ensuring the continued viability and increased productivity of an NCI-funded clinical trials system with widespread academic involvement and community outreach.

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The workshop included four panel discussions, which focused on (1) the roles of NCI and the Cooperative Groups; (2) the role of payors; (3) interactions between industry, the Food and Drug Administration, and the publicly funded cancer clinical trials system; and (4) clinical trials investigators and patient advocates. This document summarizes the content of each workshop session, which included presentations by panel members and open discussion. The views expressed in this summary are those of the speakers and discussants, as attributed to them, and are not the consensus views of the workshop participants or members of the National Cancer Policy Forum.

Key Challenges Discussed at the Workshop

- How to effectively and efficiently consolidate the current nine adult Groups into fewer Groups.
- How to monitor ongoing changes and assess outcomes derived from those changes.
- How to overcome technical, structural, and procedural obstacles to conduct cutting edge clinical trials that are likely to advance patient care.
- How to ensure that the full portfolio of NCI-funded clinical trials is adequately evaluated and appropriately allocated.
- How to sufficiently fund the Cooperative Group Program.
- How to provide positive incentives for physicians and patients to participate in clinical trials.

PANEL I: NCI AND THE COOPERATIVE GROUPS

The first session of the workshop opened with accounts from representatives of NCI and leaders of the Cooperative Groups about the responses of their respective organizations to the IOM consensus report. Their five presentations were followed by a panel discussion involving additional Cooperative Group leaders.

NCI Perspective and Current Activities

Overview of the NCI Response

Dr. James Doroshow, director of NCI’s Division of Cancer Treatment and Diagnosis, opened the session with an account of that agency’s multifaceted efforts to address the IOM consensus report. “NCI is implementing a comprehensive approach to transforming its clinical trials system to create a highly integrated network that can address rapid advances in cancer biology,” he stated, noting that this process has been informed not only by recommendations from the IOM report, but by several others—most notably those of the Clinical Trials and Operational Efficiency Working Groups (CTWG and OEWG, respectively; NCI, 2005, 2010)—as well as by input from stakeholders. Focusing on the four overarching goals and twelve recommendations put forth in the IOM consensus report (see Box 1), Dr. Doroshow provided detailed documentation of progress in these areas, which is summarized in Table 1.
<table>
<thead>
<tr>
<th>Goal</th>
<th>Recommendation</th>
<th>NCI Response as of March 2011</th>
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<tbody>
<tr>
<td>1: Improve speed and efficiency of the design, launch, and conduct of clinical trials</td>
<td>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</td>
<td>Current focus on supporting up to four adult Cooperative Groups with continued funding of one pediatric Cooperative Group</td>
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<td>2: Require or facilitate consolidation of Group “back office” operations and, working with extramural community, make process improvement in operations and organizational management a priority.</td>
<td>Planning for NCI external peer review of all Groups in same review cycle with new review criteria emphasizing collaboration and evaluating Groups as partners in a National Clinical Trials Network</td>
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<td>3: The U.S. Department of Health and Human Services (HHS) should lead a trans-agency effort to streamline and harmonize government oversight and regulation of cancer clinical trials</td>
<td>Engaged in ongoing discussion with the Cooperative Group Chairs about potential consolidation activities with some Groups already taking first steps to consolidate (RTOG-NSABP; ACOSOG-CALGB-NCCTG; ECOG-ACRIN)</td>
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<td>Instituted comprehensive, centralized 24/7 patient registration for all Group trials, with regulatory and site verification of trial participation by the Cancer Trials Support Unit (CTSU)</td>
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<td>Implemented Operational Efficiency Working Group (OEWG) timelines for concept evaluation, protocol development, and trial activation</td>
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<td>Working with Groups on a single, harmonized approach to clinical trial management, including protocol authoring, case report forms, and standardized data collection and management</td>
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<td></td>
<td>Established an interagency agreement with the Food and Drug Administration (FDA) for early review of approved Cooperative Group Phase III treatment trials, allowing for 21-day review of a concept if it has been identified as a licensing trial</td>
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<td>Developed coordinated protocol development and review processes with Groups for Phase III trials developed under FDA Special Protocol Assessment (SPA)</td>
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<td>Developed adult and pediatric NCI Central Institutional Review Boards with the HHS Office of Human Research Protections (OHRP) for Group trials with recent major improvement in review time lines and plan for accreditation by the Association for the Accreditation of Human Research Protection Programs</td>
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<td>Working with the Center for Devices and Radiological Health (CDRH) of the FDA to coordinate</td>
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4: NCI should take steps to facilitate more collaboration among the various stakeholders in cancer clinical trials

early review of investigational devices (e.g., biomarker assays, genomic signatures) used in treatment trials

NCI is working across divisions to harmonize guidelines for programs engaged in the conduct of clinical trials so that the appropriate incentives are in place for collaboration among Cooperative Groups, Cancer Centers, and Specialized Programs of Research Excellence (SPORES)

In collaboration with CEO Roundtable on Cancer, developed Standard Terms of Agreement for Research Trials (START) clauses for company and academic collaborations; accelerated clinical trials negotiations

Assessing feasibility of developing standardized Material Transfer Agreements (MTAs) that cover intellectual property (IP) considerations for industry and academic institutions

Revised IP option on all Cancer Therapy Evaluation Program (CTEP) Cooperative Research and Development Agreements (CRADAs) relating to drug development and specimen use for correlative science; published in Federal Register March 11, 2011 (CTEP, 2011)

Revising Requests for Application (RFAs) for Resource-Related Research Project-Cooperative Agreement (U24) grants by the National Institutes of Health (NIH) for National Specimen Banks to include common operating procedures for samples collected from patients enrolled in Cooperative Group and other NCI-supported trials and to reflect consolidation of the Group system

Working with Groups to develop a common review process and procedures for requests for biospecimens banked from clinical trials

Identified need to develop shared information technology (IT) infrastructure to enhance specimen inventories

Initiated the Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP) to ensure that critical correlative studies could be incorporated in a timely manner into Phase III and large, multi-institutional Phase II trials during the process of concept development

From mid-2008 to 2010, 14 of 40 concepts incorporating predominantly integral and some integrated markers were supported for a total commitment to date of $22.5 million

Children’s Oncology Group Trial AAML0531 incorporating biomarkers completed (>1000 pts):

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7: NCI, in cooperation with other agencies, should establish a consistent, dynamic process to oversee development of national unified standards

8: NCI should reevaluate its role in the clinical trials system

3: Improve prioritization, selection, support, and completion of cancer clinical trials

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 Group trials

Modernizing the clinical trials IT infrastructure by procuring a clinical trials data management system that can be used across the NCI-supported Cooperative Group System

Enhancing trial participant diversity through support for Minority-Based Community Clinical Oncology Programs, Patient Navigator Research Program, and other NCI programs

Working with patient advocates in concept development and accrual planning, along with Cooperative Groups, disease steering committees, and Patient Advocate Steering Committee

10: NCI should allocate a larger

NCI developed targeted initiatives that have increased reimbursement to sites from $2,000 to

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portion of its research portfolio to the Clinical Trials Cooperative Group Program to ensure that the Program has sufficient resources to achieve its unique mission.

$5,000 per enrolled patient for large Phase II studies; additional funding provided for select Phase III trials based on complexity, as well as for critical biomarker, imaging, and quality-of-life studies.

Without an increase in resources, changes in the funding model must be considered in the context of the number of new trials, the total accrual that can be sustained, and the need for supporting correlative science. The need to focus on high-accruing organizations (half of sites accrue approximately 80% of patients) and the need for additional infrastructure support are under discussion with Cooperative Group chairs.

4: Incentivize the participation of patients and physicians in clinical trials

11: All stakeholders should work to ensure that clinical investigators have adequate training and mentoring, paid protected research time, necessary resources, and recognition.

NCI created the Clinical Investigator Team Leadership Award to promote collaborative science and recognize outstanding clinical investigators; first awarded in 2009.

12: Health care payment policies should value the care provided to patients in clinical trials and adequately compensate that care.

Worked with HHS Centers for Medicare and Medicaid Services (CMS) to establish pilot program for reimbursement for clinical trials care under a CMS national coverage decision for agents used for colorectal cancer, as well as on data collection to evaluate use of imaging and other clinical modalities.

Leading new CMS interagency (NIH-FDA-CMS) work groups to assist in the development of approaches to reimbursement for genetic tests used to choose targeted therapy and for the use of helical computed tomography (CT) for lung cancer screening.

1 NOTE: RTOG, Radiation Therapy Oncology Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; ACOSOG, American College of Surgeons Oncology Group; CALGB, Cancer and Leukemia Group B; NCCTG, North Central Cancer Treatment Group; ECOG, Eastern Cooperative Oncology Group; ACRIN, American College of Radiology Imaging Network.

Efforts to consolidate “front office” operations among the Cooperative Groups (in response to Recommendation 1 of the IOM consensus report) were especially visible at the time of the workshop, which closely followed announcements to voluntarily consolidate the Radiation Therapy Oncology Group (RTOG) and the National Surgical Adjuvant Breast and Bowel Project (NSABP); the Eastern Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network (ACRIN); as well as ongoing efforts to consolidate the American College of Surgeons Oncology Group (ACOSOG), the Cancer and Leukemia Group B (CALGB), and the North Central Cancer Treatment Group (NCCTG). NCI’s initial approach has focused on supporting up to four adult Groups and one pediatric Group, according to Dr. Doroshow. He added that NCI intends to implement a new Funding Opportunity Announcement (FOA) over the course of the next year that will call for a simultaneous external peer review of all parties, so as to “look at organizations one against another and try to facilitate the allocation of the resources that we have in the most appropriate way.” The timeline for that initiative is shown in Box 2.

**BOX 2**

**Timeline for implementing a new Funding Opportunity Announcement for the Cooperative Group Program**

<table>
<thead>
<tr>
<th>Date Range</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>December 2010 – July 2011</td>
<td>Gather information/input from stakeholders and community for New FOA and Guidelines; develop Concept</td>
</tr>
<tr>
<td>August 2011</td>
<td>NCI Divisional/ Clinical and Translational Research Operations Committee Concept Review</td>
</tr>
<tr>
<td>September 2011</td>
<td>NCI Scientific Program Leadership Concept Review</td>
</tr>
<tr>
<td>November 2011</td>
<td>Board of Scientific Advisors Concept Review</td>
</tr>
<tr>
<td>November 2011 – March 2012</td>
<td>NCI Division of Extramural Activities Review of FOA and Guidelines</td>
</tr>
<tr>
<td>March 2012 – July 2012</td>
<td>NIH Review of New FOA and Guidelines</td>
</tr>
<tr>
<td>July 2012</td>
<td>New FOA Released/Published</td>
</tr>
<tr>
<td>November 2012</td>
<td>Receipt of Competing Applications for New FOA</td>
</tr>
<tr>
<td>February 2013</td>
<td>Review of Competing Applications by NCI Division of Extramural Activities</td>
</tr>
<tr>
<td>May 2013</td>
<td>National Cancer Advisory Board Review</td>
</tr>
<tr>
<td>After Oct 2013</td>
<td>Rollout of Awards in Fiscal Year 2014</td>
</tr>
</tbody>
</table>


The cancer clinical trials network is ripe for transformational, systemic change for the following reasons, Dr. Doroshow noted:

- Requirements for molecular screening of large patient populations to define subgroups for study necessitate that NCI-supported clinical research groups function as a coordinated network.
- Extramural scientific prioritization of the Phase III portfolio across all disease entities is essential to efficiently develop and complete multicenter trials; a smaller number of disease committees are better suited to building such consensus.

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2 A Funding Opportunity Announcement is a publicly available document by which a Federal Agency makes known its intentions to award discretionary grants or cooperative agreements, usually as a result of competition for funds. FOAs may entail program announcements, requests for applications, notices of funding availability, or solicitations, depending on the Agency and type of program.
• Currently configured Groups have disincentives to study less common cancers because disease committee may wish to avoid taking any risk of accrual failure.

• Shared information technology (IT) infrastructure with a common “front end” for clinical data management and for tissue resource management will require ongoing modification; this will be more manageable if it involves fewer independent Groups.

• Open access to a national cancer clinical trials network for clinical and translational investigators not currently involved in the current Group platform will ensure the best competition of ideas and the movement of high-priority science into the clinical trials arena.

In considering how best to meet these needs, NCI examined a variety of models for consolidating the Groups, including the creation of a single national Group, Dr. Doroshow explained. This structure would have the advantage of being fully integrated, free of operational overlap, and potentially easier to harmonize with respect to biomarker studies and IT, he said; however, he added, NCI ultimately favored a smaller network of Groups, as suggested in the IOM consensus report—and specifically, as previously noted, a network comprised of four adult Groups and a single pediatric Group.

Compared to a single national Group, the small network of Groups provides for greater competition among ideas, makes data management more feasible and less costly, and better facilitates involvement by a broad range of investigators, volunteers, and philanthropic organizations, Dr. Doroshow continued. “I think it’s important, however, to point out that a network, by itself, does not guarantee a coordinated approach across groups or the full integration of this clinical trials activity as a system,” he added. “We have to think long and hard about how to make sure that we don’t end up with five silos rather than ten.”

Similarly, Dr. Doroshow noted that NCI is considering changes in funding for the Clinical Trials Cooperative Group Program in order to optimize the use of limited resources. “There is no question but that the resources that we allocate to the Cooperative Group System are inadequate,” he observed. “They are inadequate to provide the per-case reimbursement that actually pays sites the real costs of doing the studies, and they really are inadequate to pay the real costs of the administrative infrastructure that is supported now by this enormous pro bono effort.” Additional resources—millions of dollars—made available though the auspices of past NCI directors have enabled increased reimbursement for large Phase II trials and also improved reimbursement for more complex Phase III trials, he noted; however, these funds still fall far short of need. “We are probably about a log away from the amounts of additional monies that we actually need to pay the real costs of these trials,” he said.

Therefore, NCI is actively engaged in revising its funding model for cancer clinical trials, Dr. Doroshow reported. “We have to think very seriously about the number of trials we can do, the number of patients we can accrue, so that we allow ... [the] 40 to 50 percent of our sites [that] accrue about 75 to 80 percent of our patients ... to survive and prosper and have the resources to do the trials that are the kinds of trials that everyone wants to conduct in the 21st century,” he explained. “We have certainly made no decisions in this area,” he continued, “but clearly we need to support what I would view as the critical seed corn of our clinical trials infrastructure by allowing those institutions to receive the support they need to at least pay their costs.”

The proposed organizational structure for NCI’s clinical trials program is shown in Figure 1. This model provides for a system in which all Groups interact to develop a national
agenda for clinical trials and increase efficiencies of accrual, initiation, and completion of all trials, Dr. Doroshow said. It also encourages input from Cancer Centers\(^3\) throughout the system and permits greater integration of investigators who participate in Specialized Programs of Research Excellence (SPOREs)\(^4\) and in Program Project Grants.\(^5\) Another important feature of this model is the existence of an oversight body to guide NCI’s management of the clinical trials system, which he characterized as “something that we have woefully lacked.”

The remainder of Dr. Doroshow’s presentation focused on measures NCI has taken in recent years as they relate to specific goals and recommendations of the IOM consensus report, as summarized in Table 1. For example, he reported that NCI has implemented time lines for concept evaluation, protocol development, and trial activation recommended by the OEWG (NCI, 2010) and further endorsed by the IOM committee (IOM, 2010). NCI is also pursuing the OEWG’s recommendation to adopt a single, harmonized approach to clinical trials management, including protocol authoring, case report forms, and standardized data collection and management.

Additional actions taken by NCI in response to the IOM consensus report include working with the Center for Devices and Radiological Health (CDRH) of the U.S. Food and Drug Administration (FDA) to coordinate early review of biomarkers and other investigational devices used in treatment trials; revising the intellectual property (IP) option on all Cancer Therapy and Evaluation Program (CTEP) Cooperative Research and Development Agreements (CRADAs) relating to drug development and specimen use for correlative science (CTEP, 2011); and improving review time lines for the NCI Central Institutional Review Boards (CIRBs; one for pediatric trials and one for adult trials).

\(^3\) NCI-designated Cancer Centers are recognized for their scientific excellence. They are a major source of discovery and development of more effective approaches to cancer prevention, diagnosis, and treatment. They also deliver medical advances to patients and their families, educate health care professionals and the public, and reach out to underserved populations. An NCI-designated Cancer Center may be a freestanding organization, a center within an academic institution, or part of a consortium of institutions.

\(^4\) A SPORE grant is a specialized center grant to support interdisciplinary teams of investigators who conduct translational research focused on an organ-specific human cancer (e.g., breast cancer) or a highly related group of human cancer types (e.g., gastrointestinal cancers).

\(^5\) A Program Project Grant, or P01, is an assistance award for the support of a broadly based multidisciplinary research program that has a well-defined central research focus or objective. It may also include support for common resources (cores) required for conduct of the P01 research projects. Interrelationships between projects are expected to result in a greater contribution to program goals than if each project were pursued separately.
Several participants in the subsequent panel discussion noted that the expansion of CIRB usage could further increase efficiency gains afforded by Cooperative Group consolidation. However, as Dr. Roy Herbst, of Yale Cancer Center, observed, “That will only work if the local IRBs actually recognize that central IRB.” Dr. Doroshow reported that the U.S. Department of Health and Human Services (HHS) is likely to make a rule change that will allow a single IRB for any multisite clinical trial. In that case, a trial approved by a single IRB (not necessarily NCI’s CIRB) could determine approval for a clinical trial on a national basis. Even then, however, the local IRB would have to be willing to accept a decision made by another IRB. The potential expansion of CIRB usage was further discussed during Panel III (see subsection “Central IRB and Informed Consent”, page 38).

NCI has also participated in “significant ongoing efforts” to improve the clinical trials IT infrastructure of the Cooperative Groups by procuring a clinical trials data management system that can be used across the NCI-supported Cooperative Group System, Dr. Doroshow said. This process was discussed in a subsequent presentation by Dr. Robert Gray of the Dana-Farber Cancer Institute and lead statistician for ECOG (see below).

“Developing a national clinical trials network is an ongoing process,” Dr. Doroshow observed in conclusion. “We need to hear from every stakeholder, to think about all the issues … [and at] the same time, we need to continue the process of [improving] efficiency, enhancing the
coordination activities in the system, and conducting the evaluations that are an ongoing process of this activity overall."

**Response of the NCI Community Clinical Oncology Program (CCOP)**

Following Dr. Doroshow’s overview of NCI’s efforts toward the comprehensive revision of the national cancer clinical trials system, Dr. Lori Minasian, director of the CCOP and acting director of the Division of Cancer Prevention at NCI, discussed the CCOP’s role in the clinical trials system and described how the program has begun to address the goals and recommendations of the IOM consensus report. She explained that the CCOP has three components, each of which supports its own Request for Applications (RFA)⁶: the Community Consortium to Accrue; the Minority-Based CCOPs; and the CCOP Research Base, which is comprised of Cooperative Groups and Cancer Centers funded to design, develop, and conduct clinical trials in cancer prevention and treatment.

The CCOP Research Base is NCI’s primary mechanism for funding Cooperative Groups and certain Cancer Centers that conduct clinical trials for interventions other than treatment, Dr. Minasian pointed out. “Under the CCOP Research Base, the scope of the research has grown over the last 20 years,” she said; highlights of this expansion included the launch of large, significant, cancer prevention trials and the accumulation of a growing portfolio of cancer control studies focused on methods for early detection and improvements in quality of life, continuing care, and palliative care. She emphasized that cancer prevention and quality-of-life trials require different strategies and produce different types of data than cancer treatment trials and that these differences need to be addressed in attempts to harmonize and standardize data collection and management in cancer clinical trials, as recommended in the IOM consensus report.

The planned consolidation of Cooperative Groups into four adult groups and one pediatric group presents an unusual opportunity to review and redefine cancer prevention and treatment agendas among CCOPs that are funded as Research Bases, Dr. Minasian observed. The CCOP releases FOAs on an annual basis, she explained; with the release of the CCOP Research Base RFA in the spring of 2011, competing Cooperative Groups were required to describe their current process in the transition to consolidation and examine how their cancer prevention and control agendas may evolve. “We are not expecting them in their applications to be able to foresee the next five years, but this will be a development over time,” she acknowledged.

In the meantime, Dr. Minasian reported, the Clinical Trials Support Unit (CTSU)⁷ has already begun to accept cancer control trials, and some Cooperative Groups have been using the Regulatory Support System for cancer control studies—even those that have not involved the CTSU for accrual. She also noted that the audit guidelines for the CCOP Research Bases have been incorporated into NCI guidelines for all Cooperative Groups and that all of the CCOP Research Base studies are now part of CTEP. “There is a CTEP and CCOP team working together, meeting about every two weeks now, to help coordinate and facilitate the transition so that the systems and the processes, if not the same, at least are in parallel and complementary, so that we are implementing things in the same spirit,” she said.

On the other hand, Dr. Minasian continued, it is important to recognize certain unique needs of cancer control studies; for example, because few interventions studied for cancer

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⁶ A Request For Applications (RFA) is the official statement that invites grant or cooperative agreement applications to accomplish a specific program purpose. RFAs indicate the amount of funds set aside for the competition and generally identify a single application receipt date.

⁷ https://www.ctsu.org/public/.
control are drugs, there are few partnerships with pharmaceutical companies. By contrast, cancer control studies are often chaired by Ph.D.s or investigators outside the field of oncology, she said; in those cases, the CCOP has encouraged collaborative funding from external sources (e.g., National Institutes of Health other than NCI, the American Cancer Society). However, she added, these circumstances also make it more difficult to involve investigators that are not routinely part of the treatment clinical trials program. Seeking such additional funding automatically lengthens trial development, because even after a concept is approved, protocol development cannot move forward without external funding, she explained.

Dr. Minasian noted that the IOM recommendation to incorporate innovative science and trial design is particularly appropriate for cancer control studies, and she also noted the need for translational studies on cancer prevention and control trials. "Clearly cancer control endpoints are not the same as cancer treatment endpoints, so we absolutely encourage novel trial design," she said. Two representatives of the Division of Cancer Prevention are members of the Investigational Drug Steering Committee, she reported, and are therefore well placed to identify candidate drugs for cancer control.

Dr. Minasian emphasized that cancer control assessments often hinge on criteria that differ from treatment studies, particularly with regard to neuropathy or pain. Obtaining consensus for a non-treatment concept often takes extra time, she observed; however, in cases where no treatment option exists for an indication, protocol development tends to proceed more quickly.

The development of steering committees has improved the review process for cancer control studies, Dr. Minasian said. "The advantage with the steering committee right now is that we are allowed to call on extramural individuals with expertise in neuropathy, in CAM [complementary and alternative medicine], in other topics of cancer control interest," she explained; by contrast, a large prevention trial once would have had to be submitted to independent peer review by a study section specifically developed for that trial. However, she added, there is no current need to develop a standing prevention steering committee, due to the relatively low volume of prevention studies; ad hoc groups can be assembled to draw on appropriate expertise. "If this area develops and becomes larger, we would consider a prevention steering committee at that time," she stated.

With regard to the goal of improving the diversity of patient populations in clinical trials, Dr. Minasian observed that the Minority-Based CCOP program has been instrumental in accruing minority patients onto cancer clinical trials. The Minority-Based CCOPs account for about a third of the minority accrual onto NCI clinical trials, and about 60 percent of patients accrued through Minority-Based CCOP programs are members of a minority group, she reported. She added that the CCOP strategic plan identifies the underserved population as a core issue, which has in turn sparked efforts to identify relevant research questions and to develop a transdisciplinary working group.

A related project, jointly administered by NCI and the American Society of Clinical Oncology (ASCO), is aimed at eliminating cancer disparities (the ultimate goal of increasing the diversity of clinical trial patient populations), according to Dr. Minasian. The ASCO-NCI Cancer Disparities Research Group is examining ways to increase collaboration among academic and community and public institutions, both by developing a consensus statement with recommendations and by promoting specific research projects to be undertaken by the Cooperative Groups, she said.
In terms of funding, Dr. Minasian reported that CCOP is exploring ways to incorporate multiple principal investigators in the structure of a CCOP grant. “Our usual grantees are community hospitals, and now we are seeing more health systems consolidate, and so the health systems are looking to become the CCOP grantee,” she observed. “That is creating both some unique opportunities and some unique strains on the system in terms of keeping the CCOP program primarily as a doctor- or physician-run program.”

In closing, Dr. Minasian described the results of a recent survey of more than 1,500 specialty physicians who cared for colorectal and lung cancer patients (Klabunde et al., 2011), which suggest that many physicians at CCOPs and Cancer Centers do not participate in clinical trials. In addition, a recent patient survey by Research!America found that more than 70 percent of those polled would be willing to participate in clinical trials, but that only 6 percent reported that their physicians had ever suggested doing so (Research!America, 2010), she said; another survey by the Mayo Clinic indicates that most patients expect their physicians to inform them of clinical trials (Sood et al., 2009). Together, these results suggest the need for improved and enhanced outreach to physicians, so that they engage and accrue more patients to cancer clinical trials, she concluded.

Cooperative Group Leadership Perspective and Current Activities

Cooperative Group Chairs’ Perspective

Dr. Jan Buckner of the Mayo Clinic, chair of the NCCTG and also of the Cooperative Group Chairs, introduced his presentation to the workshop with a summary of the many advances in cancer prevention, diagnosis, and treatment identified through clinical trials conducted by Cooperative Groups; these were described in the IOM consensus report and also in a recent issue of Seminars in Oncology (Perry et al., 2008). He also noted that an editorial published just prior to the workshop in the New England Journal of Medicine (Moss et al., 2011) called for an organizational structure similar to that proposed in the IOM consensus report for the conduct of clinical trials across all disease groups, not just cancer.

Reporting on the scientific and operational accomplishments of the Cooperative Groups, and on the challenges they face, Dr. Buckner observed that the Groups “have been and will continue to be vital engines to conduct multidisciplinary, practice-changing, biologically driven clinical trials in the academic and community setting” and that the Groups have demonstrated both the will and the capacity to respond to the recommendations of the IOM consensus report.

Among recent scientific accomplishments of the Cooperative Groups, Dr. Buckner noted
the collection of tumor and normal tissue samples from hundreds of thousands of cancer patients and those at risk for cancer; these biospecimens are linked to clinical outcomes and treatment protocols, as well as to follow-up data and laboratory observations. Examples of the latter include such high-impact translational research as the prospective clinical trial (TAILORx®) to assess the clinical utility of the 21-gene assay Oncotype DX, which is used to predict the risk of disease recurrence in women with early-stage node-negative, estrogen receptor-positive breast cancer, identifying those who are at high risk for recurrence and thus more likely to benefit from adjuvant chemotherapy and those who are at low risk for recurrence and thus can safely avoid additional treatment.

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"As a result of the clinical data and the biospecimens, the Cooperative Groups have been collaborating with Cancer Center investigators for many, many years," Dr. Buckner observed. In recent years, he reported, Cooperative Group clinical data and biospecimens have been used in more than 60 collaborations with Cancer Centers, 6 program project grants, and more than 10 SPORE collaborations, among others projects—including non-federally funded studies. He added that he expects this collaborative trend to continue and accelerate.

Such collaborations have led to a number of biomarker-driven trials by Cooperative Groups that have produced definitive results, according to Dr. Buckner. He provided several examples of such achievements, including the following:

- Identification of trastuzumab as an active adjuvant therapy for HER2-positive breast cancer in combination with chemotherapy;
- Evaluation of cetuximab as adjuvant therapy for patients undergoing therapy for KRAS wild-type stage III colon cancer;
- Examination of imaging as a biomarker to guide treatment decisions in non-Hodgkin's lymphoma; and
- Assessment of risk of recurrence in stage II colon cancer for patients with deletion of 18q and microsatellite instability.

These trials have benefited not only from NCI's financial support, but also from countless volunteer hours from members of the Cooperative Groups, Dr. Buckner pointed out. As shown in Table 2, nearly half of the funds necessary to conduct such trials have been provided from volunteer hours and from sources apart from NCI.

Several recent operational accomplishments by the Cooperative Groups echo the IOM consensus report recommendations, Dr. Buckner continued. In 2005, the Groups initiated a collaboration to develop detailed user-needs assessments and technical specifications for a single remote data capture system that would be utilized for all trials, he reported; system implementation has now begun. Through participation in the OEWG (as previously noted by Dr.

**TABLE 2** Overall Cooperative Group Funding Structure, Fiscal Year 2007

<table>
<thead>
<tr>
<th>Funding Component</th>
<th>Total Costs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooperative Group awards</td>
<td>$161 million (45%)</td>
</tr>
<tr>
<td>CCOP accrual support</td>
<td>$ 10 million (3%)</td>
</tr>
<tr>
<td>CTSU contract</td>
<td>$ 18 million (5%)</td>
</tr>
<tr>
<td>Accrual cost sharing</td>
<td>$ 88 million (24%)</td>
</tr>
<tr>
<td>Pro-bono investigator time</td>
<td>$ 28 million (8%)</td>
</tr>
<tr>
<td>Industry support</td>
<td>$ 41 million (11%)</td>
</tr>
<tr>
<td>Philanthropic support</td>
<td>$  6 million (1.5%)</td>
</tr>
<tr>
<td>Other support</td>
<td>$  9 million (2.5%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$361 million</strong></td>
</tr>
</tbody>
</table>

*Direct and indirect costs.

SOURCES: Judith Hautala, 2010; Buckner presentation, March 21, 2011.
Doroshov), each Group has developed internal processes and metrics to meet protocol-development milestones in a timely manner. The Groups’ statistics and data-management units have contributed to the development of innovative clinical trial designs to accommodate the increasing complexity of integrating biomarkers into design and interpretation, Dr. Buckner said. They have also partnered with clinical investigators to develop valid endpoints, reflecting the changing nature of clinical research and practice, and have worked to streamline clinical trial conduct by evaluating components of standardized clinical outcome assessment systems, such as RECIST\(^9\) and the Common Toxicity Criteria.\(^{10}\)

Among Cooperative Groups that are consolidating their front and back office operations, three (ACOSOG, CALGB, and NCCTG) have already begun integration of a single statistics and data center to support all three existing Groups, Dr. Buckner stated. These Groups have also agreed to complete integration of scientific and operational functions to create a new group. Such combined Groups will have to address several outstanding issues, he said; the most pressing of these is to develop a stakeholder-informed and rational system for setting research priorities. “The voice of the investigator community and the patient community must be paramount if clinical trials are to succeed,” he observed. “Central control often stifles innovation.”

Stakeholders must be offered concrete incentives for scientific collaboration, Dr. Buckner continued. “Academic and community investigators should be rewarded in their grant awards for participating in collaborative research,” he said; therefore, grant guidelines and terms of awards should have specific language outlining the rewards for contributing to collaborative science.

Coordinated review and support of translational science must occur in order to better integrate the aims of clinical trials and correlative science, Dr. Buckner observed. While acknowledging that BIOSFP (Biomarker, Imaging, and Quality of Life Studies Funding Program) funds have been helpful to this end, he encouraged support of additional efforts to optimize clinical and scientific collaborations, such as providing preliminary data for the next Phase III trials.

Enhancements of the systems that the Cooperative Groups have developed for multisite conduct of clinical trials are also needed, along with improved biospecimen annotation and informatics support, implementation of remote data capture systems across all groups, and assistance with overall operational management (e.g., membership concerns, regulatory affairs, finances), Dr. Buckner said. “The process of scientific prioritization, collaboration among laboratory and clinical investigators from multiple venues, and modernization of informatics support remain key issues to address in the future,” he concluded.

Group Statisticians’ Perspective

Speaking on behalf of the Cooperative Group statistical leaders, Dr. Robert Gray of the Dana-Farber Cancer Institute, who leads the Eastern Cooperative Oncology Group Statistical Center, considered the role of statistical centers in a changing the Cooperative Group System and their contribution toward meeting goals and recommendations stated in the IOM consensus report. In approaching these challenges, Group statisticians adhered to two basic principles, he

\(^9\) Since the year 2000, an international committee has promulgated unified, easily applicable criteria for measuring tumor response using X-ray, CT, and MRI, which are known as Response Evaluation Criteria in Solid Tumors (RECIST). The technique is recommended but not mandatory for NCI-sponsored trials and involves formalized rules for measurement of tumor target lesions. See http://imaging.cancer.gov/clinicaltrials/imaging/.

\(^{10}\) These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, to assess how the disease affects the daily living abilities of the patient, and to determine appropriate treatment and prognosis. See http://ecog.dfc.emory.edu/general/common_tox.html.
said: (1) biostatistics is an essential component of Group science, and (2) the complexity of the research performed by the Groups requires independent, academically based statistical leadership.

Group science needs to be integrated with the biostatistical leadership in order to encourage collaboration between statisticians, scientists, and clinical researchers, Dr. Gray continued. “The statisticians need to understand the scientific issues, the issues that are required for the research in an area, and that’s best done as an ongoing collaboration over a period of time,” he said. He also stressed the importance of integrating data management with biostatistics, due to the difficulty and expense of the data collection process. “There needs to be substantial interaction among the statistical analysts, data managers, and study chairs throughout the life of a study,” he observed. “The prioritization of data management work needs to be driven by the needs of statistical analyses and the timetables for those analyses as well.”

Most Cooperative Group statistical centers combine biostatistics and data management under a separate grant within the Cooperative Agreement, Dr. Gray explained. Group statisticians support this structure for several reasons, he noted: having a separate grant attracts leadership from top academic centers, providing them with stable support, while offering incentives for institutions to share the cost of research at statistical centers. In addition, he said, such “semi-independent” statistical centers help ensure that research is conducted properly, while at the same time being well integrated into Group science.

Dr. Gray identified several areas in which the statistical centers have addressed the IOM consensus report goals and recommendations. Patient registration has been improved through the development of a common web-based system known as OPEN (Oncology Patient Enrollment Network). Significant progress has also been made toward adoption of a common remote data entry system, Medidata Rave®, which is currently being implemented and is expected to be applied to studies by late 2011. Through the Cancer Biomedical Informatics Grid (caBIG), the statistical centers have been developing standardized case report forms (CRFs) that can address the complex data collection requirements of diverse Groups and trials.

The merger of Cooperative Groups raises several issues for the Groups’ statistical centers, Dr. Gray observed. For example, legacy databases, which include some 100,000 patients, must continue to be managed and maintained. He predicted that the combined statistical centers are likely to continue, with largely the same personnel and in the same locations, and many will operate using a multiple-principal-investigator model. He added that economies of scale do not apply to operations in the existing statistical centers, because statisticians cannot only work on so many projects, and the projects still take largely the same amount of time, regardless of how many people staff the operation. Thus, he concluded, efficiency gains will continue to come primarily from the use of common information systems infrastructure and from greater standardization of processes and data across groups.

Experience from the Consolidation of the Children’s Oncology Group (COG)
The consolidation in 2000 of four pediatric oncology Cooperative Groups—the Children’s Cancer Group, the Pediatric Oncology Group, the Intergroup Rhabdomyosarcoma

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12 The Cancer Biomedical Informatics Grid (caBIG) is an NCI-sponsored collaborative information network that includes more than 50 Cancer Centers, other NCI-supported research endeavors, and a variety of federal, academic, not-for-profit, and industry organizations. Source: https://cabig.nci.nih.gov/overview/.
Study Group, and the National Wilms’ Tumor Study Group—to form COG offers a model for present-day Cooperative Group mergers. In his presentation to the workshop, Dr. Gregory Reaman of George Washington University and past chair of COG, described the rationale for undertaking this process, the challenges it presented, and the results it produced.

The creation of COG was driven primarily by the need to develop adequate study populations, Dr. Reaman explained. “Much of the work that we did in pediatric cancer outside of the acute leukemias and neuroblastoma, where we had relatively sizable patient populations for study, necessitated collaborative efforts and an intergroup process,” he said. “We saw that we were currently, and certainly in the future, going to fail in achieving our mission to cure and prevent childhood cancer as competing entities.”

Despite this urgency, several issues had to be resolved to move the consolidation forward, he recalled. Timing was complicated by the need to continue a large number of open studies while planning new initiatives, some of which depended on results of the ongoing studies, Dr. Reaman noted; additional hurdles involved resolving differences among the legacy Groups regarding investigator and institutional membership designations, redistributing funds, and choosing which of the existing administrative operation and data centers would serve the entire COG. In light of the complexity and importance of biostatistics in clinical research and in order to preserve the crucial knowledge base developed by biostatisticians whose work had focused on pediatric cancer for decades (as Dr. Gray had previously noted), COG also established a distributed statistics department comprised of biostatisticians at legacy Group locations, as well as some independent biostatisticians at other academic institutions, he explained. A remote data entry system, originally developed by the legacy Pediatric Oncology Group, was adapted in order to handle the larger volume of studies undertaken by COG.

“What transpired as a result of the consolidation was the world’s largest childhood cancer research organization, which still encompasses more than 200 pediatric cancer programs in North America, Australia and New Zealand, Switzerland, and the Netherlands,” Dr. Reaman observed. COG, he continued, is a multidisciplinary research enterprise incorporating diverse specialties including pediatric oncology, surgery, radiation therapy, biostatistics, laboratory investigation, and epidemiology, among others.

COG’s single biopathology center is a national resource for pediatric cancer specimen banking, Dr. Reaman said; it has enabled a large number of correlative studies and unique translational research opportunities. The Group employs a system of centralized reference and resource laboratories to manage its cytogenetic and molecular genetic studies of risk-adjusted approaches to therapy and plans to implement a similar model for radiology, he added. COG has also developed a national childhood cancer registry for North American sites, the Childhood Cancer Research Network, in order to develop a research database for future epidemiologic and molecular epidemiology studies. The network enables all patients with cancer diagnoses at COG member institutions to be registered and the resulting database to be available for research, he explained. More than 98 percent of the families of the nearly 20,000 patients currently registered have consented to be contacted in the future for nontherapeutic epidemiological studies, he reported. Indeed, he added, a dramatic increase in accrual to nontherapeutic studies resulted from the formation of COG, while therapeutic study accrual has grown less consistently since consolidation.

Dr. Reaman recounted numerous accomplishments by COG to date in three main areas: (1) organization and administration; (2) clinical practice-changing research; and (3) translational science. Organizational and administrative advances included establishment of the NCI Pediatric
Central IRB, which has in turn reduced time lines for opening studies; participation in an international collaboration for osteosarcoma; development of an interoperable infrastructure for clinical research between COG and the Pediatric Blood and Marrow Transplant Consortium and the Bone Marrow Transplant Clinical Trials Network of the National Heart, Lung, and Blood Institute (NHLBI); and the performance of clinical trials for rare tumors, including retinoblastoma (which is, however, endemic in Brazil and India).

Practice-changing accomplishments by COG include the development of a clinical and biological risk-based classification scheme for acute lymphoblastic leukemia, myeloid leukemia, neuroblastoma, and Wilms’ tumor, which Dr. Reaman said would not have been possible without the collaborative efforts of the consolidated Groups. Similarly, increased patient population sizes enabled COG to demonstrate the prognostic significance of minimal residual disease in acute lymphoblastic and myeloid leukemia (ALL and AML), in neuroblastoma, and in non-Hodgkin’s lymphoma. Based on the collective results of patients treated in legacy studies by the consolidated Groups, COG has also developed exposure-related surveillance recommendations for childhood cancer survivors.

COG’s achievements in translational science include the use of gene expression and microarrays to develop cancer signatures for diagnosis and prognosis in ALL, AML, and rhabdomyosarcoma, according to Dr. Reaman. Through NCI’s Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative,\(^\text{13}\) COG researchers have genomically characterized and investigated potential therapeutic targets in ALL and neuroblastoma and will soon extend these studies to Ewing’s sarcoma and rhabdomyosarcoma, he reported. COG also participates in NCI’s Cancer Discovery and Development Network,\(^\text{14}\) which employs new scientific approaches to accelerate the translation of genomic discoveries into new treatments.

Summing up the process of consolidating four pediatric oncology Cooperative Groups to form COG, Dr. Reaman recalled that it was not easy, particularly with regard to merging data systems among the constituent Groups. However, he continued, “the results have clearly indicated that it was something that we don’t regret doing … [and] we are a much stronger group for having done so.”

Panel Discussion

Following their presentations, Drs. Doroshow, Minasian, Buckner, Gray, and Reaman were joined by 16 Cooperative Group chairs and statistical leaders for a panel discussion. It focused on three main subjects: (1) the logistics and potential consequences of Cooperative Group consolidation; (2) opportunities for encouraging collaboration among the new Cooperative Groups and other institutions, both within and beyond NCI; and (3) various mechanisms for shifting the role of NCI from oversight to support of the Cooperative Groups.

Consolidation of Cooperative Groups

Moderator and workshop chair Dr. Richard Schilsky of the University of Chicago opened the discussion by soliciting brief statements from panel participants regarding their organizations’ specific plans to address the IOM consensus report recommendations. Dr. Robert Comis, of ECOG, attributed the consolidation of ECOG with ACRIN—announced just prior to the workshop—to the IOM consensus report. “I don’t think this would have happened if the IOM

\(^\text{13}\) http://target.cancer.gov/.

report hadn’t come about, but I think that clearly we have brought together two organizations that are extremely complementary. Bringing together our biomarker programs from the genetic and proteomic side, and combining that with imaging, will make us all stronger,” he observed.

By contrast, Philip DeSaia, of the Gynecological Oncology Group (GOG), asserted that this group has thrived as a singular entity. “The backbone of the Gynecological Oncology Group is the gynecological oncologists, just like the pediatric oncologists are to the Pediatric Group,” he said, adding that most of the approximately 1,000 such specialists in the United States participate in GOG, largely on a volunteer basis. “It’s hard for my executive committee to figure out how we are going to merge,” he continued. “Would you cut us up into five pieces, four pieces, and put us in each [adult Cooperative] Group?”

Dr. Norman Wolmark of NSABP responded by asking GOG (in the form of a laughter-provoking marriage proposal) to join the NSABP-RTOG alliance.

In a related discussion, Dr. Sharon Murphy, IOM scholar-in-residence, noted that the IOM consensus report did not recommend a specific number of consolidated Cooperative Groups, and wondered why five, not four, adult groups might not be possible. “I think what we have seen is a rather hasty rush to the altar and some arranged marriages, and this was not what the IOM suggested,” she observed.

In fact, the formal IOM recommendation did not specify a particular number of groups. Rather, a hypothetical example of four multidisciplinary groups was described as just one possible approach to consolidation in Chapter 3 of the report. Dr. Mendelsohn said that, in theory, its recommendations could be fulfilled with one group, four, or ten, but he also deemed the current approach leading to the “four plus one” model “excellent.”

Dr. Walter Curran of RTOG noted that alliances such as that between RTOG and NASBP represent only one model of consolidation. “Some of the newly created relationships will look different from one another,” he observed. “Some will be one entity; some will be a confederation, or alliance, of many entities. My hope is that the federal guidelines for review will allow such flexibility.” Moreover, he continued, the relationships between these new groups and Cancer Centers or other federally funded entities are likely to vary. Several participants in this discussion shared similar hopes for flexibility in the structure of Groups and in their interactions with each other and with other institutions, particularly the Cancer Centers.

Dr. William Dalton, director of the Moffitt Cancer Center in Tampa, Florida, emphasized that each Group must be multidisciplinary, in addition to encompassing expertise in specific diseases. Rather than merely consolidate, he said, the Cooperative Groups should reorganize so as to bring together experts with specific interests across broad areas of knowledge—as currently occurs now in COG. “We have been talking about an anatomical change to the groups,” Dr. Schilsky observed, but he said that the real goal is functional reorganization.

“Working together and having flexibility ... about how we come together and how we interact is very, very important,” Dr. Comis added. He emphasized that the hybrid Cooperative Group System lies at the heart of translational clinical research and relies not only on NCI and industry funds, but also on commitment and in-kind support from the entire cancer research community.

Dr. Schilsky, who has served as both a Cancer Center director and a Cooperative Group chair, observed that nearly every Cancer Center participates in more than one Cooperative

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15 The IOM consensus report does, in one section (p. 148), suggest a possible consolidation of existing Groups by disease type, resulting in four multidisciplinary groups dedicated to adult cancers, but it does so only as an example.

Group. “In most cases, it’s Cancer Center members who provide the lion’s share, if not all, of the scientific leadership of the Cooperative Group Program,” he said.

Encouraging Collaboration

Recalling that the Cooperative Groups, SPOREs, and Cancer Centers emerged as separate entities, Dr. Monica Bertagnolli, of CALGB, reiterated the message in the IOM consensus report that these “silicd” institutions need to work together. That NCI has begun to mandate collaboration through peer review is healthy and beneficial to the overall scientific agenda, she said.

This mandate is not without its challenges, however, as several discussants pointed out. Dr. Constantine Gatsonis, of ACRIN, wondered how existing scientific expertise within Cooperative Groups could be preserved and enhanced as the Groups are consolidated. “I speak with experience from the imaging group, where we had a pretty hard time figuring out how we all fit into this [therapy-driven] system ... and how we preserve and enhance the expertise in imaging,” he said. “How do we move, for instance, toward some kind of an imaging hub that would be available for the entire network?” He therefore suggested that the RFAs defining the new groups allow for the creation of a network of strengths and expertise, rather than a reduced number of similar, competing Cooperative Groups.

Dr. Buckner asked whether guidelines for the various NCI programs are being revised so that the Cancer Centers and Cooperative Groups will have specific review criteria for collaboration. Dr. Doroshow responded that substantive changes “are actually now going to be sprinkled throughout the guidelines for Cancer Center Support Grants (CCSGs), giving substantially more weight to the role of the Cancer Centers and their collaborations with the groups.” He added that the SPORE guidelines have been revised quite extensively to emphasize collaboration with Cooperative Groups. “There is going to be a whole new section of the grant that requires the clear delineation of what the aspects of those collaborations are and a specific review criterion with a score,” he explained. “Those guidelines have not yet been approved, but they have been, after a very long period of time, finalized. They will go in the relatively near future to the scientific group, the former executive committee at NCI, and then on to NIH for their purview.”

However, he stressed that guidelines also have to be translated into the ethos of the review committee. “There will be now another step, once [the guidelines] are approved, to really think about and help to educate the cultures of these very different review committees.” Dr. Schilsky added that the Clinical and Translational Research Advisory Committee also has a subcommittee looking at ways to harmonize guidelines for CCSGs, the Cooperative Group, and SPORE to incentivize more collaboration.

In the meantime, Drs. Buckner and Bertagnolli emphasized, significant collaboration is already under way, as evidenced by numerous joint grants involving combinations of Cooperative Groups, Cancer Centers, and SPOREs. “I think there is a huge level of involvement and engagement,” Dr. Bertagnolli said, particularly given the low rate of project funding. “It requires intense engagement on the part of the scientific community in the groups to even put forward these proposals,” she observed.

Cancer Center and SPORE investigators need to be better educated about the kinds of studies that lend themselves to collaboration with Cooperative Groups, how such studies are developed, and the various mechanisms by which they might be funded, Dr. Buckner said. Dr. Bertagnolli noted that extramural investigators might become discouraged if they fail to
understand that a study accepted by a Cancer Center may not be approved by a steering committee.

Extramural investigators also need to be educated about the existence and availability of specimens from Cooperative Group tissue banks, Dr. Schilsky pointed out. “All of the groups have experience operating those tissue banks now for quite a long time and engaging the investigator community broadly,” he said, “but there still are large segments of the scientific community that either don’t know how to access those specimens or don’t believe that they are available for the broader scientific community.”

Another form of collaboration was raised by audience member Dr. Jeffrey Humphrey of Bristol Myers-Squibb, Inc.: the participation of newly consolidated Cooperative Groups in public-private partnerships. He observed that the pharmaceutical industry has created several high-level positions to support more functional partnerships with the Cooperative Groups in order to take advantage of their investigators’ superior expertise in disease management. “There is an increasing understanding in pharma (the pharmaceutical industry), particularly under its own financial pressures, that there has to be a selective integration with people who do things truly well, and [since] the true disease expertise resides in many of these Cooperative Groups ... there is a need for public-private partnerships,” he said. Further discussion of such partnerships occurred in the Panel III discussion on interactions between industry, the FDA, and the publicly funded cancer clinical trials system (see “Partnership Between Industry and the Cooperative Groups”).

Reducing NCI Oversight of the Cooperative Groups

Noting that the recommendations in the IOM consensus report addressed the theme of shifting the role of NCI from oversight of the Cooperative Groups to facilitation of their work, Dr. Schilsky raised this issue for discussion. Dr. John Crowley of the Southwest Oncology Group (SWOG) observed that while cooperative agreements once resembled grants, many are now more like contracts. He urged a return to agreements that are more investigator-initiated, rather than being controlled by NCI.

Dr. Doroshow said that defining the role of NCI in the clinical trials system is a very important issue. He pointed out that original program “that went into operation in 1956 was a system in which all the trials and all the review were, for many, many years—decades, done exclusively by the NCI.” “That’s not the way a system should work. We should utilize the best available evidence that is discussed and evaluated by the experts,” he said, but he added that the Cooperative Groups have come a long way since 2004, when NCI conducted every review, entirely without extramural oversight. NCI has revised the prioritization process for large Phase II and Phase III treatment trials by creating steering committees in specific diseases and across modalities. “The NCI clearly has a voice in these committees, but by no means does it have the dominant voice … roughly 3 or 4 votes out of 20 or 25 in any of these committees,” he said. Currently, NCI is focused on enlisting the help of “investigator experts” in prioritizing types of studies to be done, he said. However, he added that the institute is “just in the beginning phase” of establishing a much-needed extramural group that would represent a spectrum of constituencies in discussions of national strategic priorities across diseases.

Dr. Mendelsohn stated that disease site-oriented scientific steering committees should be charged with reducing redundancy among Cooperative Group studies and with improving both the quality and the completion rate of clinical trials. Also, in times of restricted funding for trials,
scientific steering committees should be well equipped to prioritize the most cost-effective trials, he said.

"Just to be clear, the scientific steering committees have been going on for some time already, even before our report," Dr. Schlisky noted. However, it's important to assess whether and how such committees may encumber the approval process for clinical trials, particularly in light of the possibility that an "overarching oversight committee" might be added to the chain of approval, he added. Dr. Doroshow responded that the purpose of such an oversight committee would not be to add another layer of review to the approval process, but instead "to take a look several years down the line, to say where there are scientific opportunities and provide input to NCI about where the priorities ought to be."

"I certainly applaud the concept of the NCI steering committees," Dr. Curran stated, "but what I don't want to see is a trend for the scientific core and the development process of new and exciting trials to shift [away] from the Group committees, where there is true expertise ... [as well as] information and content and trials and translational research to interrogate as the beginning of the hypothesis generation." The scientific development process should reside in the Group committees, in conjunction with Cancer Centers, SPOREs, and other colleagues, he insisted; steering committees should review, rather than generate, trials.

Since Cooperative Groups, SPOREs, and Cancer Centers compete for the same pot of money, steering committees should be established to review the entire cancer research portfolio, not just the Cooperative Groups, Dr. Comis asserted. "Whenever CTEP or DCTD [the Division of Cancer Treatment and Diagnosis] spends a dollar on clinical research ... you ought to have a steering committee review everything and make sure every dollar is spent right," he said.

**Going Forward**

Reflecting on the process of transformation of the cancer clinical trials system in light of the IOM consensus report recommendations, Dr. Peter Adamson of the Children's Hospital of Philadelphia, a member of COG, noted that it remains to be determined which among the many changes underway will produce significant improvements. "Right now my overarching concern is, How are we going to attract the best talent?" he said, adding that a more cumbersome and complex clinical trials system will surely deter the participation of the best scientists.

"Ideas will fail late in this system, [which is] understandable, because it's a matrix organization that is very difficult to manage," Dr. Adamson explained. Such a system is geared to lose talent, because investigators become frustrated after committing two or three years of their lives to an idea, only to have it "blow up three years later," he observed. Therefore, he said, "if we really don't know what's going to work, let's incentivize innovation and lead to flexibility. I don't think of us, including COG, have the perfect model."

Mr. Michael Katz, a Cooperative Group advocate, urged consideration of the possible advantages of some redundancy in the cancer clinical trials system. "We tend to paint with a very broad brush and we say things like 'redundancy is bad,'" he observed. "When we are manufacturing Toyotas and we are buying PCs, scale is a black-and-white thing; it's a good-and-evil thing. But when we are doing things like research, sometimes we explicitly have competing efforts," he said. Steering committees are often plagued by competing conflicts of interest among their members, he added, so "it is very possible that we will now set the system to fail [too] early instead of failing too late."
"I think we all have a great concern that research by committee tends toward the safe and not the brave and the innovative," Dr. Bertagnolli replied. "We cannot forget that our work will greatly suffer if we stifle innovation."

**PANEL II: PAYORS**

Because the IOM consensus report included recommendations directed toward health care insurers and others who set health care payment policies, the second session of the workshop focused on the relationship between clinical providers and the payors who cover all or part of the costs of patient care within cancer clinical trials. It included presentations by representatives of two large insurance companies, the HHS Center for Medicare and Medicaid Services (CMS), a major academic research center, and ASCO. The presenters then joined a panel discussion moderated by Dr. Lee Newcomer of United HealthCare.

**Payor Policies**

Dr. James Cross of Aetna, Drs. Sharon Levine and Louis Fehrenbacher of Kaiser Permanente, and Dr. Louis Jacques of CMS outlined their employers’ payment policies for patients participating in clinical trials.

*An Insurer’s Perspective*

Every insurer handles its dealings with clinical trial providers differently, Dr. Cross observed, noting that his remarks would reflect Aetna’s perspective. Most insurance contracts distinguish between goods and services that are medically necessary, which are covered, and those considered experimental or investigational, which are excluded from coverage, he explained. Applying that distinction can be particularly challenging in the context of clinical trials, and he noted that some payors—but not most major insurers—would simply refuse to cover any treatment provided as part of a clinical trial.

First, he noted that Aetna covers off-label cancer treatments that have been shown to be efficacious through peer-reviewed literature and/or have a favorable evaluation from the National Cooperative Cancer Network (NCCN)17 or in other nationally recognized guidelines, Dr. Cross reported. These clinical practice guidelines recommend appropriate treatments based on the level of scientific evidence and consensus supporting their efficacy for particular cancers (see Box 3), and they include the off-label use of drugs in cancer treatment. Aetna covers treatments accorded an NCCN category of evidence of 2B or higher, he reported.

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17 The National Comprehensive Cancer Network®, a not-for-profit alliance of 21 of the world’s leading Cancer Centers, develops information for stakeholders in the health care delivery system. NCCN serves as an arbiter of cancer care by creating clinical practice guidelines appropriate for use by patients, clinicians, and other health care decision makers. Source: http://www.nccn.org/about/default.asp.
Public Comment

Guiding Principles to Ensure Successful Reconfiguration of the Cancer Cooperative Groups

May 19, 2011

Statement of Need

On September 20, 2010, cooperative group chairs, through the Coalition of Cancer Cooperative Groups (Coalition), issued a public comment fully endorsing the Institute of Medicine (IOM) analysis “A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program” (April 2010). The statement urged that the IOM’s recommendations be adopted in their entirety, and it voiced our willingness as the cooperative group leadership to work with the IOM, National Cancer Institute (NCI), advocacy organizations, and other stakeholders throughout the academic, governmental, and commercial sectors to develop reasoned implementation plans to transform the cooperative group program as recommended.

In this second public comment, we voice our consensus opinion on upcoming changes to the federal funding mechanism by which the cooperative groups will apply for multi-year grant awards from the NCI. The as-yet-to-be-written Funding Opportunity Announcement (FOA) will set forth new criteria by which the groups will be reviewed, ranked, judged, and funded in the future. It is expected that many of the IOM recommendations will coalesce in this FOA; thus, it carries the heavy weight of permanence in that it will set the groups’ scientific and operational parameters over the long-term. However, simultaneous to the FOA development, several groups are in the midst of voluntary consolidations (IOM Recommendation #1) whose scientific and operational details are being defined. The irreversible forward momentum of these two parallel timelines has created a need for us to comment publicly.

The NCI has circulated a tentative timeframe for the FOA development, including a period for public comment through July 2011. After the period of public comment concludes, various internal NCI committees and the National Institutes of Health (NIH) will develop the FOA, which is scheduled for release in July 2012. We believe that during the period of public comment, it is imperative to clarify and define the components of a successful re-configuration of the cooperative groups. We have agreed upon a set of guiding principles to ensure that we ourselves advocate consistently for reasoned implementation plans to transform the
cooperative group program as recommended. By making these principles publicly available, we trust that we are providing greater clarity for stakeholders during these final days of the public comment period.

The IOM report was the catalyst for various changes to the system that are now underway, and it has generated a new level of enthusiasm within the cooperative group leadership. Over the last several months, group leadership, working with the NCI, has made considerable progress in implementing many of the recommendations in the IOM report, such as increasing the efficiency of group operations, implementing a cross-group information technology (IT) system, and developing plans to consolidate the activities of certain groups into new relationships and entities. There are two over-arching principles on behalf of cancer patients in all of these activities: the first is to provide the framework for the groups to design and conduct innovative, science-driven clinical trials across the clinical research spectrum for the benefit of cancer patients--from advancements in treatment standards and improvements in quality of life to cutting edge early detection, prevention, and diagnostic capabilities. The second principle was well articulated in the IOM report, that “it is imperative to preserve and strengthen unique capabilities of the cooperative group program as a vital component in the NCI’s translational research continuum.”

Guiding Principles to Ensure Successful Reconfiguration of the Cancer Cooperative Groups:

1. Patients are best served by having strong scientific programs

2. The cooperative groups will function as an integrated hub for large Phase II and Phase III studies

3. Flexibility is required to maximize the potential of the restructured system

4. The strong membership culture of the groups is worth preserving

5. The study review process should incentivize scientific innovation

6. The viability of the new cooperative group hub is linked to its critical resource needs

7. Multi-sector involvement generates funding and science that would not otherwise happen

8. Applicants for cooperative group funding should possess certain Essential Characteristics

**Principle #1 : Patients are best served by having strong scientific programs**
The cooperative groups are, at their core, multi-disciplinary, multi-institutional, and multi-disease oriented science-driven clinical research organizations which perform clinical trials designed to move the standard of care forward. The re-configuration should enhance the ability of the groups to perform innovative, science-driven clinical trials. To do so, the new review funding criteria for the groups should give the greatest consideration to each group’s scientific expertise, followed by what it brings to the network as a whole. This will help ensure that the groups remain focused on improving the outcomes for patients with cancer.

- The new review criteria should judge the groups upon their ability to design and perform science-based large Phase II and Phase III studies that complement and balance the more tailored approach of industry toward FDA primary and secondary filings for drug approval, e.g. evaluating new targeted agents across disease types not encompassed in the initial FDA filings; determining the optimum characteristics for patient selections across disease types based upon their molecular and genetic characteristics, and designing trials in selected subsets of patients based upon those characteristics; direct comparisons of competing new therapies or combinations of therapies, some of which may be held by more than one company, or may be non-pharmaceutical therapies; and quality of life research.

- In order to perform such studies, the groups must have ready access to agents in development. It is important to acknowledge that while the groups will be judged for their science, and for what they bring to the newly integrated network, it is the role of the NCI to provide ready access to agents within its portfolio.

- A major reflection of the quality of science being performed in the groups is their ability to call upon the specific strengths of their membership to produce NCI funding via R01s, P01s, SPORES, contracts, and other publicly and privately funded peer review mechanisms. The new review criteria should stimulate scientific innovation to flow more efficiently from the cancer centers to the cooperative groups by coordinating leadership and prioritizing cancer centers’ biomarker-based research, genomics, novel study designs, and promising Phase II studies.

- The system is best served by continuing to have independent, academically-based statistical leadership integrated into each group’s scientific leadership.

- Annotated biospecimens, and the biorepositories that process and hold them, are essential to science-based studies. There are three needs in this area: 1) to maintain the current practice of integrating them into group operational/scientific structures; 2) to provide the IT infrastructure to link biorepositories together aka a virtual
biorepository; and 3) to develop a more robust system to provide to biospecimens for peer-reviewed research.

**Principle #2**: The cooperative groups will function as an integrated hub for large Phase II and Phase III studies. Cooperative groups are connected by their cross-group scientific and administrative interactions. While each possesses unique capabilities, the cooperative groups are best viewed collectively, within the newly integrated network, as the hub for Phase II and Phase III studies. The NCI should clearly declare that the re-configured cooperative group system is its major vehicle for performing large Phase II and Phase III studies within its translational research continuum.

- Together, we are committed to developing, performing, and providing the logistical and infrastructure support for large Phase II and Phase III studies independent of which group originates the study. As a corollary, the new criteria should reward network participation by giving equal credit for all trials in which a group and its members participate.

- We are committed to developing a governance structure to manage cross-group scientific and administrative functions, in conjunction with the NCI, which will include developing guidelines for interactions between the group scientific structure and the steering committees, aligning scientific priorities, creating consensus, and enforcing decisions made by the network leadership.

- Together, the groups are working with the NCI on an integrated IT infrastructure to support studies performed within the network, including the development of a “virtual biorepository” to facilitate access to biospecimens.

- The groups are working with the NCI to continually improve operational efficiencies.

**Principle #3**: Flexibility is required to maximize the potential of the restructured system

The cooperative groups are in the process of restructuring, and once consolidations are complete, the groups will look different from one another based upon their need to preserve and enhance areas of scientific and functional expertise. It is likely that some groups will remain as currently structured, some will combine into one entity, and some into a confederation alliance of several entities. The new federal guidelines for grant review should allow groups to make their own decisions about the formation of their structures—scientifically and operationally.

- Flexibility is needed to preserve and enhance areas of scientific expertise within the groups, e.g. one group may relate more
successfully to patients, physicians, researchers, and other people working in a particular disease specialty, or it may be the groups need to form an imaging hub or laboratory to be available for the entire network; flexibility will be required for the groups to determine how such capabilities fit into the entire system.

- The new federal funding guidelines should not require excessive homogeneity in the cooperative groups, or in other words, the criteria should not require groups to be too similar in structure, purpose, or capabilities. Otherwise, if every one of the groups looks the same, there will only be a general competition for funding rather than the more optimal mixing and matching of different scientific and functional expertise in the various groups.

**Principle #4**: The strong membership culture of the groups is worth preserving

The cooperative groups are member driven networks, which engender a culture of team science, commitment and volunteerism across three core areas of membership: cancer centers and academic sites; Community Cancer Oncology Programs (CCOPs), Minority-Based CCOPs and other community based practices; and patient advocates involved in research. The new review criteria should reward their strong membership culture as follows:

**Cancer Centers and Academic Programs**: the NCI-designated cancer centers, their clinical investigators, and laboratory programs provide the scientific engine that drives the development and design of Phase II and III studies within the cooperative group system. The reconfigured system should amplify these interactions.

- Under the existing structure, the groups and the cancer centers have benefited mutually from their scientific interactions, e.g. during the last five years 66 RO1s, 6 P01s and 19 SPOREs relating to group work have been awarded to cancer center investigators.

- The entire NCI clinical research infrastructure including the cancer centers, R01 and related grants, SPOREs, Program Projects, and the reconfigured cooperative group system must be aligned accordingly to maximize the functional interactions among these programs. We endorse the recommendations of the Ad Hoc Guidelines Harmonization Working Group as presented to the Clinical Trials and Translational Research Advisory Committee (CTAC), and support their earliest possible implementation.

- The U10 grant mechanism currently provides an integral connection between the scientific programs of the cooperative groups, cancer centers, and academic institutions; the number of U10 grants in the program should be increased so that additional qualifying institutions can connect to the groups.
• U10 Principal Investigators and individuals with senior leadership positions within the cooperative groups should be recognized in the senior leadership structure of the cancer centers, and the science they perform within the groups should be acknowledged and rewarded in the cancer center review process. The cancer center core grants should add metrics of success and impact for cooperative group participation via senior leadership positions and participation in active committee membership positions.

• In order to increase opportunities for young investigators to develop and lead clinical trials in the groups, we recommend that both the cancer center core grants and cooperative grant mechanism add aligned metrics of success and impact in the area of “career development.”

**Community-Based Researchers**: CCOPs, Minority-Based CCOPs (MBCCOPs), and community practices affiliated with the cooperative groups are an integral component of the existing system and account for over half of the accrual onto group studies. Community-based researchers view the cooperative group structure as their scientific “home” where they can participate at all levels. They are best served by a cooperative group structure that is multi-disciplinary, multi-institutional and multi-disease oriented. The new review criteria should preserve and strengthen their membership ties with the groups.

• The current structure provides the opportunity for CCOPs and MBCCOPs to align primarily with one cooperative group, but also allows them to participate in the activities of groups of their choosing through the Expanded Participation Project; this practice should continue.

• To provide a stable funding base, high accruing community practices should be provided the opportunity to receive increased per-case reimbursement and infrastructure support through an expanded U10 mechanism, or other such federally funded mechanisms. This is not currently the practice.

• The groups should continue to support, through the CCOP mechanism, risk assessment, early detection, prevention, symptom intervention, health outcomes, and special populations research.

**Cooperative Group Patient Advocates**: Approximately 100 individuals serve voluntarily as patient advocates in research across the groups; in each, advocates are involved in all aspects of study development, execution, and trial monitoring. The reconfigured cooperative group system must maintain the integral function of patient advocates in its scientific structure.

• We recommend that the consolidation of some of the groups should
not result in a substantial reduction in the number of advocates who participate in the groups.

- The high level of involvement of the advocates in all phases of trial development and execution should be maintained.

- In the newly configured system, patient advocates who participate in disease steering committees, SPORES and other parts of the integrated network, would benefit from having increased access to, and interaction with, the cooperative group advocates. Currently, functional interactions among the cooperative group advocates occur primarily through a structured program within the Coalition of Cancer Cooperative Groups.

**Principle #5 : The study review process should incentivize scientific innovation**

In the area of scientific proposal review, we agree that extramural peer review facilitated by the NCI should be employed in assessing scientific proposals, and in helping to define the strategic landscape for a given malignancy. The steering committee approach is in varying stages of development and implementation across diseases; this approach should be evaluated primarily for its ability to encourage and incentivize scientific innovation. The entire concept of task forces should be reconsidered. We are developing a white paper discussing the Steering Committee process and its optimization. Listed here are some top line recommendations:

- Steering committees should be charged with reviewing studies, not designing or re-designing them, and the role of the NCI should be facilitative, rather than controlling, in the process.

- The entire process should be open and transparent.

- Unnecessary layers of review should be eliminated, particularly regarding establishment of multiple task forces.

- As noted in Principle 2, in conjunction with the NCI, we are committed to developing a governance structure to manage cross-group scientific and administrative functions. One imperative of the governance structure will be to develop guidelines for interactions with steering committees, particularly those needed to stimulate innovative trial approaches using disease specific markers and novel study designs.

**Principle #6 : The viability of the new cooperative group hub is linked to its critical resource needs**

While it is widely known, accepted, and acknowledged by the IOM report that the cooperative group system is grossly underfunded, we also recognize the enormous economic challenges that face our
nation. Unfortunately, the crisis in the economy occurs at a time when we are all committed to re-thinking how we operate and work together to enhance the opportunities for patients to participate in innovative ground-breaking clinical trials. As funding priorities within the NCI, NIH, and the federal government are assessed; it is still important to define the critical needs:

- **Per Case Reimbursement.** Recently, the NCI adjusted the base level funding for large Phase II studies to $5,000/case. The case reimbursement structure for Phase III studies must be addressed in the new federal funding opportunity; the base level funding of $2,000/case has become so non-competitive that it endangers the entire national clinical trials system regardless of its configuration. Current per case reimbursement for Phase III studies does not come close to covering the costs of participation in cooperative group trials. This places a burden upon institutions that participate in cooperative group studies to make up the difference through cost-sharing and dedicated staff members who donate their time—an unsustainable reliance upon volunteerism considering the rising cost of medicine. The case-reimbursement floor for Phase III studies should increase to $4,000, with additional reimbursement set trial-by-trial based on complexity and priority. Whatever the reimbursement for a given trial, the funding level should be the same for high accruing sites, whether they are academically or community based.

- **Number of U10 Grants.** The U10 grant mechanism currently provides an integral connection between the scientific programs of the cooperative groups, cancer centers, and academic institutions; an increase in the number of U10 grants in the program will enable additional qualifying institutions and their researchers currently “outside the system” to become members of the groups.

- **Investigator Compensation.** The U10 grant funding should increase, above and beyond case reimbursement, to adequately support investigators for their scientific participation in the groups.

- **Common IT Platform.** We appreciate the NCI’s recent commitment of funds to a cross-group IT platform. Funding is needed for continued development and implementation of the uniform IT infrastructure, which includes protocol authoring, clinical trials data management, and biospecimen management.

- **Biorepositories.** Funding is required to fully support the groups’ biorepositories. Three needs described in Principle #1 are restated here: 1) to maintain the current practice of integrating the banks into group operational and scientific structures; 2) to provide the IT infrastructure to link biorepositories together aka a virtual biorepository; and 3) to develop a more robust system to provide to biospecimens for peer-reviewed research.
**Principle #7**: Multi-sector involvement generates funding and science that would not otherwise happen

The groups bring significant incremental resources to the publicly funded system. Aside from the increased levels of funding defined above, the federal guidelines must continue to provide the flexibility for the cooperative groups to seek and maintain multi-sector funding relationships. These relationships provide a critical financial supplement to the federal funding, in support of NCI-approved clinical and laboratory based studies.

- Close working relationships with industry yield additional resources, on a trial-by-trial basis, to increase inadequate case reimbursement, support laboratory based integral and integrated biomarker studies, and/or address exploratory laboratory investigations. In the latter example, supplemental funding has led to more precise definition of disease and a better understanding of basic tumor biology.

- In addition to industry, the groups successfully generate funds from the non-profit sector, in support of NCI-approved studies relating to specific diseases, supportive care, and survivorship.

- The peer review system should reward groups for generating science through their foundations and bringing it to the network.

**Principle #8**: Applicants for cooperative group funding should possess certain Essential Characteristics

The purpose of the new federal funding guidelines should be to produce excellence in science and ensure groups remain focused on improving the outcomes for patients with cancer. To do so, we recommend that applicants to the upcoming funding opportunity possess the following Essential Characteristics:

1. Strong scientific base with representation from cancer centers, academic institutions, and community-based programs, including the Cancer Community Oncology Program (CCOP) and Minority-Based CCOP members;

2. Established track record in designing and executing clinical trials that move the science and standard of cancer care forward and/or change clinical practice;

3. Documented history of accruing large numbers of patients to high quality clinical research trials;

4. Strong, integrated, and established biorepositories and IT systems;

5. Proven track record in producing NCI RO1, PO1, and SPORE grants and contracts;
6. Capability to perform clinical trials that incorporate integral and integrated biomarkers, including imaging;

7. Operations/headquarters offices capable of conducting multi-institutional federally funded trials;

8. Academically-based statistical support and data management centers with a successful history of developing, monitoring, and analyzing multi-institutional Phase I-III clinical trials;

9. Robust and established membership structure that brings together both academic and clinically based experts into a multi-disciplinary, multi-disease, and multi-institutional structure; and

10. Track record in abiding by the timelines and guidelines of the NCI Operational Efficiency Working Group.

Signed,

American College of Radiology Imaging Network
*Mitchell D. Schnall, MD, PhD, Chair*

American College of Surgeons Oncology Group
*Heidi Nelson, MD and David Ota, MD, Co-Chairs*

Cancer and Leukemia Group B
*Monica Bertagnolli, MD, Chair*

Children’s Oncology Group
*Peter C. Adamson, MD, Chair*

Eastern Cooperative Oncology Group
*Robert L. Comis, MD, Chair*

Gynecologic Oncology Group
*Philip J. DiSaia, MD, Chair*

National Surgical Adjuvant Breast and Bowel Project
*Norman Wolmark, MD, Chair*

North Central Cancer Treatment Group
*Jan C. Buckner, MD, Chair*

Radiation Therapy Oncology Group
*Walter J. Curran, Jr., MD, Chair*

SWOG
*Laurence H. Baker, DO, Chair*

The Coalition of Cancer Cooperative Groups is an independent non-profit organization working to improve physician and patient access to cancer clinical trials through education, outreach and advocacy. For more information, visit [www.CancerTrialsHelp.org](http://www.cancertrialshelp.org) or contact Diane D. Colaizzi, MA, Executive Advisor and Media Relations Liaison, 215.789.3612 and dcolaizzi@cancertrialshelp.org.

Newly Formed Cancer Cooperative Group Selects Name

New group integrates the scientific and operations activities of the Cancer and Leukemia Group B (CALGB), the North Central Cancer Treatment Group (NCCTG) and the American College of Surgeons Oncology Group (ACOSOG)

Alliance for Clinical Trials in Oncology (“Alliance”) has been selected as the name for the newly formed cooperative group, which will integrate the scientific and operations functions of the Cancer and Leukemia Group B (CALGB), the North Central Cancer Treatment Group (NCCTG) and the American College of Surgeons Oncology Group (ACOSOG). More than 2,000 members of the three groups selected the name by electronic ballot.

The governing boards of CALGB, NCCTG and ACOSOG have endorsed the proposed Alliance constitution, bylaws and transition plan. The first Alliance Board of Directors Meeting will be held on July 15, 2011, in Chicago. Each group has selected delegates to attend the meeting and establish the governance structure of the new group.

The Alliance scientific program leaders, along with scientific leadership from CALGB, NCCTG and ACOSOG, will meet in September, in Chicago, to define the group’s scientific agenda going forward.

The first joint Alliance meeting, which will include all members, will be held November 17-19, 2011, in Chicago.

For more information on Alliance activities, visit the group’s Web site at www.Alliance-website.org.

# # #
FOR IMMEDIATE RELEASE

Biomarker-Driven Science at the Heart of New ACRIN-ECOG Structure

Philadelphia, PA [March 18, 2011]: The American College of Radiology’s Imaging Network (ACRIN) and the Eastern Cooperative Oncology Group (ECOG), National Cancer Institute (NCI) Clinical Trials Cooperative Group members, today announced their intent to merge their clinical cancer research programs.

The groups plan to form an alliance that combines their complementary strengths. The new organization will include three areas of research emphasis: early detection and diagnosis of cancer; biomarker-driven Phase II and Phase III therapeutic studies for multiple cancer types and stages; and genetic, molecular and imaging marker research to predict and monitor treatment response.

As leading research organizations, ECOG and ACRIN’s individual programs have significantly contributed to improved clinical care. The new alliance will bring together the organizations’ unique capabilities to build a program with expanded scientific scope and depth of expertise. ECOG has strengths in performing large-scale trials with molecular endpoints in major diseases; the results of these studies have changed the treatment of cancer patients, and helped to individualize that therapy. ACRIN’s clinical trials encompass the full range of medical imaging research: from landmark cancer screening trials to early phase trials evaluating imaging biomarkers and novel imaging technologies. While maintaining these areas of separate expertise, the alliance will press the tailoring of therapy to the individual patient’s tumor, and accelerate the integration of biological advances into clinical practice.

“This partnership offers the research community a new sphere of engagement,” says Robert L. Comis, MD, Chair of ECOG. “It will greatly enhance our position in the public and private sectors to perform biomarker-driven studies and develop more innovative clinical trial designs. ACRIN has an exceptional imaging research program and IT infrastructure which can be applied to compile and store not only radiologic images, but also, relevant laboratory based images. Our modality and disease committees will have the opportunity to become involved in the development of cutting edge early detection and

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diagnostic studies, and ACRIN investigators will benefit from being fully integrated into our therapeutically oriented programs.”

“We are excited by the ECOG partnership opportunity to develop a unique multidisciplinary organization positioned to study the entire cancer care path from early detection through management of advanced disease,” says Mitchell D. Schnall, MD, PhD, ACRIN Network Chair. “We will leverage the complementary scientific expertise of each group to develop multidisciplinary scientific committees to address each of the three emphasis areas for which there will be immediate opportunities for interaction and collaboration. The integration of ECOG and ACRIN patient advocacy and clinical research associate committees will bring together an impressive knowledge base representing the patient perspective and participant recruitment best practices – a significant support for getting the research done.”

“Clinical research has been an important component of the American College of Radiology (ACR) for over 40 years, comments Harvey L. Neiman, MD, FACR, the ACR’s chief executive officer. “I commend the decision to bring together the extensive resources of ACRIN and ECOG to carry out clinical research that combined has even greater potential to bring forth new scientific discoveries to detect cancer earlier and to improve the care and quality of life of cancer patients.”

Transition planning is underway, and group leaders are developing the business, administrative and scientific structures. The new organization will sustain its research portfolio with public and private support. Relative to public funding, the NCI announced last November that it will reorganize its Cooperative Group program to support up to four adult cooperative groups, and will issue a new Funding Opportunity Announcement (FOA) in Spring 2012; the new organization will respond on behalf of ECOG and ACRIN.

About ACRIN
The ACRIN network is made up of investigators from over 100 academic and community-based facilities in the United States and abroad. ACRIN’s oncology mission is to develop information through clinical trials of medical imaging that increase the length and quality of life of cancer patients. ACRIN also carries out research through its cardiovascular and neuroscience committees. Its imaging core laboratory supports the imaging operations of the ACRIN enterprise as well as other organizations carrying out imaging research. [www.acrin.org](http://www.acrin.org).

About ECOG
ECOG was established in 1955 as one of the first cooperative groups to perform multi-center cancer clinical trials. Today ECOG has evolved from a five member consortium of institutions on the East Coast to one of the largest clinical cancer research organizations in the United States with almost 6000 physicians, nurses, pharmacists, statisticians, and clinical research associates from the U.S., Canada, Peru, Israel, South Africa, and Ireland. Institutional members include universities, medical centers, Community Clinical Oncology Programs, and Cooperative Group Outreach Programs. All of
these members contribute to ECOG’s strong track record of designing and completing cancer clinical trials that change or improve cancer treatment methods, including the two largest biomarker-based trials ever performed in the US, TailorRx and E 5202. www.ecog.org

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If today’s new understandings of cancer biology are to benefit cancer patients on a broad scale, they must be coupled with a modernized system for conducting cancer clinical trials. This system must enable clinical researchers across the nation to acquire tumor specimens and conduct genetic tests on each patient, to efficiently sequence the DNA from those samples, to manage and secure vast quantities of genetic and clinical data, and to identify subsets of patients with tumors that demonstrate changes in specific molecular pathways—pathways that can be targeted by a new generation of cancer therapies. And all of this must be done one patient at a time.

As part of its effort to transform the cancer clinical trials system, NCI asked the Institute of Medicine (IOM) in 2009 to review the Clinical Trials Cooperative Group Program. This program involves a national network of 14,000 investigators currently organized into nine adult Cooperative Groups and one pediatric cooperative group that conduct large-scale cancer clinical trials at 3,100 sites across the U.S. The IOM report, issued in April 2010, noted that the current trials system—established a half-century ago—is inefficient, cumbersome, under-funded, and overly complex. Among a series of recommendations, the report urged that the existing adult cooperative groups be consolidated into a smaller number of groups, each with greater capabilities and the ability to function with the others in a more integrated manner.
In December 2010, NCI announced its intent to begin consolidating the current nine adult cooperative groups into up to four state-of-the-art entities that will design and perform improved trials of cancer treatments, as well as explore methods of cancer prevention and early detection and study quality-of-life issues and rehabilitation during and after treatment. The sole pediatric cooperative group was created by consolidating four pediatric cooperative groups a number of years ago, and that group will not be affected by the current consolidation effort.

NCI also intends to consolidate nine existing tumor banks into three to give researchers improved access to a nationally integrated tissue resource. Currently, optimal use of tissue specimens from NCI-supported prospective trials is impeded by the lack of a national IT system for locating tissue, the lack of standard operating procedures, and the lack of a transparent process to prioritize the distribution of specimens on a national scale.

Revitalizing a cancer clinical trials system must enable researchers across the nation to acquire tumor specimens and conduct genetic tests on each patient, efficiently sequence DNA, and identify subsets of patients with tumors that demonstrate changes in specific molecular pathways.

The consolidation of the cooperative groups is also intended to improve the efficiencies of operations centers and data management centers, and to facilitate the training of investigators in applying molecularly based approaches to large-scale clinical trials. In addition, NCI envisions using the Cooperative Group Program as a means for preparing the oncology community, including community physicians, for the widespread introduction of molecularly-based therapies.

The consolidation of the Cooperative Group Program is the most recent in a series of changes initiated by NCI, through its Division of Cancer Treatment and Diagnosis and the Coordinating Center for Clinical Trials, to revitalize the nation’s cancer clinical trials system. Other transformative changes introduced in recent years include those outlined in a working group report which can be found at http://ccct.cancer.gov/files/OEWG-Report.pdf:

• Reduce by half the time to initiate new clinical studies and terminate studies not begun within 18 to 24 months of concept approval.

• Revamp the prioritization process for large phase II and phase III treatment trials by creating disease-specific and modality-specific steering committees.

• Improve the use and efficiency of the NCI Central Institutional Review Board, which reduced the average time for final sign-off on protocols for national trials from 150 days in 2007 to 42 days in 2010.

• Increase reimbursement to clinical trials sites.
I was sworn in as the new Director of the National Cancer Institute just nine months ago, so this is the first time that I have been privileged to voice my pride in NCI’s past accomplishments and the promise of future achievements in its annual report on budget needs and priorities.

Although I am new to this position, I am not new to cancer research or to the NCI. I received my scientific training here more than 40 years ago, started to work on cancer-causing viruses shortly thereafter, and have been supported by NCI funds throughout my career. In these intervening years, I have witnessed profound changes in our knowledge about the biology of cancer. When I began to study animal models of cancer in the early 1970s, the collective understanding of the origins and progression of cancer was negligible; now we are able to describe such events in minute detail at the molecular level. This transformation has been accompanied by gradual—and occasionally dramatic—improvements in the control of human cancer. In an increasing number of cancers, new concepts about the biology of cancer are now driving beneficial changes in the ways we prevent, diagnose, and treat disease.

The importance of the NCI throughout this rich history can best be appreciated by considering the amazing diversity of the approaches it has undertaken to control cancer—through basic research on normal cells, genes, and proteins; through studies of the pathogenesis of various forms of cancer; and through efforts to improve the prevention, diagnosis, and treatment of cancers.

In the first half of this report, we have tried to convey the depth of these enterprises, while emphasizing at least three big ideas. First, cancer constitutes a complex set of diseases. It is not simply one disease that happens to afflict many organs of the body; it is, instead, many different disorders that display some common themes, including mutations in many important genes, alterations in essential cell functions, and novel interactions with the cellular environment in which tumors grow. Second, cancers can be controlled in many different ways. As reflected in their biological complexity, cancers invite several strategies to improve control. These include a number of approaches to prevention, multiple methods to screen for early stages of carcinogenesis, more precise diagnostic tests, and better
therapies. The improved treatments are based on knowledge of specific genetic changes in cancer cells, the functions of the immune system, the susceptibilities of cancer cells to various drugs and radiotherapy, and an understanding of the symptoms and complications of these diseases.

Third, advances against cancer that benefit people depend on science of many kinds. Progress in the control of cancer has required new knowledge from the many fields of research that the NCI supports—from molecular and cell biology, genetics, virology, immunology, and chemistry; from animal models of cancer; from the behavior and biology of human beings; and from many other directions. In brief, cancer represents one of the greatest challenges to the strength of modern medical science.

My colleagues and I have chosen to illustrate these ideas, and the complexity they embody, by describing recent progress made against six kinds of cancer, chosen somewhat arbitrarily from a much larger repertoire of successes. We acknowledge that none of these six stories is over; in all situations, we have much more to do. But each narrative reveals a promising path to further progress.

The men and women who have achieved these successes and who are poised to extend them represent our greatest resource. With the additional funds requested here, their ambitions and talents can be unleashed, ensuring that the NCI can take the greatest possible advantage of the opportunities created by its remarkable history.

Harold Varmus, M.D.
Director, National Cancer Institute
This budget request consists of two components: the increase required to maintain our present level of operations (current services) and the increase required to initiate new initiatives and expand existing ones.

It should be noted that we have carefully reviewed our current expenditures and have found important efficiencies and savings. The current services increase is the amount that will be required to sustain NCI programs, restore some of the funding cuts that have been implemented over the past several fiscal years, and provide for some minimal growth. Noncompeting Research Project Grants (RPGs) would be funded at committed levels, the number of competing RPGs would be maintained at the FY 2010 level, and most other mechanisms would receive sufficient increases to cover cost of living adjustments based on the Biomedical Research and Development Price Index (BRDPI). This budget level also includes funds to make critically needed capital repairs and improvements at the NCI-Frederick Federally Funded Research and Development Center.

The additional funds requested reflect the Institute’s assessment of where more funding will make the greatest difference in reducing cancer incidence and mortality. Together, with growing the research grants portfolio, these new or expanded initiatives—cancer genomics, transformation of the clinical trials system, and more effective translation of research results to clinical utility—offer the greatest current hope of advances against cancer.

### National Cancer Institute

#### At a Glance  [dollars in thousands]

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<thead>
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<th>Description</th>
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<tr>
<td>Fiscal Year 2011 Estimate</td>
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#### Fiscal Year 2012 Additional Resources

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<td>Support Individual Investigators</td>
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<td>Clinical Trials</td>
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