# DEPARTMENT OF HEALTH AND HUMAN SERVICES
# PUBLIC HEALTH SERVICE
# NATIONAL INSTITUTES OF HEALTH
# NATIONAL CANCER INSTITUTE
# 22nd CLINICAL TRIALS AND TRANSLATIONAL RESEARCHADVISORY COMMITTEE (CTAC) MEETING

**Summary of Meeting**
**March 12, 2014**

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

**CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE**
**BETHESDA, MARYLAND**
**Summary of Meeting**
**March 12, 2014**

The 22nd meeting of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) was held on Wednesday, March 12, in Conference Room 10, C Wing, 6th Floor, Building 31, on the National Institutes of Health (NIH) main campus in Bethesda, Maryland. The CTAC Chair, Dr. James L. Abbruzzese, Chief, Division of Medical Oncology; Associate Director, Clinical Research, Department of Medicine, Duke Cancer Institute, Duke University Medical Center, presided. The meeting was adjourned at 2:18 p.m.

**Chair**
James L. Abbruzzese

**CTAC Members**
Susan G. Arbuck (absent)
Monica M. Bertagnolli
Curt I. Civin
Kevin J. Cullen
Nancy E. Davidson
J. Phillip Kuebler
Scott M. Lippman
Mary S. McCabe
Edith P. Mitchell
Nikhil C. Munshi
Lisa A. Newman
Peter G. Shields
George W. Sledge, Jr.
Chris H. Takimoto
Gillian M. Thomas (absent)
Frank M. Torti (absent)
Miguel A. Villalona-Calero
George J. Weiner

***Ad Hoc* Members**
Peter C. Adamson
Michael LeBlanc

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

**Executive Secretary**
Sheila A. Prindiville, NCI

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## I. CALL TO ORDER AND OPENING REMARKS—DR. JAMES L. ABBRUZZESE

Dr. Abbruzzese called the 22nd meeting of the CTAC to order and welcomed participants to the meeting. He also welcomed two ad hoc members to the meeting: Dr. Peter C. Adamson, Professor, Pediatrics and Pharmacology, and Chief, Clinical Pharmacology and Therapeutics, The Children's Hospital of Philadelphia; and Dr. Michael LeBlanc, Research Professor, Department of Biostatistics, University of Washington, and Group Statistician and Director of Statistical Center, Southwest Oncology Group.

Dr. Abbruzzese reviewed the confidentiality and conflict-of-interest practices required of Committee members during their deliberations. He invited members of the public to send written comments on issues discussed during the meeting to Dr. Sheila A. Prindiville, Director, Coordinating Center for Clinical Trials, NCI, within 10 days of the meeting. Dr. Abbruzzese reminded members that the meeting was being videocast by NIH Events Management and that the videocast would be available for review following the meeting at http://videocast.nih.gov.

**Motion.** A motion to accept the minutes of the 21st meeting of the CTAC, held on November 6, 2013, was approved unanimously.

## II. DEPUTY DIRECTOR'S REPORT—DR. JAMES H. DOROSHOW

Dr. James H. Doroshow, Deputy Director, Clinical and Translational Research, NCI, provided an update on recent clinical and translational research activities at NCI.

**Pancreatic Cancer.** Dr. Doroshow thanked Dr. Abbruzzese for chairing the CTAC Pancreatic Cancer Working Group, which recently prepared a report on pancreatic ductal adenocarcinoma, *Scientific Framework for Pancreatic Ductal Adenocarcinoma (PDAC)*, available at http://deainfo.nci.nih.gov/advisory/ctac/workgroup/pc/PDACframework.pdf. NCI submitted this report to Congress in February in response to the Recalcitrant Cancer Research Act. The report reviews many major issues in pancreatic cancer, NCI's research portfolio, and a framework for moving forward. The report's major recommendations address the relationship between diabetes and pancreatic cancer, longitudinal biomarker screening for early detection of PDAC and its precursors, immunotherapeutic strategies, and new treatments that interfere with RAS oncogene-dependent signaling pathways. Dr. Doroshow also thanked everyone else who helped prepare the pancreatic cancer report for Congress.

**Small Cell Lung Cancer.** The Small Cell Lung Cancer (SCLC) Working Group has made progress with its report, which should be completed in May or June of 2014. Dr. Charles M. Rudin, Professor, Department of Oncology, School of Medicine, The Johns Hopkins University, will provide a final update on this report when it is ready for submission to Congress. Like the PDAC report, the SCLC report will have important recommendations regarding this understudied disease.

**Changes in NCI Leadership.** Peter Garrett is the new Director of the Office of Communications and Education. John Czajkowski is leaving his position as Deputy Director for Management at NCI to become Associate Dean for Administration at Harvard Medical School.

**Early Therapeutics Clinical Trials Network (ET-CTN) and National Clinical Trials Network (NCTN).** Dr. Doroshow had hoped that this meeting would include a formal presentation on the launch of the ET-CTN and the NCTN. However, the Office of Management and Budget has not yet approved the budgets for these programs. Without the final fiscal year (FY) 2014 budget allocations, NCI has been unable to send notices of award to the new grantees. Dr. Doroshow expected the notices of award for the NCTN to be sent out later this month. The next CTAC meeting will include presentations on both the ET-

CTN and the NCTN. Both of these activities, which are extremely important, have required substantial input from CTAC members and investigators around the country.

**NCI Budget.** NCI expects partial restoration of the budget cuts that resulted from the federal government sequester. NCI's expenses rise every year due to inflation. Unless NCI's budget increases by approximately 1 percent every year, the amount of funding available for programs also decreases.

**NCI Cancer Clinical Investigator Team Leadership Award (CCITLA).** Dr. Doroshow recognized the 2013 NCI CCITLA awardees. Every year, NCI gives this award to 10 to 12 outstanding mid-level clinical investigators at NCI-designated Cancer Centers who actively participate in NCI-funded collaborative clinical trials. The awards provide $50,000 in total costs per year for 2 years to investigators who are nominated by a Cancer Center director. The awards free recipients from some of their clinical obligations so that they can devote more time to clinical research. Many previous recipients have become PIs of clinical research grants or led other important clinical research activities.

The 2013 awardees were:

- Sikander Ailawadhi, M.D., Mayo Clinic, Florida
- Jessica Altman, M.D., Robert H. Lurie Comprehensive Cancer Center and Northwestern University Medical School
- Lauren Byers, M.D., M.S., M. D. Anderson Cancer Center, University of Texas
- Sarah Cooley, M.D., University of Michigan Comprehensive Cancer Center
- N. Lynn Henry, M.D., Ph.D., University of Michigan Comprehensive Cancer Center
- Cynthia Ma, M.D., Ph.D., Alvin J. Siteman Cancer Center, Washington University School of Medicine
- Mohammed Milhem, M.D., University of Iowa Holden Comprehensive Cancer Center
- Timothy Showalter, M.D., University of Virginia Cancer Center
- Abby Siegel, M.D., Herbert Irving Comprehensive Cancer Center, Columbia University
- John H. Stewart, IV, M.D., Wake Forest Comprehensive Cancer Center
- Eunice Wang, M.D., Roswell Park Cancer Institute, State University of New York at Buffalo

### *Questions and Discussion*

Dr. Abbruzzese asked Dr. Doroshow for an update on the February 27, 2014, National Cancer Advisory Board (NCAB) meeting and the March 11, 2014, Cancer Center Directors' meeting.

Dr. Doroshow reported that the NCAB meeting focused primarily on the 50th anniversary of the Surgeon General's 1964 report on smoking and health. Presenters reviewed the etiology, carcinogenesis, and control of tobacco-related diseases as well as electronic cigarettes and the progress that the field still needs. The meeting included a report on the human papillomavirus vaccine by the President's Cancer Panel. Dr. Doroshow also mentioned that the meeting was videocast by NIH Events Management and that the videocast is available for public viewing at http://videocast.nih.gov.

Dr. Doroshow explained that the NCI Cancer Center Directors' 2014 annual meeting took place at the Advanced Technology Research Facility (ATRF) in Frederick, Maryland. The meeting included a presentation by the NCAB Ad Hoc Cancer Centers Working Group on a new model for funding Cancer Centers. This model would change the formula for Cancer Center P30 grants to reduce the disparities among the funding amounts for different Cancer Centers that have resulted from such factors as longevity, size of NCI budget at the time of award, and prior performance. The model is not yet complete; therefore, NCI has not made a final decision on Cancer Center funding.

Dr. George J. Weiner, C.E. Block Chair of Cancer Research, Professor, Department of Internal Medicine, and Director, Holden Comprehensive Cancer Center, explained that the NCAB Ad Hoc Cancer Centers Working Group recommended that Cancer Center awards include a base award determined by center type, merit funding as a percentage multiplier of the base award, and an adjustment for Cancer Center size. Dr. Kevin J. Cullen, Director, Greenebaum Cancer Center, University of Maryland, added that Dr. William Hite, Chair of the NCAB Ad Hoc Cancer Centers Working Group, also reported on this new funding model at the February 27, 2014, NCAB meeting, which is available for public viewing at http://videocast.nih.gov.

Dr. Miguel A. Villalona-Calero, Division Director, Medical Oncology, Division of Hematology and Oncology, The Ohio State University, asked whether NCI caps the number of NCI-designated Cancer Centers. Dr. Doroshow replied that NCI does not cap this number.

Dr. Nancy E. Davidson, Director, University of Pittsburgh Cancer Center, requested information about the ATRF, where the Cancer Center directors' meeting took place. Dr. Doroshow explained that the ATRF is a new building with Good Manufacturing Practice (GMP) space that NCI uses to make vaccines and antibodies for the extramural research community in Frederick, Maryland. The ATRF frees up some NCI space at Fort Detrick for other uses. NCI hopes to invite investigators to Frederick—either at the ATRF or at a building at Fort Detrick—to conduct short-term studies with investigational agents that would otherwise not be possible. Dr. Doroshow noted that NCI has approximately 600 investigational molecules used in clinical trials in sufficient quantities for animal studies at this location.

## III. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations, NCI, reported on the status of appropriations, congressional activities, and legislation of interest to the CTAC.

**FY2014 Appropriation.** Congress's Budget Conference Committee has now created a spending plan that sets discretionary spending levels for FY2014 at $1.012 trillion and for FY2015 at $1.014 trillion. The committee revised the sequester to reduce its impact; however, the revision required an extension of the sequester for an additional 2 years. The committee found the money to pay for the sequester reduction by reducing the spending levels on certain programs, such as pensions for military retirees and government contributions to federal employee pensions. It was noted that the FY2014 appropriation for NIH was set at $29.9 billion; as for NCI, the total appropriation was set at $4.92 billion. NCI's FY2014 appropriation is higher than its FY2013 level of $4.78 billion. However, the 2014 amount is lower than NCI's 2012 budget of $5.06 billion.

**FY2015 Appropriation.** The President had recently announced his FY2015 budget, which includes $30.4 billion for NIH and $4.93 billion for NCI—a very small increase from the Institute's FY2014 budget. The House was expected to pass a budget resolution and begin holding subcommittee hearings later in March. The NIH hearing is scheduled for March 26; Dr. Francis Collins, Director of NIH, will be the primary witness. Four NIH Institute directors, including Dr. Harold Varmus, Director of NCI, will accompany Dr. Collins to the hearing to answer questions. Senator Patty Murray (D-WA), Chair of the Senate Budget Committee, has announced that the establishment of a discretionary spending limit in the December 2013 budget agreement alleviates the Senate's need to pass a budget resolution. The timing of the Senate subcommittee hearings is not known; however, NIH will have a hearing in the Senate, possibly in May.

**Congressional Activities.** Senate Majority Leader Harry Reid (D-NV) has expressed his intention to focus on economic issues, including raising the minimum wage and extending unemployment benefits. House Majority Leader Eric Cantor (R-VA) plans to focus on health care, education, and jobs.

Several members of Congress recently visited NIH. Senator Barbara Mikulski (D-MD) met with Dr. Collins and a small group of Institute and Center (IC) Directors, toured Dr. Marston Linehan's NCI laboratory, and hosted a press event on February 24. Senator Richard Durbin (D-IL) and Representative Joseph Pitts (R-PA) toured the NIH Clinical Center, met with IC directors, and toured research laboratories separately on February 3. On February 28, Representative Leonard Lance (R-NJ) gave the opening remarks at NIH's Rare Disease Day symposium and toured the NIH Clinical Center. On February 21, House Majority Appropriations staff met with Dr. Collins and several IC directors to discuss priorities in the FY2014 omnibus appropriations report. Dr. Crystal Mackall, Chief of NCI's Pediatric Oncology Branch, will discuss advances in immunotherapy research at an American Association for Cancer Research briefing for two House members on March 13. Finally, Dr. Prindiville and Dr. Toby Hecht, Associate Director, Translational Research Program, Division of Cancer Treatment and Diagnosis (DCTD), NCI, will brief the Subcommittee on Health of the House Committee on Energy and Commerce on the pancreatic cancer report.

**Legislation.** The House and Senate have passed the Gabriella Miller Kids First Research Act (H.R. 2019), which would eliminate taxpayer financing of political party conventions and use the money saved to pay for a 10-year pediatric research initiative administered through the NIH Common Fund. The President has not signed the bill or indicated his intentions regarding this bill. If President Obama does sign the bill, several issues would need to be addressed before the pediatric research fund could be created. The Cancer Treatment Parity Act has been introduced in the House and Senate (H.R. 1801 and S. 1879). The bill would require health insurers to cover oral anticancer drugs on terms that are no less favorable than those for anticancer medications administered by a health care provider. Twenty-six states and the District of Columbia have enacted laws that address this issue. The Breast Density and Mammography Reporting Act (H.R. 3404) would amend the Mammography Quality Standards Act of 1992 to require that reports of mammography results, including those for patients, indicate relative breast density. The bill had been introduced in the previous Congress but did not move; to date, there has been no activity on the bill in the current Congress.

### *Questions and Discussion*

Dr. Edith P. Mitchell, Clinical Professor, Medicine and Medical Oncology, and Program Leader, Gastrointestinal Oncology, Kimmel Cancer Center, Thomas Jefferson University, asked about the projected impact of restoring cuts to military pensions on the NCI budget. Ms. Erickson replied that every budget increase must be paid for somehow; however, there is no indication that funding would be taken from NIH to cover the costs of restoring military pensions. Mr. Patrick McGarey, Director, Office of Budget and Finance, NCI, added that restoring these cuts will not affect the domestic discretionary budget due to the fact that savings would need to be identified from the defense discretionary budget. An alternative solution is for revenues to be increased globally to cover the costs of restoring military pensions.

Dr. Mitchell wondered whether cuts might be made in the Congressionally Directed Medical Research Programs, which include cancer research, in order to restore the cuts to military pensions. Mr. McGarey commented that more than $0.5 billion; the defense discretionary budget is cancer-related (and another $0.3 billion is non-cancer research). It was noted that these funds are potentially at risk.

Dr. Abbruzzese asked the breast cancer experts on the CTAC to comment on the science supporting the legislation requiring mammography reports to address mammographic density. Although not a federal

mandate, many states have a similar law. Dr. George W. Sledge, Jr., Chief, Division of Oncology, Stanford University, reported that reasonably good data show that increased breast density is associated with a higher risk of breast cancer. However, it is not clear where breast density ranks compared to other key risks for breast cancer. Dr. Peter G. Shields, Deputy Director, Comprehensive Cancer Center, and Professor, College of Medicine, The Ohio State University Medical Center, commented that the risk of breast cancer rises in a linear fashion with breast density, according to investigators who found a 25 percent difference in risk between the top and bottom quartiles. Unfortunately, because experts do not know how to reduce breast cancer risk in women with dense breasts (beyond the standard recommendations to maintain a healthy weight, eat well, and exercise), this remains a research question.

## IV. NCI 2014 BUDGET CONSIDERATIONS—MR. PATRICK MCGAREY

Mr. McGarey provided an overview of the FY2014 and FY2015 NCI and full federal budgets. He reported that NCI's FY2014 budget, at $4.92 billion, is a 2.8 percent increase compared to the FY2013 budget. It restores approximately half of the funding that NCI lost as a result of the sequestration in 2013. Of the $134 million increase, NCI expects to spend $45 million on mandatory cost increases for salaries and infrastructure, leaving $89 million (or 1.9 percent more than in FY2013) for new programs or increases in existing NCI programs.

To avoid another sequester, restore some of the 2013 cuts, and normalize the FY2014–FY2015 budget process, Congress passed the Bipartisan Budget Act of 2013 (BBA), which provided a government-wide FY2014 increase of $22.4 billion compared to FY2013. This is a temporary bump in funding that does not affect the budget baseline, however. For FY2015, the BBA provides a government-wide increase of $0.6 billion, an amount that is essentially the same as FY2014. The FY2015 increase is about 0.1 percent government-wide. NCI fared slightly better, with a 0.2 percent increase in its proposed FY2015 Budget to Congress.

Over a 17-year period starting in 1998, with dollars adjusted for inflation, NCI's annual budget has declined steadily, except for increases in 2009 and 2010 as a result of the American Recovery and Reinvestment Act of 2009. NCI's real spending power is 40 percent lower than it would have been if its budget had kept pace with inflation.

### *Questions and Discussion*

Dr. Chris H. Takimoto, Vice President, Translational Medicine Early Development, Janssen Pharmaceuticals, Inc., asked what determines the rate of growth in the NCI budget projections from 2017 through 2021. McGarey explained that that the projected growth in the NCI budget is based on the projection for growth of the overall domestic discretionary budget, based on the 2011 Budget Control Act. The growth is not as great as it would have been without the 2013 sequester.

Further, Mr. McGarey explained that NCI spending for rising infrastructure costs is projected to grow by 1.9 percent in FY2014. If the Institute receives a 0.2 percent increase in 2015, it will need to make cuts in some projects to pay for anticipated growth in infrastructure costs next year. The proposed FY2015 budget increase for NCI of 0.2 percent, or $7.9 million, is considerably less than the anticipated growth in infrastructure costs.

Mr. McGarey added that Congress does not need to spread the growth in discretionary spending evenly. Congress can pass a budget that is more favorable to NIH or NCI compared with what it provides to other domestic discretionary programs. However, Congress can only increase the budget for NCI or other NIH components if it makes cuts to other domestic programs.

Dr. Doroshow commented that even before the sequester, when NIH did not receive a budget increase of more than 1 percent, the Institute had to cut programmatic expenses to cover the increases in its infrastructure costs. Mr. McGarey explained that when the NCI budget does not return to at least its pre-sequester level, existing programs must be reduced if NCI plans to fund new activities.

## V. NCI CLINICAL TRIALS REPORTING POLICY—DR. JAMES H. DOROSHOW

Dr. Doroshow discussed a proposed NCI Clinical Trials Reporting Policy.

**Background.** All of the results from NIH-funded research need to be shared with the public to contribute to the body of scientific knowledge. However, the lag time between study completion and publication of results is often very long. Further, reports of studies with negative results often fail to appear in print.

The Food and Drug Administration Amendment Act (FDAAA) requires investigators to register all Phase II through IV clinical trials involving drugs, devices, or biologic agents in ClinicalTrials.gov. In general, investigators must report the results of registered studies of approved products within 12 months of completing the study. Investigators who do not comply with these requirements could face withholding of NIH grant funding and fines of up to $10,000 per day. However, investigators have no legal requirement to report the results of Phase 0 or I clinical trials or of trials of investigational products.

The authors of a 2012 article (*BMJ* 2012;344:d7292) evaluated published reports of 635 completed clinical trials funded by NIH and registered at ClinicalTrials.gov in 2010. Of these studies, less than half had been published in a peer-reviewed medical journal within 30 months of study completion; approximately one-third of the studies had not been published within 4 years.

**Proposed Policy.** The principle underlying the proposed NCI Clinical Trials Reporting Policy is that investigators, clinicians, and patients greatly benefit when the final results of trials are made available to the public shortly after the completion of the trial, largely due to the fact that the results could affect patient care. The policy covers all NCI-supported extramural or intramural interventional clinical trials in all disciplines and trial phases, regardless of whether they are completed. The policy applies to all trials with partial or complete financial support from NCI, but not to those conducted by NCI-designated Cancer Centers that are privately funded.

In an effort to avoid confusion, the policy will be aligned with the requirements of ClinicalTrials.gov. NCI will require investigators to report results within 12 months of the trial's primary completion date or, for incomplete trials, the date when data were collected on the last participant. Investigators will need to report these results in a publicly accessible way, which could include in peer-reviewed scientific journals, in ClinicalTrials.gov, in other publicly accessible clinical trial registries, or in journals that publish brief study summaries under less vigorous peer review than full-length articles.

This policy will be spelled out in the terms of award for grants or contracts. NCI program and project officers will enforce the policy at the time of the final progress report or at another time for clinical trial networks. Noncompliance could result in the recovery of funds or withholding of future support.

When NCI published the policy (NOT-CA-14-005) in the NIH Guide, it received overwhelmingly supportive responses. The next step is to present the proposed policy to a joint meeting of the NCAB and the Board of Scientific Advisors (BSA) in June 2014 to obtain their approval.

### *Questions and Discussion*

Dr. Deborah Zarin, Director, ClinicalTrials.gov, National Library of Medicine, was one of the authors of the *BMJ* article on publication of NIH-sponsored clinical trials. She noted that many investigators are unaware of the FDAAA, and she commended Drs. Varmus and Doroshow, as well as other NCI leaders, for addressing the need to publish the results of all clinical trials. The new policy avoids the challenge of trying to determine whether the FDAAA requires a given clinical trial's results to be reported by mandating the reporting of all NCI-funded clinical trial results. Dr. LeBlanc added that the International Committee of Medical Journal Editors has stated that the journals it represents will not regard registration of results in ClinicalTrials.gov as prior publication.

**Consistency of Reporting Requirements.** Dr. Adamson commented that investigators use the Cancer Therapy Evaluation Program's (CTEP's) Common Terminology Criteria for Adverse Events to report adverse events and describe their severity. CTEP's Adverse Event Reporting System (formerly the Adverse Event Expedited Reporting System) calls for investigators to report only adverse events from study arms involving an investigational agent. However, investigators must report all adverse events and serious adverse events above a certain threshold in ClinicalTrials.gov. Hence, it was noted that these adverse event reporting requirements should be harmonized.

**Publication Options.** Dr. Weiner commented that the biggest challenge to implementing the proposed policy will be finding ways to publish the results of studies that investigators open, but never complete due to a failure to accrue participants, for example.

Dr. Villalona-Calero asked whether NCI might create a journal to report the negative results of NCI-sponsored studies. Dr. Doroshow replied that *The Oncologist* accepts brief reports of studies and is a reasonable place to publish negative clinical trial results. NCI is unlikely to develop its own journal for this purpose. Dr. Shields added that *Cancer Epidemiology, Biomarkers & Prevention* publishes a "Null Results in Brief" section whose papers have a reasonable citation record. Dr. Zarin stated that although ClinicalTrials.gov does not publish narrative background, summary, or conclusion information, it could publish searchable lists of journal articles.

Dr. Curt I. Civin, Associate Dean of Research, Professor of Pediatrics, and Director of the Center for Stem Cell Biology and Regenerative Medicine, University of Maryland School of Medicine, suggested publishing progress reports on NCI-supported clinical trials as a way to share clinical trial results. Dr. Villalona-Calero asked how CTEP uses progress reports and whether it publishes them in ClinicalTrials.gov. Dr. Doroshow explained that investigators can use their progress reports as a starting point for short papers; however, it would not be appropriate for CTEP to publish these reports. NCI assumes that all of the trials reported to CTEP have been registered in ClinicalTrials.gov and that the data do not need to be reported due to the fact that the studies involve investigational agents. Cancer Center directors and other large NCI-funded programs are responsible for ensuring that the investigators of center studies publish the results in journals or in ClinicalTrials.gov.

Dr. Civin pointed out that being able to publish textual information in ClinicalTrials.gov would allow investigators to ensure that their results are published. Whether the results are published is a decision to be made by the journals. Dr. Zarin explained that, by law, ClinicalTrials.gov does not accept subjective information. It can, however, allow users to link entries to websites. Investigators are doing a great job of entering information into ClinicalTrials.gov that goes beyond the legal minimum. Dr. Zarin also noted that NIH would like to find ways to give academic and other credit for entering information into ClinicalTrials.gov in an effort to incentivize the investigators.

**Importance of Publishing Results.** Dr. Monica M. Bertagnolli, Professor of Surgery, Harvard Medical School, Brigham and Women's Hospital, Dana-Farber Cancer Institute, commented that NCTN group leaders have discussed a policy requiring peer review and publication of all NCTN study results as part of a broader discussion about data sharing. Dr. Takimoto reported that a major topic in industry is data transparency, which involves sharing not only results but also raw data. Johnson & Johnson has a partnership with Yale University to review requests for access to raw data from the company's studies. Other companies have similar programs.

Dr. Rosemarie Hakim, Epidemiologist, Centers for Medicare and Medicaid Services (CMS), reported that CMS agreed to pay for off-label use of a colorectal cancer drug based on nine NCI-sponsored clinical trials some 8 or 9 years ago. When she recently searched the published literature, she found the results of only one of the nine trials. Dr. Hakim also noted that CMS uses published information on clinical trials to make coverage decisions for Medicare; therefore, publishing trial results is important.

**Publication of NCI Trial Data.** Dr. Lee Helman, Chief, Pediatric Oncology Branch, and Deputy Director, Center for Cancer Research, NCI, asked whether the data reported in *BMJ* on NIH-sponsored trials would be similar for NCI-sponsored trials. Dr. Zarin replied that the data did not vary greatly by IC.

Dr. Sledge commented that the important issue today is how to make the enormous amount of genomic, proteomic, and epigenomic data collected in large clinical trials accessible to the scientific community. Dr. Doroshow suggested inviting Dr. Warren Kibbe, Director, Center for Biomedical Informatics and Information Technology (CBIIT), NCI, to a future CTAC meeting to report on the recent activities of the CBIIT, including the NCI Cancer Genomics Cloud Pilot. This program will develop "clouds" to store genomic data from across NCI.

**Policy Implementation.** Dr. Abbruzzese asked about the implementation of the proposed policy. Dr. Doroshow replied that if the BSA and the NCAB approve the policy, NCI will need to finalize the details and find ways to minimize the burden associated directly with following the new policy. Sorting out all of the issues for NCI-sponsored studies that CTEP does not oversee is likely to take at least 6 months.

Ms. Nancy Roach, Consumer Advocate, C3: Colorectal Cancer Coalition, in written comments suggested that CTAC be updated regularly once the policy has been implemented to assess the compliance with the policy. She also noted that a potential next step would be requiring that all publically-funded data be shared in some way.

## VI. SPECIALIZED PROGRAM OF RESEARCH EXCELLENCE (SPORE) PROGRAM EVALUATION WORKING GROUP REPORT—DR. NANCY DAVIDSON

Dr. Davidson, who chaired the SPORE Program Evaluation Working Group, reported on the recent activities of the Working Group. This group is assessing the SPORE program in preparation for the release of the new SPORE program announcement in the fall of 2014 for submissions in January 2015 and beyond.

Dr. Doroshow thanked the Science and Technology Policy Institute (STPI), which did an excellent job of providing data to help the Working Group and NCI assess the SPORE program. The Working Group's report will be submitted to NCI leadership, who will consider this report when they discuss approval of the SPORE program announcement reissuance.

**Evaluation Process.** Dr. Davidson explained that STPI conducted a formal evaluation of the SPORE program as part of the standard procedure for renewing program announcements for large programs. The

CTAC decided to form a working group to provide advice on the value of the SPORE program and to make recommendations regarding its future. The group included several CTAC members, Cancer Center Directors, former SPORE PIs, and other experts, including Dr. Doroshow, who was a NCI liaison assigned to the Working Group.

The Working Group was charged to present a set of recommendations to the CTAC as well as a report of their findings. During a 1-day meeting, the Working Group reviewed the STPI 2013 SPORE Evaluation Report, which included STPI's compilation of distinguished contributions of the SPORE program, major SPORE advances, and the program's success in achieving a "human endpoint." The working group also examined the updated SPORE P50 funding opportunity announcement (FOA) as well as the P01 FOA.

**SPORE Accomplishments.** The Working Group concluded that it remains critical for NCI to have a funding program focused exclusively on translational research. The SPORE program is a longstanding effort that has been successful in filling this niche. The overall output of the SPORE program is exceptional due to the fact that the program speeds up translational research and leads to the introduction of interventions and biomarkers into clinical practice.

The SPORE program has revolutionized translational research by:

- Serving as a catalyst for translational research at institutions and nationwide;
- Enhancing the quality of translational research at non-SPORE institutions;
- Facilitating the leveraging of funds from other sources, especially industry;
- Promoting creative "bottom-up," investigator-initiated, translational research; and
- Building and sustaining a strong translational research infrastructure.

Major advances of the SPORE program include (1) making substantial and material contributions to oncology research and practice; (2) leveraging of substantial industry support for clinical trials of SPORE-derived interventions and biomarkers; and (3) serving as a nucleus for coalescing foundation-funded consortia, especially to support early-phase trials. Further, SPOREs have made progress in all disease sites and have used the SPORE infrastructure to establish clinical trial networks that conduct early-phase trials with foundation support.

**Enhancing the SPORE Program.** Ways in which NCI could enhance the SPORE program's effectiveness include facilitating even greater coordination with the NCI clinical trials program (e.g., NCI Experimental Therapeutics program, Cancer Centers, the new N01/U01 early-phase trial programs, and NCTN groups) and even greater interactions with targeted basic research initiatives (e.g., The Cancer Genome Atlas and the Physical Science Oncology Centers). The program would also benefit from increased encouragement of joint funding by industry, foundations, and other such entities, as well as its emphasis on research of patient care and clinical practice.

**Working Group Recommendations.** The Working Group offered the following recommendations:

- Modernize, expand, and make more explicit the meaning of "groups of highly-related cancers" that can serve as the focus of SPORE awards, and provide examples of these groups in the program announcement;
- Solicit new SPOREs in response to NCI research priorities without establishing "set-aside" funding for these SPOREs;
- Continue the requirement to reach a "human endpoint" within 5 years;
- Require SPOREs to build on collaborations and make the program announcement's language about collaborations more specific;

- Establish no arbitrary limits on the numbers of SPOREs per organ sites and, instead, distribute SPOREs across organ sites based on the quality of the science;
- Avoid limiting the number of consecutive 5-year renewals for a given SPORE;
- Maintain the flexibility option;
- Maintain support for biospecimen/pathology cores; and
- Maintain developmental research and career development programs, but combine them into a single fund.

Most Working Group members favored the requirement that all SPOREs should have an early detection, prevention, or population science project. But a minority supported the current requirement for such a project, which applies only to SPOREs focused on colon, breast, prostate, or lung cancer.

The Working Group's unanimous overall recommendation was to re-issue the SPORE program announcement and continue the program in its current conformation with minor modifications.

### *Questions and Discussion*

**Requirement for Early Detection, Prevention, or Population Science Project.** Dr. Scott M. Lippman, Director, Moores Cancer Center, and Senior Associate Dean and Associate Vice Chancellor for Cancer Research and Care, Chugai Pharmaceutical Chair in Cancer Research, University of California, San Diego, and a member of the SPORE Program Evaluation Working Group, strongly believes that all SPOREs should have a prevention component.

Dr. Shields reported that members of the American Society of Preventive Oncology recently discussed requiring all SPOREs to have a prevention project to emphasize the entire spectrum of translational science. Most society members believe that imposing this requirement on some SPOREs but not others is not justified. Dr. Takimoto agreed that all SPOREs should have this requirement as long as it is defined broadly. Dr. Abbruzzese noted that broadening the definition would increase the number of high-quality projects that fall under prevention or population science. However, explaining a broadened requirement in a program announcement would be challenging. Dr. Lippman commented that the SPORE program is the only large NCI program that encourages collaboration among population, basic, and clinical scientists in conducting translational research.

Dr. Davidson supported applying the requirement for a prevention or population science project only to SPOREs focused on the four most common cancers. For certain cancers, it might be difficult to meet this requirement. Dr. Davidson reported that some Working Group members believed that SPOREs should not be required to conduct prevention or population science research. Instead, they felt that the SPOREs should select the projects that their leaders believe will make the most progress in the targeted disease.

Dr. Helman commented that the therapeutic and clinical contributions of the SPOREs appear to have been more substantial than their contributions in population sciences. The return on investment, therefore, appears to be better for therapeutic science than for population science. Dr. Lippman explained that only a few SPOREs are required to conduct population science studies, so less data are available on this type of research. A mechanism to stimulate more population science should be available; however, it is highly unlikely that the creation of a new population science mechanism will break down existing silos.

Dr. Abbruzzese, who was a SPORE PI at one time, noted that he supports the population science requirement even for SPOREs focused on less common cancers. Population scientists on SPORE teams are vital for bench-to-bedside translation of SPORE research findings. Conducting such research can be very challenging, but doing so is important for the long-term health of translational research.

Dr. Lisa A. Newman, Professor of Surgery and Director of Breast Care Center and Multidisciplinary Breast Fellowship Program, University of Michigan Comprehensive Cancer Center, asked whether the mandate to conduct population and prevention studies was the most significant barrier to obtaining funding. She also inquired whether the population and prevention studies conducted by SPOREs have had successful outcomes. Dr. Abbruzzese explained that imposing this requirement on all SPOREs might make it challenging for SPOREs focused on certain organ sites, such as pancreatic cancer and perhaps leukemia, to compete successfully for a grant.

Dr. Nikhil C. Munshi, Associate Director, Jerome Lipper Myeloma Center, Dana-Farber Cancer Institute, and Associate Professor of Medicine, Harvard Medical School, asked whether the amount of funding that SPOREs must devote to population science research is appropriate. Dr. Davidson suggested that the SPORE directors should allocate their funding based on the needs of their research.

**Balancing the NCI Portfolio.** Dr. Adamson asked about the Working Group's recommendations to balance the NCI portfolio given its recommendation not to cap the number of SPORE awards. Dr. Davidson explained that the number of SPORE awards will continue to be determined by the scientific review process and NCI leadership.

Dr. Abbruzzese asked what advice should be given to NCI with regards to balancing the funding for SPOREs and other large programs, such as the Early Detection Research Network, the NCTN, and P01 programs. Dr. Davidson replied that the Working Group supports continuing the SPORE program. Most of these programs have been thoroughly evaluated in recent years. NCI, therefore, knows the individual programs' accomplishments and potential, and will consider these accomplishments when making decisions about its portfolio.

Dr. Civin said that the BSA is likely to raise questions about the need to continue to fund SPOREs instead of more clinical or translational P01 research program projects. Dr. Abbruzzese explained that the Working Group concluded that the SPORE program has made important contributions to translational science. The P01 program, especially P01 projects that are translational, would need to undergo a similar assessment before NCI could determine whether SPOREs or P01 centers represent a more successful approach to translational research.

Dr. Davidson added that the flexibility of the SPORE program should not be underestimated. PIs are charged with ending projects in Year 2 if they are not making translational progress. Furthermore, the SPORE program has helped build the careers of a new generation of translational scientists and continues to be engaged with the patient advocate community.

**SPOREs Focused on Pathways or Targets.** Dr. Munshi agreed with the recommendation to support SPOREs that focus on a pathway or target instead of an organ site. He asked whether NCI should identify these target areas or leave them open and let the review process determine which SPOREs to fund. Dr. Davidson clarified that this option has been available for some time.

**Unique Contributions of SPORE Program.** Dr. Bertagnolli strongly supports continuing the SPORE program, which she characterized as "an absolute treasure" due to the fact that the SPOREs have eliminated institutional silos and have leveraged a small fraction of money to address specific problems. Furthermore, the SPOREs have been transformative in Cancer Centers and have contributed to the enhancement of the entire spectrum of research.

**Opportunities for New SPOREs.** Ms. Mary S. McCabe, Director, Cancer Survivorship Program, Memorial Sloan Kettering Cancer Center, asked whether the Working Group's recommendations address opportunities for institutions who do not have a SPORE to obtain one. Dr. Davidson replied that the

recommendations do not address this issue. NCI awards grants to institutions that submit the best applications and does not have a bias in favor of renewing existing SPOREs versus funding new ones.

Dr. Judith Hautala, Research Staff Member, STPI, estimated that approximately half of all SPORE grants have gone to new centers over the past several years. Dr. Hecht added that even when SPORE grants are awarded to existing SPORE programs for research on the same organ site, these programs often have new PIs and investigative teams.

Dr. Cullen reported that the barriers for smaller institutions to obtain a SPORE grant are high. He asked about the numbers of active SPOREs. Dr. Hecht replied that NCI currently supports 56 active SPOREs at approximately 27 institutions in 19 states. However, one sarcoma SPORE is based on a consortium of approximately 12 institutions. Approximately one-third of NCI Comprehensive Cancer Centers have a SPORE.

**Pediatric Cancers.** Dr. Cullen asked how many active SPOREs focus on childhood cancer. Dr. Hecht replied that none of the active SPORE centers focus on pediatric cancer. However, some organ-site SPOREs (such as brain cancer and sarcoma SPOREs) are conducting research on pediatric cancers. NCI would consider pediatric cancers to be a group of highly related cancers and, thus, an appropriate focus for a SPORE. The Institute encourages institutions to submit applications for such a SPORE.

Dr. Munshi commented that the SPOREs represent a substantial investment in infrastructure and wondered what happens to this infrastructure when a SPORE is not renewed. Dr. Davidson replied that this issue was not within the Working Group's charge. In her experience, when a SPORE is not renewed, the institution must find other ways to maintain the infrastructure created through the SPORE.

**Minority Populations.** Dr. Mitchell commented that the American Cancer Society's annual reports note that all populations in the United States have benefited from the advances in cancer science and technology over the years. However, the gap between minority and majority populations has increased. As the size of the minority population in the United States grows, the SPOREs should address cancer health disparities, especially with respect to cancers whose incidence or mortality rates are highest in certain minority populations. Dr. Davidson explained that applicants may choose to focus on cancers in minority populations; several SPOREs conduct studies involving certain minority populations in their regions. For example, the breast cancer SPORE at the University of North Carolina at Chapel Hill has conducted research in African American women in North Carolina who have a high risk of triple-negative breast cancer and poor outcomes.

**Partnerships with Community Oncologists.** Dr. J. Phillip Kuebler, PI, Columbus Community Clinical Oncology Program (CCOP), Columbus Oncology Associates, Inc., reported that community oncologists have benefited from the results generated by SPOREs. However, these oncologists do not collaborate with SPOREs on research activities, such as collecting data. In the future, NCI might require SPOREs to collaborate with community oncologists and give oncologists credit for participating in SPORE trials.

**Multi-Institutional Consortia.** Dr. Abbruzzese asked whether the working group discussed the pros and cons of multi-institutional SPOREs, which would enable more small Cancer Centers to participate in SPORE research. Dr. Davidson replied that the Working Group did not discuss the issue.

**SPORE International Research.** Dr. Newman asked about international research in SPOREs. Dr. Hecht replied that several institutions are conducting research projects in collaboration with investigators in other countries, including Canada, Peru, and China. NCI does not provide funding directly to institutions in other countries; those institutions must use their own funding mechanisms to participate in SPORE studies.

**Advocates.** Ms. Roach in written comments noted that one of feautres of SPOREs is that requirement that advocate be engaged. Sometimes that is successful and other times less so, mostly because a lot of researchers don't understand how to engage advocates effectively. She recommended considering bringing a group together to develop advocacy 'best practices' for SPOREs.

**Next Steps.** Dr. Davidson asked about next steps now that the Working Group has completed its report. Dr. Doroshow replied that DCTD will present the Working Group's report and a summary of the deliberations at a meeting with Dr. Varmus, who will review DCTD's request for approval to reissue the SPORE program announcement. Because DCTD is not asking for approval to release a request for applications, the request will not be directed towards the BSA.

**Motion.** Dr. Davidson made a motion to reissue the Specialized Programs of Research Excellence (SPORE) program announcement and continue the program in its current configuration with minor modifications. However, the motion was then amended to accept or reject the SPORE Program Evaluation Working Group's report. The motion was seconded and approved unanimously. Two members, Drs. Weiner and Lippman, did not vote because of their conflict of interest with the SPORE Program.

## VII. NCI COOPERATIVE GROUP ACCRUAL: 2000–2010—DRS. ED KORN, MEG MOONEY, AND LORI MINASIAN

**NCI Cooperative Group Phase III Treatment Trials: Historical Accrual Experience of Trials Activated in 2000–2010 and Assessment of the CTEP Slow Accruing Guidelines.** Dr. Meg Mooney, Chief, Clinical Investigations Branch, CTEP, DCTD, explained that NCI's Clinical Trials Cooperative Group Program has undergone an extensive evaluation that included a report from the Institute of Medicine and feedback from numerous stakeholders. This review led to the identification of four consensus goals for the transformed Cooperative Group program. The purpose of this series of presentations was to highlight NCI's progress on one of these goals: improving the speed and efficiency of development and conduct of clinical trials.

In 2013, NCI implemented the timelines for protocol development recommended by the Operational Efficiency Working Group to help ensure that trials are launched in a timely fashion. NCI is currently taking additional steps to ensure that Cooperative Groups achieve their accrual goals after they open trials (*J Natl Cancer Inst* 2013;105:954-9).

CTEP published an analysis of Cooperative Group accrual rates between 2000 and 2007 (*J Clin Oncol* 2010;28:5197-201). This study provided a baseline for the updated analysis presented by Dr. Ed Korn, Mathematical Statistician, Biometric Research Branch, DCTD, of accrual in 254 Cooperative Group trials activated in 2000–2010. Two hundred and three trials have completed their accruals, and of these, 119 have accrued at least 90 percent of their target sample sizes; 84 have not. Of the 51 trials that are still accruing participants, 41 have accrued at least 90 percent of their target sample sizes, and 10 have accrued less than 90 percent of their target sample sizes.

Reasons for low accrual include stopping of the trial by the Data Safety Monitoring Committee due to interim monitoring for superiority or futility (18 trials), external information (such as the result of another clinical trial that makes the study irrelevant; 11 trials), unacceptable toxicity (3 trials), drug supply difficulties (2 trials), and achievement of a sufficient number of events (1 trial). It was noted that four trials were stopped due to interim monitoring and external information. All of these trials can be characterized as successful. On the other hand, 53 trials did not reach the 90 percent accrual threshold, because their accrual rate was inadequate.

NCI projects that 21.1 percent of the 254 trials activated in 2000–2010 will end with less than 90 percent of their target accrual because of inadequate accrual rates. This represents only 1.6 percent of patients enrolled on trials, because when trials stop early for inadequate accrual, they usually have very low numbers of patients on those trials. Proportions of trials that enrolled more than 90 percent or less than 90 percent of their accrual targets were similar in 2000–2007 and 2000–2010.

Dr. Mooney explained that NCI contacted the PIs and biostatisticians of the 50 adult trials and 3 pediatric trials that have completed their accrual yet did not reach the 90 percent threshold due to inadequate accrual rates. For 36 percent of trials, a reason for the inadequate rate was the challenge of randomizing participants to two different treatment modalities or to a treatment modality or observation. Other reasons included challenging randomization because of the therapeutic approach (e.g., an investigational agent became commercially available; 15 percent of trials), comparisons of investigational agents to commercially available agents (17 percent), insufficient site interest in the treatment approach (15 percent), competing studies (9 percent), and other (8 percent).

Dr. Korn stated that, based on an analysis of previous clinical trials, in 2005, CTEP implemented the following slow accrual guidelines for Phase III Cooperative Group treatment trials:

- If the accrual rate in Quarters 5 and 6 is 20 percent or lower than the target rate, stop the trial;
- If the accrual rate is greater than 20 and less than 50 percent in Quarters 5 and 6, give the study team 6 months to improve its accrual rate; and
- If a trial with greater than 20 percent and less than 50 percent accrual rate in Quarters 5 and 6 has an accrual rate below 50 percent in Quarter 8, amend the trial protocol to reflect the actual accurate accrual rate, as long as this new rate does not compromise study relevance or feasibility.

The table below summarizes the effects that these guidelines would have had on trials activated in 1988–2001 and the effects the guidelines did have on trials activated between 2004–2011:

| **Results from Quarters 5 and 6** | **Trials activated in 1988–2001, no. (%)** | **Trials activated between April 1, 2004, and June 30, 2011, no. (%)** |
|---|---|---|
| Stopped before the end of Quarter 6 | Not available | 8 (6) |
| ≤ 20% of projected accrual target | 15 (6) | 20 (14) |
| 20–50% of projected accrual target | 52 (22) | 34 (23) |
| ≤ 50% of projected accrual target | 172 (72) | 91 (63) |
| Total | 239 (100) | 145 (100) |

Of the 20 trials activated between 2004 and 2011 that did not accrue at least 20 percent of their target by Quarters 5 and 6, CTEP stopped 8 trials and granted an exception to 12 trials. Of these 12 trials, 7 did not achieve their accrual goals, 2 succeeded, and 3 are ongoing. Of the 34 trials whose accrual rate in Quarters 5 and 6 was between 20 percent and 50 percent, 15 achieved at least a 50 percent accrual rate by Quarter 8, and 19 did not. Of these 19 trials, CTEP stopped 2 for poor accrual, amended the protocols for 10 trials to reflect the projected accrual rate, and gave 7 trials exceptions to continue. Of those seven trials, one closed early as a result of drug supply issues, three reached their accrual targets, and the status of the final three trials is too early to be determined.

Dr. Mooney explained that CTEP is continuing its analysis, including comparing the attributes of trials that have reached their accrual targets to those that have not and examining whether it is possible to identify trials that might have accrual problems earlier than Quarters 5 and 6. Because the central registration process for the NCTN will provide real-time reports on accrual, accrual problems should be identified earlier. CTEP will report on these activities at a future CTAC meeting.

Dr. Mooney asked the CTAC to discuss whether exceptions should continue to be made for trials with accrual rates lower than 20 percent in Quarters 5 and 6. She also asked the CTAC to discuss what would be a reasonable percentage for trials that do not accrue well, given that 100 percent accrual is unlikely.

### *Questions and Discussion*

Dr. Abbruzzese asked whether it might be possible to identify trials with accrual problems before Quarter 5 and whether early intervention by CTEP would enable these trials to complete accrual. Dr. Mooney responded that in addition to addressing this during concept development and review, CTEP is trying to find ways to identify trials before or immediately after activation that are likely to have accrual difficulties. One barrier to early identification is the delay caused by institutional review board (IRB) approval and site activation of a study. Now that most sites participate in the central IRB, that lag will diminish. Also, given the NCTN's central enrollment process, CTEP will receive accrual reports more quickly, which will enable CTEP to intervene earlier.

Dr. Mitchell asked how many studies closed during the analysis timeframe due to lack of accrual and what measures could be put in place to reduce the substantial amount of resources required to activate unsuccessful trials. Dr. Mooney explained that 21 percent of trials activated between 2000–2010 were closed solely because of poor accrual rates. NCI has identified some of their attributes and is fine-tuning its projections of accrual rates to avoid activating trials with characteristics associated with poor accrual rates.

Dr. Bertagnolli commented that 20 percent was a reasonable expectation for trials that fail to accrue, given the types of trials conducted by the NCTN, and especially when international collaborators are involved. Although the accrual rates of trials with difficult randomizations might be challenging to increase, attempts to lower this proportion further might prevent some important studies from being conducted. Many of the most important activities to improve public health are particularly risky. Dr. Bertagnolli approved of the approach and scrutiny that CTEP has developed and supports giving investigators an opportunity to appeal a decision to stop a trial because of poor accrual.

Dr. Adamson agreed that global collaboration is a challenge to accrual and stated that a 20 percent trial failure rate was unacceptable for pediatrics. He noted the correlation between the number of sites that activate a given trial and successful accrual. To mitigate the financial risk for sites that only see a handful of patients a year who might be eligible for a given trial, the Children's Oncology Group used philanthropic funds to launch the High Impact Initiative, which bundled four rare cancer trials together and paid sites a lump sum when the trials opened. The number of sites activating those four trials has risen substantially along with their accrual rates.

In response to a question from Dr. Lippman about applying the slow accrual guidelines to Phase II trials, Dr. Korn responded that because Phase II trials accrue more quickly than Phase III trials, there are other guidelines for Phase II trials. Dr. Mooney explained that small and large Phase II trials might be considered differently.

Dr. Munshi commented that an important difference between pediatric and adult studies is the location of the patients at community versus academic sites. He asked about the enrollment from CCOP sites versus

academic sites for studies that reached or did not reach their accrual targets. He also asked, for the 75 percent of studies that met their accrual, how the projected time for accrual compared to the actual time. Dr. Mooney responded that CTEP has not examined accrual rates by type of institution and that the additional analysis might prove useful. Dr. Korn noted that he is considering time for accrual in his current analysis.

Dr. Villalona-Calero asked about the amount of activation time for successful and unsuccessful trials. Dr. Mooney explained that CTEP is collecting data on the amount of time from activation date to accrual in successful trials. CTEP surveys institutions that participated in previous trials in a given disease to enhance subsequent accrual in that disease.

Dr. Takimoto reported that his company probably stopped only 5 percent of all trials in the last 6 years. At monthly meetings, the company compares real-time accrual data for all trials with their accrual targets. As soon as staff identifies a deviation, they intervene—successfully, in most cases.

Dr. Kuebler commented that CCOP sites review trials, especially those in rare diseases, before opening them to determine how far their interventions deviate from the standard of care. Community physicians do not want to enroll patients in trials with interventions that are very different from the standard of care.

Dr. Bertagnolli expressed concern that differences in case reimbursement between the Network Lead Academic Participating Sites (NLAPS) and other sites might discourage non-NLAPS from opening trials, especially for studies in rare cancers. She agreed with the idea of bundling trials described by Dr. Adamson.

Dr. Sledge commented that it is hard to predict which trials succeed and which fail. Therapeutic equipoise is essential, but viewed differently by radiation therapists, surgeons, and medical oncologists. This is what leads to difficult randomizations and thus slow accrual. However, it is exactly those types of questions that should be addressed by the NCTN.

Dr. Helman disagreed that a 20 percent rate of failed trials is appropriate. For approximately half of all trials that failed to reach their accrual targets, accrual rates were inadequate. These rates would be difficult to improve. However, the failure to reach accrual targets for the other 50 percent of trials could be predicted and addressed more easily. For example, if a trial fails to reach its accrual target because the agent being studied will be commercialized, this issue should be addressed. Therefore, the acceptable rate of trials that fail to reach their accrual target should be lower than 20 percent.

Ms. Nancy Roach, Consumer Advocate, C3: Colorectal Cancer Coalition, in written comments noted that she thought the percentage of trials not completing accrual is too high. She is familiar with a couple of colorectal cancer trials that did not accrue well, and in hindsight, thinks that a better evaluation of feasibility upfront would have made a difference.

**CCOP Enrollment Data Analysis Project—Trials Activated in 2000–2010.** Dr. Lori Minasian, Deputy Director, Division of Cancer Prevention (DCP), reported on a CCOP analysis of enrollment in cancer prevention and control clinical trials activated in 2000–2010. This analysis included only pilot feasibility, randomized Phase II and Phase III, and a few observational studies with samples of less than 2,000 participants. (Large cancer prevention trials were excluded because they require a different approach than treatment trials.) The DCP analysis used the same start dates and criteria for accrual completion as the CTEP analysis.

Unlike cancer treatment trials' endpoints, cancer control trials' endpoints are typically symptom responses or cancer incidence instead of survival or disease response. Interventions are often administered

for less time. As a result, their follow-up periods might be shorter. In some cases, cancer control trials have lower institutional priority and wait longer for IRB review. Some CCOP trials (which are not disease-specific and appropriate for most of a site's patients) can bolus-enroll patients, so their accrual rates might be different from those of treatment trials.

Between January 1, 2000, and December 31, 2010, DCP activated 171 studies. Of the 11 studies that are still accruing patients, 4 have accrued at least 90 percent of their targets, 3 have accrued between 80 percent and 89 percent, and 1 has accrued between 70 percent and 79 percent. DCP expects these trials to complete their accruals. However, three studies have accrued less than 60 percent of their target subjects, and DCP cannot guarantee that these studies will reach their target.

Of the 160 studies that completed accrual, 58 (40 percent) accrued less than 90 percent of their target subjects at study closure. The primary reasons behind the closure of these trials included inadequate accrual rates (36 studies), drug supply problems (14 studies), and external information (8 studies). With a 21 percent rate of inadequate accrual, the DCP result is quite similar to that of CTEP.

DCP also analyzed the impact of the CTEP guidelines, which the Data Safety Monitoring Committees applied to cancer prevention and controls at the same time. Of the 44 drug trials (as opposed to behavioral intervention trials) that DCP reviewed, 18 had an accrual rate of at least 50 percent in Quarters 5 and 6 and were on target. Another 6 trials had a 20 percent to 50 percent accrual rate in Quarters 5 and 6 and were re-evaluated. Finally, 20 trials had an accrual rate that was lower than 20 percent in Quarters 5 and 6. Of these studies, 16 eventually accrued more than 90 percent of their sample targets, including 10 that completed their accrual more rapidly than expected and 6 that took longer than originally expected, requiring a median of 7 additional months.

Assessing accrual rates in Quarters 5 and 6 to predict a trial's ability to reach its sample target is probably not appropriate for DCP-supported drug trials. Some trials recruit more than half their participants in Quarter 4 because of bolus recruitment, but their accrual rates drop after that. DCP needs to assess all of its studies and develop a reasonable set of guidelines to monitor cancer control and prevention trials.

DCP's analysis showed unique needs for trials with a behavioral intervention. For example, a behavioral intervention given at the treating site must be easy to administer, or accrual will be difficult. Alternatively, if the subject can be referred to an established site to conduct the intervention, accrual likely will be successful. DCP will provide follow up information on accrual behavioral intervention studies at a later date.

### *Questions and Discussion*

Dr. LeBlanc said that because of the variability in the kinds of studies DCP supports compared with the CTEP studies, DCP might need several sets of guidelines.

Dr. Kuebler said that cancer control trials have very broad eligibility requirements, making it easy for these trials to accrue patients. Treatment trials can only recruit patients with the right stage of the disease. This is one reason why these different types of trials need different accrual guidelines.

Dr. Davidson suggested sharing the slides from this session with the Scientific Steering Committee co-chairs, whose discussion of clinical trials would benefit from understanding the types of trials that do not accrue well. Dr. Mitchell added that the presentations should also be released to patient advocates. Dr. Lippman added that addressing slow accrual will become even more important as personalized medicine grows and common diseases are divided into rarer subgroups.

Dr. Civin suggested that investigators be encouraged to publish reports on trials with inadequate accrual rates, including details on study design and whether a different design might offer a more effective way to answer the research question. Dr. Minasian noted that the research questions addressed in trials with inadequate accrual rates are often still relevant, and other aspects of these trials might need to be addressed. For example, many CCOP smoking cessation studies involving behavioral interventions had accrual problems, whereas those with a combination of a pharmacological agent and a behavioral intervention had good accrual rates. Dr. Civin added that for types of trials are hard to accrue to—for example, comparing radiotherapy to surgery—perhaps an alternative to a traditional randomized design could be devised. Dr. Minasian agreed, noting that one well-designed study comparing radiation to cryotherapy for bone metastases was unable to accrue any patients.

## VIII. ONGOING AND NEW BUSINESS—DR. JAMES L. ABBRUZZESE

**Program Planning Working Group Update.** During his update, Dr. Abbruzzese commented on the fact that he wants to continue to ensure that the CTAC is as active as possible in advising NCI and that this meeting provided several examples of the challenges that NCI faces pertaining to legislative, budgetary, and programmatic issues.

Dr. Abbruzzese reviewed the structure of the CTAC subcommittees and working groups, which play a major role in the CTAC's activities and currently consist of the following:

- Informatics Working Group
- SPORE Program Evaluation Working Group
- Clinical Trials Strategic Planning Subcommittee
- Pancreatic Cancer Working Group
- SCLC Working Group

Dr. Abbruzzese noted that the NCI NCTN Working Group and the Cross-Disease Prioritization Working Group report to the Clinical Trials Strategic Planning Subcommittee and that Dr. Prindiville is working with her staff to assemble the Informatics Working Group.

The Pancreatic Cancer Working Group was formed to help NCI respond quickly to the Recalcitrant Cancer Research Act. It was noted that the Working Group recently issued its report and that challenges include how to continue to make progress in this area and where to find the needed resources. The SCLC Working Group is continuing to address the issues outlined in the Act. As for the Clinical Trials Strategic Planning Subcommittee, its Working Group continues to be very active. The NCTN Working Group advises NCI on clinical trials evaluated by scientific steering committees; the Cross-Disease Prioritization Working Group provides advice on a process for prioritizing clinical trials in the NCTN.

Further, the Program Planning Working Group plans CTAC meetings to maximize their informational value for members, continuously reviews emerging issues, coordinates CTAC subgroup activities, and assesses the CTAC's progress and implementation of its recommendations. Dr. Abbruzzese chairs this committee, whose members are Drs. Bertagnolli, Cullen, Kuebler, Lippman, and Shields as well as Ms. Nancy Roach, Consumer Advocate, C3: Colorectal Cancer Coalition. The group meets by telephone or at lunch during CTAC meetings.

The Program Planning Working Group's meeting on February 26, 2014, focused on providing guidance to the NCI NCTN Working Group in areas such as setting disease-specific strategic priorities for NCTN trials, principles for guiding strategic priorities, and a process for establishing these priorities. The Program Planning Working Group also provided input on cross-disease prioritization, including criteria to

be used, trials that are subject to prioritization, stakeholders in the prioritization process, and the process that the Cross-Disease Prioritization Working Group has pilot-tested.

**New Business.** Dr. Davidson commented that at the Cancer Centers Directors' meeting, Dr. Varmus reported that the number of senior investigators who participate in peer review has declined. Dr. Davidson mentioned that as a CTAC member, she is not permitted to participate in reviews of SPORE applications or site visits of Cancer Centers. She asked about the rules regarding peer review by CTAC members. Dr. Paulette Gray, Director, Division of Extramural Activities, explained that CTAC members may not be standing members of study sections in an IC if they are members of an initial review group or program advisory committee of that IC. However, CTAC members may participate in these study sections as ad hoc or temporary members if the scientific review officer obtains a waiver. These waivers are sent to the Deputy Director of NIH and are virtually always approved.

## IX. ADJOURNMENT—DR. JAMES L. ABBRUZZESE

There being no further business, the 22nd meeting of the CTAC was adjourned at 2:18 p.m. on Wednesday, March 12, 2014.

National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

# NCI Update

James H. Doroshow, MD

March 12, 2014

CTAC Meeting

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National Cancer Institute

# Scientific Framework for Pancreatic Ductal Adenocarcinoma (PDAC)

- Released February 2014
- http://deainfo.nci.nih.gov/advisory/ctac/workgroup/pc/PDACframework.pdf

National Cancer Institute

# NCI Cancer Clinical Investigator Team Leadership Award (CCITLA)

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

# Award Purpose

- Recognize and support outstanding mid-level clinical investigators at NCI-designated Cancer Centers participating extensively in NCI-funded collaborative clinical trials whose participation and activities promote a culture of successful clinical research.

- Promote the retention of clinical investigators in academic clinical research careers.

National Cancer Institute

# Funding

- First awards made in 2009 with 57 recipients to date
- ~ 10 to 12 new awards per year
- Award duration is two years with funding of $50,000 total costs per year

- Allowable costs
  - Salary
  - Courses, seminars, conferences, workshops
  - Travel (up to $2500/year)

- Awardee must devote 15%-20% effort to the activities associated with this award and the sponsoring institution must protect the awardee's time for these activities.

National Cancer Institute

# Eligibility

- Nominated by Cancer Center Director
- One application per Cancer Center
- Engaged in the conduct of NCI-funded cancer clinical trials
- Currently practicing in the oncology clinical setting and board certified in specialty area
- Full-time faculty member, assistant or associate professor level, eligible for promotion/tenure or with permanent status
- Physician (e.g., M.D., D.O.) or oncology nurse, clinical psychologist, or similarly qualified clinician with a doctoral degree
- Practicing at least 3 years but no more than 10 years post-fellowship
- Must not currently serve or have previously served as
  - PI of an NIH R, K, P, U, T, DP, RC, SC or TU series grant (with the exception of career development awards or other mentored grants)
  - Project leader within a Program Project award
  - Project co-leader within a SPORE award

National Cancer Institute

# Supported Activities

Include, but not limited to

- Organizing courses, lecture/seminar series, educational sessions, or workshops
- Attending courses, seminars, meetings, conferences, or workshops
- Engaging fellows and new faculty in collaborative clinical research efforts
- Mentoring junior staff/fellows/trainees
- Participating on a particular cancer center committee
- Developing a clinical trial concept and/or protocol
- Designing and implementing initiatives to better coordinate, support and integrate a clinical trials culture at the institution
- Developing streamlined processes for the awardees' institution’s (IRB), Data Safety Monitoring Board (DSMB), or Scientific Review Committees
- Resolving activation or accrual issues

National Cancer Institute

# Application Evaluation Criteria

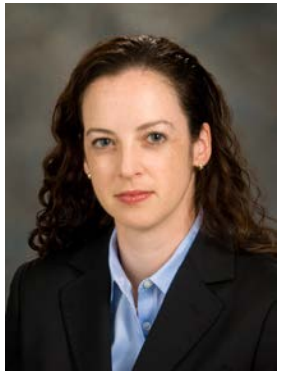
- Training and experience
- Leadership experience in clinical research activities/clinical trials
- Extent of participation in clinical trials and related activities
- Nominee's planned activities to promote a successful clinical research culture at his/her institution
- Clear institutional commitment to allow at least 15% effort for activities proposed in the application
- Is the level of institutional commitment to the career development of the nominee appropriate?

National Cancer Institute

# 2013 CCITLA Awardees

Sikander Ailawadhi, M.D.
Award received at USC Norris Comprehensive Cancer Center
Currently at Mayo Clinic Florida

Jessica Altman, M.D.
Robert H. Lurie Comprehensive Cancer Center
Northwestern University



Lauren Byers, M.D., M.S.
M.D. Anderson Cancer Center

National Cancer Institute

# 2013 CCITLA Awardees

Sarah Cooley, M.D.
Masonic Cancer Center
University of Minnesota

N. Lynn Henry, M.D., Ph.D.
University of Michigan Comprehensive Cancer Center

Cynthia Ma, M.D., Ph.D.
Alvin J. Siteman Cancer Center
Washington University School of Medicine

National Cancer Institute

# 2013 CCITLA Awardees

Mohammed Milhem, M.D.
University of Iowa Holden Comprehensive Cancer Center

Timothy Showalter, M.D.
University of Virginia Cancer Center

Abby Siegel, M.D.
Herbert Irving Comprehensive Cancer Center
Columbia University

National Cancer Institute

# 2013 CCITLA Awardees

John H. Stewart, IV, M.D.
Wake Forest Comprehensive Cancer Center

Eunice Wang, M.D.
Roswell Park Cancer Institute

National Cancer Institute

# Congratulations to the 2013 NCI Cancer Clinical Investigator Team Leadership Awardees

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

## NCI Cancer Clinical Investigator Team Leadership Award (CCITLA) Recipients

### 2013 Award Recipients

Dr. Sikander Ailawadhi, Norris Comprehensive Cancer Center, University of Southern California
Dr. Jessica Altman, Lurie Comprehensive Cancer Center, Northwestern University
Dr. Lauren Byers, MD Anderson Cancer Center, University of Texas
Dr. Sarah Cooley, Masonic Cancer Center, University of Minnesota
Dr. Norah Lynn Henry, University of Michigan Comprehensive Cancer Center
Dr. Cynthia Ma, Siteman Cancer Center, Washington University
Dr. Mohammed Milhem, Holden Comprehensive Cancer Center, University of Iowa
Dr. Timothy Showalter, UVA Cancer Center, University of Virginia
Dr. Abby Siegel, Herbert Irving Comprehensive Cancer Center, Columbia University
Dr. John Stewart IV, Wake Forest Comprehensive Cancer Center, Wake Forest University
Dr. Eunice Wang, Roswell Park Cancer Institute

### 2012 Award Recipients

Dr. Lyudmila Bazhenova, Moores Comprehensive Cancer Center, University of California, San Diego
Dr. Lisa Bomgaars, Dan Duncan Cancer Center, Baylor College of Medicine
Dr. Alberto Broniscer, St. Jude Children's Research Hospital
Dr. Daniel DeAngelo, Dana-Farber/Harvard Cancer Center, Dana-Farber Cancer Institute
Dr. Konstantin Dragnev, Dartmouth - Norris Cotton Cancer Center
Dr. Shirish Gadgeel, Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine
Dr. Shannon Puhalla, University of Pittsburgh Cancer Institute
Dr. Bart Scott, Fred Hutchinson Cancer Research Center
Dr. B. Douglas Smith, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University
Dr. Jonathan Strosberg, Moffitt Cancer Center, University of South Florida
Dr. Antoinette Tan, Cancer Institute of New Jersey, Robert Wood Johnson Medical School
Dr. Jason Zell, Chao Family Comprehensive Cancer Center, University of California, Irvine

### 2011 Award Recipients

Dr. Julie Bauman, University of New Mexico Cancer Center
Dr. Tanios Bekaii-Saab, Ohio State University Comprehensive Cancer Center
Dr. Anthony El-Khoueiry, University of Southern California Norris Comprehensive Cancer Center
Dr. David Gerber, Harold C. Simmons Cancer Center, University of Texas Southwestern Medical Center
Dr. Andrew Ko, UCSF Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco
Dr. Antonio Omuro, Memorial Sloan-Kettering Cancer Center
Dr. Chong-xian Pan, University of California, Davis Cancer Center
Dr. John Sarantopoulos, Cancer Therapy & Research Center, UT Health Science Center at San Antonio
Dr. Scott Schuetze, University of Michigan Comprehensive Cancer Center
Dr. Tait Shanafelt, Mayo Clinic
Dr. Brenda Weigel, Masonic Cancer Center, University of Minnesota

## 2010 Award Recipients

Dr. Rafat Abonour Melvin and Bren Simon Cancer Center, Indiana University
Dr. Jeffrey Bradley, Siteman Cancer Center, Washington University
Dr. Steven Cohen, Fox Chase Cancer Center
Dr. Linda Duska, UVA Cancer Center, University of Virginia
Dr. Naomi Haas, Abramson Cancer Center, University of Pennsylvania
Dr. Elisabeth Heath, Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine
Dr. Susan Kelly, MD Anderson Cancer Center, University of Texas
Dr. Smitha Krishnamurthi, Case Comprehensive Cancer Center, Case Western Reserve University
Dr. Suresh Ramalingam, Winship Cancer Institute, Emory University
Dr. David Rizzieri, Duke Comprehensive Cancer Center
Dr. Cheryl Saenz, Moores Comprehensive Cancer Center, University of California, San Diego
Dr. Sheri Spunt, St. Jude Children's Research Hospital

## 2009 Award Recipients

Dr. Jordan Berlin, Vanderbilt-Ingram Cancer Center
Dr. Jeffrey Clark, Dana-Farber/Harvard Cancer Center, Dana-Farber Cancer Institute
Dr. Steven Devine, Ohio State University Comprehensive Cancer Center
Dr. Jeffrey Lancet, Moffitt Cancer Center, University of South Florida
Dr. Robert Maki, Memorial Sloan-Kettering Cancer Center
Dr. Wells Messersmith, University of Colorado Cancer Center
Dr. Julian Molina, Mayo Clinic
Dr. Melanie Royce, University of New Mexico Cancer Center
Dr. Christopher Ryan, OHSU Knight Cancer Institute, Oregon Health & Science University
Dr. Melanie Thomas, Hollings Cancer Center, Medical University of South Carolina
Dr. Antonio Wolff, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University

**Sikander Ailawadhi, M.D.**
**Senior Associate Consultant**
**Division of Hematology/Oncology, Department of Medicine, Mayo Clinic Florida**
**Award received while at USC Norris Comprehensive Cancer Center**

**Sikander Ailawadhi, M.D.** was awarded the 2013 NCI CCITLA as an Assistant Professor of Medicine at the Norris Cancer Center, University of Southern California (USC), Los Angeles CA. Subsequently, he has joined the Division of Hematology and Oncology at Mayo Clinic in Florida as a Senior Associate Consultant in order to pursue his career goal of clinical, translational and outcomes-based research in B-cell malignancies, especially plasma cell disorders. Prior to his move from USC, under the scope of CCITLA, Dr. Ailawadhi was involved with the following efforts:

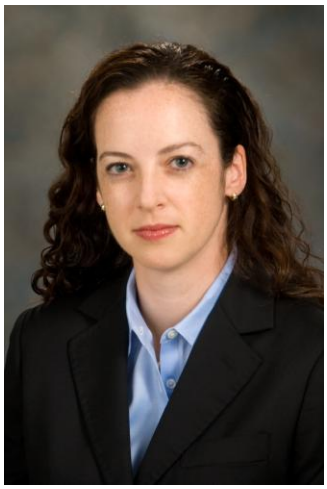
1. Expansion and continuation of the function of the Quality Assurance and Monitoring Committee (QAMC) and Clinical Investigation Support Office (CISO): As the QAMC Chair, Dr. Ailawadhi was involved in an effort to expand the membership of the QAMC by recruiting more clinicians and allied staff from diverse backgrounds to the committee.
2. Development of disease-specific clinical trial pathways in hematologic malignancies: Dr. Ailawadhi developed four disease-specific clinical trial pathways for dysproteinemia, acute leukemias, chronic leukemias and lymphomas so that all the open clinical trials within the Division of Hematology would be prioritized and the clinicians/housestaff would know about the salient inclusion criteria as well as prioritization of disease-specific clinical trials at a glance. These were then delegated to respective faculty with interest in specific disease types to maintain in a prospective manner.
3. Monitoring and promoting racial/ethnic diversity in clinical trial participation at USC: Dr. Ailawadhi prepared a proposal to the IRB that was approved and was aimed at defining the ethnic mix of patients reported to the California Cancer Registry, patients seen at USC and those enrolled in clinical trials at USC to define the catchment population as well as the actual accrual population and their ethnic mix. This would be used to develop tools to increase clinical trial participation by ethnic minorities.
4. Expansion of the Cooperative Group clinical trial participation in hematologic malignancies at USC: Dr. Ailawadhi continues as the Study Chair of S1304 and co-Chair of S1211 Intergroup clinical trials and secured a randomized phase 2 clinical trial concept in Waldenstrom's macroglobulinemia through his involvement with SWOG. He is currently working on submitting the letter of intent to NCI/CTEP for their approval.

**Jessica Altman, M.D.**
**Director of the Leukemia Program for Northwestern Medicine Developmental Therapeutics Institute**
**Robert H. Lurie Comprehensive Cancer Center**
**Associate Professor of Medicine, Northwestern University Medical School**

**Jessica Altman, M.D.** is an Associate Professor of Medicine in the division of hematology/oncology at Northwestern University. She graduated from Brown University in 1997 with a BA in Economics and obtained her medical degree from the University of Pittsburgh School of Medicine. She then completed her residency in Internal Medicine at the University of Chicago. Dr. Altman served as chief fellow during her hematology/oncology fellowship at Northwestern University and then joined the faculty at Northwestern in 2007. She focuses her practice on caring for adults with leukemia and has a major interest in novel therapeutics.

Dr. Altman's primary research efforts are based on increasing the understanding of the role of aberrant signal transduction pathways in the development of leukemias; defining molecular targets for the treatment of leukemias; and generating clinical trials based on such research work. She has extensive experience in translational work in this area. She is very involved in developing early phase clinical trials for adults with leukemia. In addition, she is a core member of the leukemia committee of the Eastern Cooperative Oncology Group and an active member of the National Comprehensive Cancer Network panels for acute myeloid leukemia, chronic myeloid leukemia, and adolescent and young adult patients.

The Cancer Clinical Investigator Team Leadership Award has allowed Dr. Altman the protected time necessary to conduct early phase trials and closely mentor fellows. She has developed and opened a phase I study of metformin and cytarabine for the treatment of relapsed and refractory AML (NU11H03). The award has allowed her to mentor her fellow in the development of a phase I trial of an FGF inhibitor and a hypomethylating agent for adults with a particular cytogenetic abnormality who are not candidates for chemotherapy, a concept based on detailed laboratory work by Dr. Elizabeth Eklund, a colleague at Northwestern. This award has allowed Jessica to work closely with Dr. Eklund and translate this work to trial development. Jessica developed a seminar series for the hematology/oncology fellows with a focus on mentorship and career development. This will be extended to junior faculty later this year. This award has been instrumental for Dr. Altman's academic growth.



**Lauren Byers, M.D., M.S.**
**Assistant Professor**
**Department of Thoracic/Head and Neck Medical Oncology**
**M.D. Anderson Cancer Center**
**University of Texas**

**Lauren Byers, M.D., M.S.** is an Assistant Professor in the Department of Thoracic/Head and Neck Medical Oncology at the University of Texas M. D. Anderson Cancer Center. She received her medical degree from Baylor College of Medicine and completed internal medicine training at Johns Hopkins Hospital. She then came to M.D. Anderson Cancer Center as a medical oncology fellow and was selected for the Division of Cancer Medicine's Advanced Scholars Program. Dr. Byers is currently a physician-scientist in the MD Anderson Physician Scientist Program. Her research focuses on the application of reverse phase protein array and other molecular profiling technologies for identifying novel therapeutic targets and predictive markers in lung and head and neck cancer. Dr. Byers is an investigator on several major research efforts, including the TCGA, Lung and HN SPOREs, and Department of Defense PROSPECT. In recognition of her research accomplishments, she has received a number of prestigious awards, including the Sidney Kimmel Scholar Award, an award from the Lung Cancer Research Foundation, the National Lung Cancer Partnership Young Investigator Award, and a LUNGevity Foundation Career Development Award.

Supported by the NCI Cancer Clinical Investigator Team Leadership Award, Dr. Byers has expanded her clinical research activities, serving as the Institutional or Overall PI on 5 clinical trials. As a direct result of her laboratory research which identified that PARP-1 was overexpressed in small cell lung cancer (SCLC) cell lines and patient tumors (Byers et al, Cancer Discovery 2012), Dr. Byers is currently leading several clinical trials testing PARP inhibitors in SCLC patients. These studies are ongoing, but early results are promising, indicating that a PARP inhibitor (BMN-673) exhibits striking single agent activity in SCLC patients. These results confirm both the clinical activity of this drug and PARP1 as a true clinical target in SCLC patients. Unlike NSCLC, SCLC has no approved targeted drugs and standard of care chemotherapy has remained largely unchanged for more than 20 years. These early clinical trial results, therefore, are extremely exciting and hold much promise for improved treatment of this deadly disease.

**Sarah Cooley, M.D.**
**Assistant Professor of Medicine, Division of Hematology, Oncology and Transplantation**
**Director, Oncology Medical Informatics and Services**
**Associate Director, Cancer Experimental Therapeutics Initiative**
**Masonic Cancer Center**
**University of Minnesota**

**Sarah Cooley, M.D. i**s an Assistant Professor of Medicine in the Division of Hematology, Oncology and Transplantation at the University of Minnesota. Her clinical time is spent is on the adult Blood and Marrow Transplant service, and her research interest is to translate state-of-the-art research in immunobiology into effective new immune-based therapies for cancer. She has been funded by a K23 entitled "Innate Immunity and Cancer Therapy" and is now funded by the Doris Duke Charitable Foundation and is supported on two Program Project Grants to serve as principal investigator for several clinical trials, to lead immunogenetic analyses, and to run the informatics and data management cores which support multicenter Phase I trial and the analysis of large integrated data sets. She is very involved in improving the clinical research infrastructure at the University of Minnesota. She is the Associate Director of the Cancer Experimental Therapeutics Initiative (CETI), and the Medical Director of the Masonic Cancer Center's Oncology Medical Informatics and Services Core. She recently obtained board certification in the new subspecialty of Clinical Informatics.

The CCITLA will support Dr. Cooley to meet several important goals. She will ensure a smooth transition of the OnCore clinical trials management system from the MCC to the UMN CTSA. She will partner with Fairview Health System and University of Minnesota Physicians to launch the transition the MCC BMT program to an updated database application (and associated workflows) which will receive feeds from the electronic health record system (EPIC) and other clinical applications, and will feed the national Stem Cell Transplant Outcomes Database (CIBMTR SCTOD) via an interface engine feeding CIBMTR's AGNIS interface. The new BMT database will use the BRIDG model created at the NCI in partnership with the CIBMTR and NMDP. She will use the BMT database upgrade as a model to optimize EPIC for discrete data collection for other tumors to support develop a United Cancer Patient Registry to provide basic information on all cancer patients to serve all MCC clinical researchers. She will continue to develop the MCC's ability to leverage their research data via dashboards and automated or customized reporting to serve the clinical, research, operational and administrative needs of MCC researchers and staff.

**N. Lynn Henry, M.D., Ph.D.**
**Assistant Professor of Internal Medicine**
**University of Michigan Medical School**
**University of Michigan Comprehensive Cancer Center**

**N. Lynn Henry, M.D., Ph.D.** is an Assistant Professor at the University of Michigan (UM) Medical School, and Director of the Breast Cancer Survivorship Program a member of the Breast Oncology Program at the UM Comprehensive Cancer Center. She received her Ph.D. in Structural Biology from Stanford University School of Medicine, her M.D. from Washington University School of Medicine, and then completed a residency in Internal Medicine at Brigham and Women's Hospital in Boston and a fellowship in Hematology/Oncology at UM. Dr. Henry's research focus is on the predictors of response to and toxicity from breast cancer treatment, with a particular focus on the musculoskeletal side effects of aromatase inhibitors.

As a recipient of the Cancer Clinical Investigator Team Leadership Award, Dr. Henry will perform a variety of activities to further the clinical mission of the UM Comprehensive Cancer Center. She is increasing the amount of mentoring that she will provide to clinical fellows and residents related to both research and career development. Dr. Henry will also continue to develop her clinical research program in personalized therapy and symptom management for breast cancer survivors, including collaborating closely with colleagues in SWOG. Finally, she is cultivating her leadership skills through participation in the ASCO Leadership Development Program, which will enable her to establish herself as a leader in clinical research both locally in the UM Comprehensive Cancer Center and nationally through organizations such as ASCO and SWOG.

**Cynthia Ma, M.D., Ph.D.**
**Associate Professor of Medicine**
**Alvin J. Siteman Cancer Center**
**Washington University School of Medicine and Barnes-Jewish Hospital**

**Cynthia Ma, M.D., Ph.D.** received her M.D. at Beijing Medical University in the People's Republic of China in July 1990, and her Ph.D. in Developmental Biology at the University of Cincinnati, Ohio in July 1997. She subsequently completed Internal Medicine residency training at New Hanover Regional Medical Center in North Carolina between 1998 and 2001, followed by a Hematology/Medical Oncology fellowship at Mayo Clinic in Rochester, Minnesota. In July 2005, Dr. Ma joined the Division of Oncology at Washington University School of Medicine in Saint Louis as an Assistant Professor. She was promoted to Associate Professor of Medicine in July 2012. Dr. Ma is a physician scientist, with a particular focus on Breast Oncology. Dr. Ma has designed and led multiple investigator-initiated trials of targeted cancer therapies that incorporate biomarkers and genomics in the treatment of resistant breast cancer. Examples of these studies include the multi-center phase II trial of neratinib in HER2 mutated metastatic HER2 negative breast cancer and the ALLIANCE ALTERNATE trial, a neoadjuvant study that aims to validate a Ki67 based biomarker approach for risk stratification in patients with estrogen receptor positive breast cancer. In addition, she has an active laboratory effort to investigate targeted therapeutics using patient-derived xenograft models of triple negative breast cancer.

Under the CCITLA, Dr. Ma will continue to collaborate with basic scientists, clinicians and translational researchers as well as NCI CTEP, Cooperative Groups and industry partners to design and conduct high impact biomarker directed clinical trials. She will continue as study chair for 3 ongoing NCI trials and in her leadership role at the Mayo Phase II Consortium. She plans to continue her laboratory studies for further mechanistic investigations. In addition, she will continue to mentor junior faculty members and trainees in concept development and protocol execution, particularly in the field of targeted therapeutics evaluation and individualized treatment of breast cancer patients.

**Mohammed Milhem, M.D.**
**Deputy Director for Clinical Services**
**Associate Professor of Internal Medicine**
**Director of the Melanoma and Sarcoma Programs**
**University of Iowa Holden Comprehensive Cancer Center**

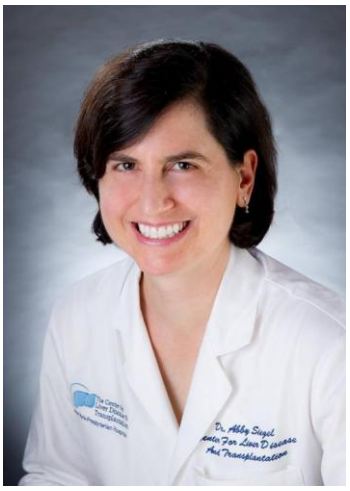
**Mohammed Milhem, M.D.'s** major appointment is at the University of Iowa Hospital and Clinics where he provides inpatient and outpatient consultative service for melanoma and sarcoma patients. He is the Deputy Director for Clinical Cancer Services at the Holden Comprehensive Cancer Center and leads the melanoma and sarcoma clinical research efforts. In the past year, these programs have accrued 72 subjects to therapeutic clinical trials and 312 subjects to a prospective tumor registry.

Dr. Milhem is board certified in Hematology/Oncology with expertise in the areas of melanoma and sarcoma. He's helped coordinate the formation of the multidisciplinary groups for these two tumors and has successfully integrated a number of clinical trials from both industry and cooperative groups.

**Timothy Showalter, M.D.**
**Assistant Professor**
**Department of Radiation Oncology**
**University of Virginia School of Medicine**
**Member, University of Virginia Cancer Center**

**Timothy Showalter, M.D.** is a radiation oncologist who specializes in male and female pelvic cancers and brachytherapy. He is focused on improving treatments and outcomes for patients through comparative effectiveness research, clinical trials, and the evaluation of advanced techniques in radiation therapy. He joined the faculty at the University of Virginia in August 2012. He was an active member of the Radiation Therapy Oncology Group and will serve on the Genitourinary Cancers and Patient Centered Outcomes Research Committees of NRG Oncology. He is the recipient of the 2011 Ben Franklin Prostate Cancer Foundation Young Investigator Award and the American Society for Radiation Oncology Comparative Effectiveness Award.

With the Cancer Clinical Investigator Team Leadership Award, Dr. Showalter will help increase accrual to cooperative group trials at UVA, and he is the physician lead for a department-level Clinical Trials Team Training Program. He is principal investigator of an investigator-initiated trial, “Hypofractionated post-prostatectomy radiotherapy for prostate cancer to reduce toxicity and improve patient convenience: A Phase I/II trial”, which is open at multiple centers in Virginia and North Carolina. He is working with colleagues at UVA on additional investigator-initiated trials, including a pilot study of a new form of intraoperative radiation therapy for breast cancer. Additionally, he is collaborating with colleagues from Massey Cancer Center at Virginia Commonwealth University to increase enrollment on therapeutic cancer trials.



**Abby Siegel, M.D.**
**Assistant Professor of Medicine**
**Herbert Irving Comprehensive Cancer Center**
**College of Physicians & Surgeons**
**Columbia University**

**Abby Siegel, M.D.** is a medical oncologist who focuses on hepatobiliary malignancies. She currently holds an NIH K23 award examining novel biomarkers in newly-diagnosed hepatocellular carcinoma patients. Dr. Siegel is the Co-Chair of the Hepatobiliary Subcommittee in SWOG, and sits on the NCI Task Force for Hepatobiliary Malignancies.

As part of the Cancer Clinical Investigator Team Leadership Award, Dr. Siegel plans to develop clinical trials and education around trials in three areas: in SWOG, at Columbia University, and for potentially underserved groups in the NYC area. Specifically, she is developing two hepatobiliary trials through SWOG, and is implementing a mentorship program pairing junior faculty with senior SWOG investigators with similar interests. At Columbia, she is providing education to trainees and junior faculty around ethical and practical conduction of clinical trials. Finally, she is reaching out to several populations throughout the city to provide education about trials and understand barriers to clinical trial participation.

**John H. Stewart, IV, M.D.**
**Associate Professor of Surgery**
**Associate Dean for Clinical Research and Innovation**
**Vice Chair for Academic Affairs, General Surgery**
**Wake Forest Comprehensive Cancer Center**

**John H. Stewart, IV, M.D.** is one of eight faculty members of the Wake Forest Baptist Health Surgical Oncology Service. Prior to completing his residency in general surgery at the Vanderbilt University Medical Center in 2004, Dr. Stewart completed fellowships in surgical oncology and tumor immunotherapy at the National Cancer Institute under the direction of Dr. Steven Rosenberg.

The focus of his laboratory work is on the induction of cell death in gastrointestinal malignancies using oncolytic viruses. At present, Dr. Stewart's research efforts on cancer-killing viruses are funded by the National Cancer Institute. In addition, he was a Harold Amos Fellow of the Robert Wood Johnson Foundation.

Dr. Stewart's clinical interests are in general surgical oncology with a focus on melanoma as well as breast, gastrointestinal, and peritoneal surface malignancies. He will utilize the CCTLA to bridge the gap between basic science discoveries and clinical trials for oncolytic viral therapy for peritoneal dissemination of gastrointestinal cancers.

Dr. Stewart has published over 60 peer-reviewed manuscripts in journals including Cancer, the Journal of Thoracic and Cardiovascular Surgery, the Journal of Immunotherapy, Annals of Surgical Oncology, the Journal of Surgical Research, the American Journal of Surgery and Transplantation.

**Eunice Wang, M.D.**
Associate Professor
Leukemia Service, Department of Medicine
Departments of Medicine
Roswell Park Cancer Institute and
Department of Medicine, School of Medicine and Biomedical Sciences, State University of New York at Buffalo

**Eunice Wang, M.D.** joined the faculty of Roswell Park Cancer Institute in 2003 and was appointed to the Leukemia Section of the Department of Medicine. She earned her medical degree from the Keck-University of Southern California School of Medicine and completed residency training in Internal Medicine at Yale-New Haven Hospital, Yale University, New Haven, CT in 1999. From 1999 to 2003, she completed a clinical hematology-oncology fellowship at Memorial Sloan-Kettering Cancer Center in New York, NY. She is a member of the American Society of Clinical Oncology, American Association for Cancer Research, and American Society of Hematology.

In addition to her clinical practice, Dr. Wang maintains an active translational laboratory research program focused on the role of angiogenesis and telomerase in hematological malignancies, screening anti-angiogenic and other biological agents for effects on clinically relevant human leukemia *in vivo*, and early stage clinical trials for acute leukemia. She also serves as Associate Program Director of the joint Roswell Park/SUNY-UB Hematology-Oncology Fellowship program and was awarded the Best Teaching Award by the graduating fellows in 2013.

Under the CCITLA, Dr. Wang intends to (a) develop additional novel investigator-initiated clinical trials for acute leukemia based on her laboratory research; (b) actively promote the importance and culture of clinical cancer research among medical (fellows, residents and students) trainees as well as nursing, clinical research and other institute staff members.

National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

# NCI Legislative Update

## Clinical Trials and Translational Research Advisory Committee

**March 12, 2014**


Susan Erickson

Director, Office of Government and Congressional Relations

# Discussion Topics

Appropriations Status

Congressional Activities

Legislation of Interest

# Status at November Meeting

## What's Next?

- Budget conferees create spending plan by 12/13
- Appropriation Subcommittees use new spending level to work on individual bills
- Bills combined into Omnibus bill and passed

## If Not --

Full year CR? - Short term CR? - Another shutdown?

# Believe It Or Not…

- ✓ Budget conferees create spending plan by 12/13
  - Discretionary 2014=$1.012 T; 2015=$1.014T
  - Revised sequester 2014 & 2015; Extended 2 yrs
  - Savings found in specific programs
- ✓ Appropriation Subcommittees use new spending level to work on individual bills
- ✓ Individual bills combined in Omnibus and passed
  - Passed both House and Senate in <
  - NIH = $29.9B NCI = $4.92B

vs. 2013
$4.78B
---
vs. 2012
$5.06B

# Appropriations Status – FY 2015

President's Budget announced March 4

- NIH = $30.4 B;  NCI = $4.93B

House Action

- Budget Resolution expected
- Subcommittee hearing March 26

Senate Action

- No Budget Resolution
- Subcommittee hearing likely in early May

# Congressional Activities

- Priorities?

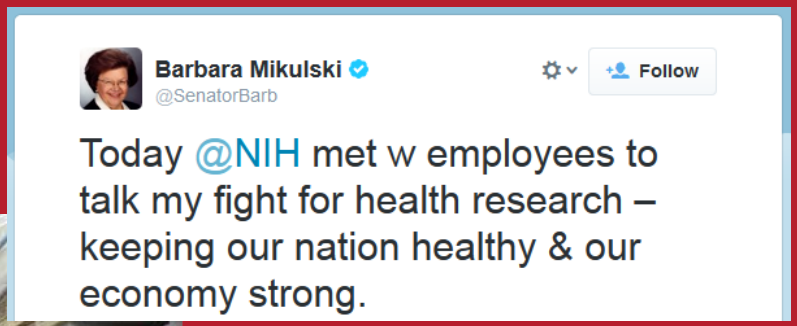
*“First thing [for the Senate] is to make sure that those people who are waiting and waiting to find a job still get the important check that they deserve.”*

*“As we continue to work to finalize our Obamacare replacement plan, we will also act to highlight and address the serious consequences of the law.”*

# Congressional Activities - NCI

## Visits to NIH

- February 24th: **Sen. Barbara Mikulski** (D-MD) toured Dr. Marston Linehan's lab and hosted a press event




# Congressional Activities - NCI

## Visits to NIH

- February 3rd**:** In separate visits, **Sen. Richard Durbin** (D-IL) and **Rep. Joseph Pitts** (R-PA) met with IC Directors and toured the NIH Clinical Center

# Congressional Activities - NCI

## Visits to NIH

- February 28th: **Rep. Leonard Lance** (R-NJ) gave opening remarks at NIH's Rare Disease Day symposium and toured the NIH Clinical Center
- February 21st: **House Majority Appropriations Staff** met with Dr. Collins and a number of IC Directors to discuss priorities identified in the FY14 Omnibus Appropriations Report

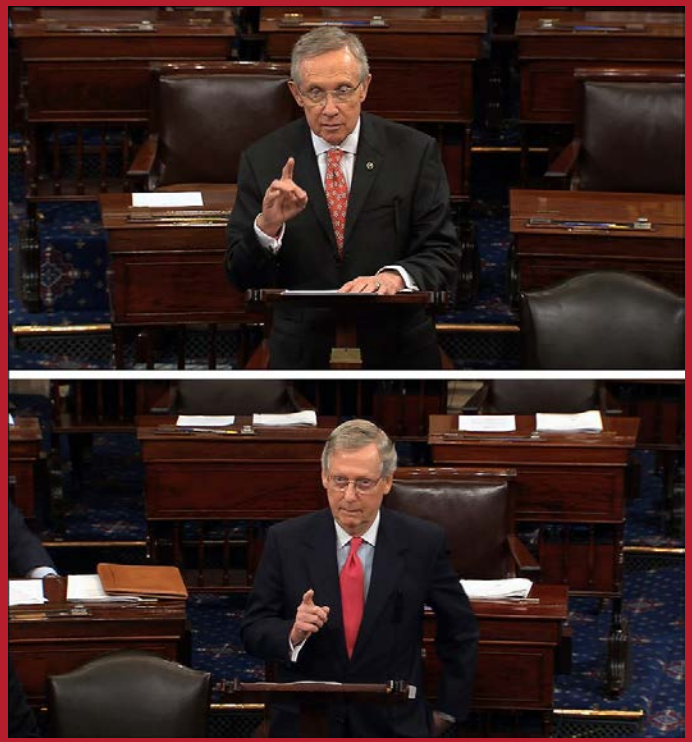
## Briefings

- Tomorrow, Dr. Crystal Mackall, Chief of NCI's Pediatric Oncology Branch, will speak about immunotherapy research at an AACR congressional briefing

# Legislation of Interest

- Gabriella Miller Kids First Research Act, H.R. 2019
  - Eliminates taxpayer financing of political party conventions and reprograms savings to provide for a 10-year pediatric research initiative administered through the NIH Common Fund.
  - However, funds would only be made available to NIH "to the extent and in such amounts as are provided in advance in appropriation Acts."
  - The bill was originally introduced by Rep. Gregg Harper (R-MS), and has been championed by House Majority Leader Eric Cantor (R-VA).
  - The bill did not proceed through mark up, and did not pass out of committee, as is usually the case before a bill is considered for a vote. The House passed H.R. 2019 in December, and the Senate passed it yesterday.

# Legislation of Interest



*“[What] we've done today is only an authorization and the public out there should understand it's only an authorization until money is appropriated, there will be nothing go to pediatric research at the National Institutes of Health. We have to carry forward and not have all these banner headlines the kids are going to suddenly get help that they deserve. That will not happen until we appropriate money for this.”*

*“H.R. 2019, which will go to the president for signature, the original author of which is Eric Cantor in the House will eliminate taxpayer financing of political party conventions and reprogram savings to provide for a ten year pediatric initiative for the common fund administered by the NIH.”*

# Legislation of Interest

- Cancer Treatment Parity Act, S. 1879/H.R. 1801
  - The bill aims to require health insurers to provide for coverage of oral anticancer drugs on terms no less favorable than the coverage provided for anticancer medications administered by a health care provider.
  - The bills were introduced by Sen. Al Franken (D-MN) and Rep. Brian Higgins (D-NY).
  - 26 states and the District of Columbia have enacted oral chemotherapy access laws, and a law passed in Missouri last week awaits the governor's signature

# Legislation of Interest

- Breast Density and Mammography Reporting Act, H.R. 3404
  - The bill would amend the Mammography Quality Standards Act (MSQA) of 1992 to require mammography results, including the patient summary, to report relative breast density.
  - The bill was introduced by Rep. Rosa DeLauro (D-CT).
  - 13 states have enacted laws requiring some form of breast density reporting, and similar laws are pending in 8 states.

DEPARTMENT OF HEALTH AND HUMAN SERVICES·USA

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**March 12, 2014**

# Legislative Update

# for the

# Clinical Trials and Translational Research Advisory Committee

## Activities of the 113th Congress-

## Second Session

Susan Erickson, Director,
Office of Government and Congressional Relations
National Cancer Institute
Building 31-10A48
ncilegislative@mail.nih.gov
301-496-5217

Visit the Office of Government and Congressional Affairs website at:
http://legislative.cancer.gov

## *I. Appropriations*

On January 17th, the President signed Consolidated Appropriations Act of 2014 into law following Congressional passage of the omnibus funding bill with a House vote of 359-67 on 1/15/14, and a Senate vote of 72-26 on 1/16/14. Despite efforts to move the bill before the continuing resolution (CR) expired on January 15th, Congress was unable to do so and therefore needed to pass an emergency three-day Continuing Resolution (CR) to continue funding the government through January 18th.

This "omnibus" appropriations act contains funding for all 12 Congressional Appropriation bills, including Labor-HHS-Education. It provides a $1 billion increase for NIH over the post-sequester funding level of FY2013 ($29.9 billion for FY2014 for NIH, including $4.92 billion for NCI). While this is an increase over the FY2013 funding level, the bill funds NIH and NCI at a level lower than FY2012, as well as lower than FY2011 and FY2010 levels.

The funding levels provided by the omnibus bill are based on spending levels established by the Bipartisan Budget Act, an agreement reached between House Budget Chair Paul Ryan and Senate Budget Chair Patty Murray (House amendment to H.J.Res. 59/P.L. 113-67; passed by the House and Senate and signed into law by the President in December 2013). The budget act restored a portion of sequestration cuts, providing an additional $63 billion in discretionary spending authority ($45 billion FY2014, $18 billion FY2015, split evenly across defense and non-defense). This is offset by $85 billion in cuts to mandatory programs and non-tax revenue increases (which provides an additional $23 billion in deficit reduction).

Additionally, the Labor-HHS section of the appropriations act includes language directing each agency or operating division with research and development expenditures in excess of $100,000,000 per year to develop a Federal research public access policy to provide for free online access to peer-reviewed manuscripts supported in whole or in part by federal funds, within 12 months of publication. This effectively directs the Centers for Disease Control, the Agency for Health Research and Quality, and the Department of Education to implement a public access policy similar to NIH. The omnibus bill also continues existing government-wide conference and travel restrictions, specifically, executive agencies must submit detailed reports to their Inspector Generals about conferences costing over $100,000, and the head of the agencies must also report within 15 days details about any conference costing more than $20,000. All travel and conference activities must continue to be in compliance with the guidance memo issued by the Office of Management and Budget on 5/11/12.

Conference report language accompanying the appropriations bill, called the Joint Explanatory Statement, includes additional policy directives for NIH, NCI, and other institutes. For example, the NIH Director is directed to conduct an NIH-wide review of how the priority-setting process affects program goals and the overall NIH research portfolio, and that of each IC. The NIH Director is also expected to develop an NIH- wide process to reduce duplication across communications activities – to consolidate and improve efficiencies, improve coordination of messages, and generally reduce costs in this area. Language specific to the NCI encourages certain pediatric brain tumor research efforts (biospecimen collection, genetic models, xenograft models), and requests more information regarding the use of bioinformatics in pediatric cancer research.

As noted above, the Bipartisan Budget Act also set discretionary spending levels for FY2015 and House and Senate Appropriators will use these figures to begin planning for the FY2015 appropriations process. The release of the President's FY2015 budget began on March 4, and included summary information for the budgets of agencies such as the Department of Health and Human Services. This budget includes $30.4 billion for NIH, an increase of $211 million over FY2014. It is important to note that, while the proposed NIH budget is an increase relative to FY2014, it is less than the NIH FY2012 appropriation of $30.86 billion. The FY2015 proposal includes approximately $4.93 billion for NCI. Like NIH, this proposed budget is an increase ($8 million) relative to FY2014, however it is less than the NCI FY2012 appropriation of approximately $5.07 billion.

## *II. Special Topics*

**E-cigarettes: Ongoing Congressional Interest**

Sen. Tom Harkin (D-IA), Chairman of the Senate Health, Education, Labor, and Pensions Committee, and Chairman of the Senate Appropriations Subcommittee on Labor-HHS-Education, indicated in a recent press interview that encouraging FDA regulation of electronic cigarettes is among his top priorities before he retires at the end of this year. Sen. Harkin is one of a number of members of Congress who continue to express concerns over electronic cigarette marketing and regulation.

Currently, E-cigarettes are not regulated by the U.S. Food and Drug Administration (FDA) as a tobacco product, although the FDA has indicated that it intends to issue a proposed rule extending its tobacco product authorities to include regulation of e-cigarettes. There is broad agreement that there are many important research gaps regarding these products. The NCAB December 2013 Legislative Update included a summary of congressional interest in e-cigarette use and regulation, including in response to a September 2013 Centers for Disease Control and Prevention report that e-cigarette use doubled among middle and high school students from 2011-2012.

Along with Sen. Harkin, Senators Barbara Boxer (D-CA), Richard Blumenthal (D-CT), Sherrod Brown (D-OH), Richard Durbin (D-IL), and Ed Markey (D-MA) wrote to the Federal Trade Commission (FTC) in December 2013, calling on the FTC to investigate e-cigarette marketing practices, particularly false, deceptive, or misleading advertising and marketing toward children and teens. The Senators asked the FTC to include e-cigarettes in its annual reports on tobacco product sales, advertising, and promotion – the FTC currently issues reports on cigarettes and smokeless tobacco products.

This group of Senators, along with a few House colleagues, continue to focus on e-cigarettes in the new year. Rep. Henry Waxman (D-CA) joined his Senate colleagues in writing to the House Office Building Commission and the Senate Committee on Rules asking that the ban on smoking on Capitol grounds be extended to include e-cigarettes. Additionally, after e-cigarettes were featured during the opening skit of the televised Golden Globe Awards, Senators Durbin, Blumenthal, Brown, and Markey wrote to the Hollywood Foreign Press Association and NBC Universal asking that future ceremonies refrain from intentionally featuring e-cigarettes.

Most recently Senator Harkin, Rep. Waxman, and Rep. Peter Welch (D-VT) wrote to their states' Attorneys General urging them to classify e-cigarettes as cigarettes under the Tobacco Master Settlement Agreement (a 1998 settlement between the Attorneys General of 46 states and tobacco companies; in addition to a financial settlement, terms include restrictions on marketing tobacco products to youth). Harkin, Waxman, and Welch write, "We believe e-cigarettes meet all the criteria for the definition of cigarette (and tobacco product) in the Master Settlement Agreement. In fact, the MSA contemplated that novel products -- like e-cigarettes -- would later meet the definition of cigarette. Inclusion of these products in the definition of cigarette is consistent with the MSA's overarching goal of protecting America's youth from the harms of tobacco use. . . . By taking action to apply the MSA to e-cigarettes, you could make a giant stride in protecting kids from a lifelong addiction to nicotine."

### Oral Chemotherapy Parity: State and Federal Legislation

***Recent laws and current proposals***

Twenty six states and the District of Columbia have enacted laws that require insurance plans that provide coverage for intravenous (IV) or injected chemotherapy treatments to provide coverage for orally administered chemotherapies at the same cost. Oregon was the first state to do so in 2008, and in the past year alone seven states signed similar bills into law. In the current Congress, a number of legislators have expressed interest in a more consistent application of this policy and have introduced legislation to accomplish this at the federal level.

Traditionally, insurance plans have covered IV or injected chemotherapy as a medical benefit, meaning that a patient would be billed for a doctor's office visit, often a co-payment in the range of twenty to thirty dollars. Oral

chemotherapies, however, are usually classified as prescription drugs, and therefore covered under an insurance policy's prescription benefit, if the policy includes one. Prescription benefits are often structured as co-insurance, or cost sharing, where a patient would be required to cover a percentage of the cost of the oral chemotherapy. Many oral chemotherapies are newly approved drugs, with no equivalent generic alternative, and therefore can result in high out-of-pocket costs for patients with a cost sharing prescription benefit, or with an insurance plan that does not include a prescription benefit. For example the drug crizotinib, recently approved for the treatment of ALK-positive small cell lung cancer, is only available in the U.S. as brand-name Xalkori, and is considered a specialty medication. The price for a typical daily dose (two 250 mg pills) is approximately $384, and patients continue on this dosage until disease progression or until the drug is no longer tolerated. Results from the international Phase III trial that crizotinib's FDA approval was based upon indicate that patients taking crizotinib had on average 7.7 months of progression-free survival. A 7.7 month supply of crizotinib costs approximately $89,000.

The current national picture of the way oral chemotherapies are treated by payers is quite patchy. While a majority of states now require private insurance plans to cover all chemotherapies equally to eliminate high out-of-pocket costs for patients taking oral chemotherapies; more than 20 states do not have policies in place, although some have legislation pending. At the federal level, Medicare Part B currently covers any oral chemotherapy drug that is identical to an IV chemotherapy drug as a medical benefit. Oral chemotherapies that do not have an identical IV chemotherapy are covered under the Medicare Part D prescription plan.

Federal companion bills, introduced in the House by Rep. Brian Higgins (D-NY) and in the Senate by Sen. Al Franken (D-MN), were designed to substitute a consistent national standard of oral chemotherapy parity for the current status of comparable coverage required only in states with individual state laws. In addition, the federal proposals include provisions calling for a study to assess how closing the Medicare Part D "donut hole" (a gap in Medicare prescription drug coverage) effects Medicare coverage for orally administered anti-cancer medications. A summary of the Cancer Treatment Parity Act of 2013 (S.1879) and the Cancer Drug Coverage Parity Act of 2013 (H.R. 1801) is included in the "Legislation of Interest" section of this update.

***Oral anti-cancer drugs: examples and ongoing research***

The U.S. Food and Drug Administration (FDA) approved the first oral chemotherapy in 1998, the drug capecitabine (Xeloda) to treat patients with metastatic colorectal and metastatic breast cancer. Since that time the FDA has approved a growing number of oral anti-cancer drugs, including the first generic formulation of capecitabine, in September 2013 (the patent on capecitabine expired in December 2013, allowing generic formulations to enter the market). A typical two-week cycle of Xeloda costs approximately $2,500 and patients often undergo up to eight cycles. A two-week cycle of generic capecitabine costs approximately $1,475.

Advances in cancer genomics are identifying potential therapeutic targets across various cancer types, and continue to inform the development of targeted therapies, including those that are commonly administered orally. Many cancer immunotherapy agents, another area of promising research, are also oral medications. For example, a number of immunotherapies used to treat the blood cancer multiple myeloma are administered orally, including lenalidomide (Revlimid, approved for the treatment of multiple myeloma in 2006). A 25 mg dose of Revlimid is usually taken on days 1-21 of a 28 day cycle. Revlimid is associated with a median progression-free survival of 25.5 months. The cost for a 21-day supply is approximately $9,500 (the cost of a 25.5 month supply of Revlimid is approximately $252,000).

Anti-cancer targeted therapies known as small molecule inhibitors, which interfere with specific molecules known to drive a cancer's growth and progression, are usually orally administered drugs. Examples include imatinib (Gleevec), approved in 2002 for the treatment of chronic myeloid leukemia and advanced or metastatic gastrointestinal stromal tumor, and more recently crizotinib (Xalkori), mentioned above, approved in 2013. In the case of both imatinib and crizotinib, clinical trials demonstrated significantly prolonged progression-free survival with these targeted therapies as compared to existing chemotherapies. Gleevec is scheduled to come off patent in 2015, and until that time imatinib is only available in the U.S. as brand-name Gleevec. The starting dose is 400 - 600 mg per day, although some patients may be prescribed up to 800 mg per day. Most patients take Gleevec daily to

control their cancer, and continue to do so for years without disease progression. A daily dose of 400 mg costs approximately $270. Generic pricing is not yet available.

Since the approval of capecitabine in 1998, the FDA has approved more than 50 oral anti-cancer drugs, with more oral therapies in development – estimates indicate that 25 to 30 percent of oncology drugs in the pipeline are oral medications.

## Breast Density Reporting: State and Federal Legislation and Policy

***Recent laws and current proposals***

Breast density reporting legislation is gaining momentum at the state level, and interest is building at the federal level as well, from both a legislative and regulatory perspective. Breast density, which varies with the proportions of fat, glandular, and connective tissue in the breasts as seen on a mammogram, can cause difficulty in detecting breast cancer through the use of mammography. A breast with high density would yield a mammography image that is uniformly white throughout, making it difficult to distinguish normal tissue from tumors, which also appear white, due to the lack of contrast. Recent bills and regulatory actions would require that measures of breast density, and explanations about possibly related breast cancer risk, be reported to patients receiving mammogram results.

Representative Rosa DeLauro (D-CT), an ovarian cancer survivor, introduced the Breast Density and Mammography Reporting Act of 2013 on 10/20/13. Rep. DeLauro has introduced and co-sponsored similar proposals in past sessions of Congress; however the bills saw little activity. Rep. DeLauro's bill would amend the Mammography Quality Standards Act (MQSA) of 1992, which established quality standards for mammography facilities, and requires mammography facilities to provide patients with a report, in lay language and within 30 days, that summarizes the exam results. Rep. DeLauro's proposal would require the lay summary report to also include: (1) the patient's relative breast density, (2) their relative risk of developing breast cancer associated with their level of breast density, and (3) information communicating that individuals with more dense breasts may benefit from supplemental screening. Specific measures of breast density and language regarding relative risk and supplemental screening are to be determined by the HHS Secretary in consultation with leading experts and based on current scientific knowledge and medical practice. The bill also includes a clause specifying that, if passed, the federal legislation would not preempt any state requirements regarding breast density reporting. Upon the bill's introduction, Rep. DeLauro commented, "By providing this simple piece of information, we can help women and their doctors make more informed decisions about their risks for developing breast cancer, helping improve their chances for early detection and survival."

At the same time- and independent of Rep. DeLauro's proposal - the FDA scheduled a Notice of Proposed Rule Making for a breast density reporting amendment to the MQSA for December 2013, however the notice has yet to be issued. The abstract indicated that "FDA is taking this action to address changes in mammography technology and mammography processes, such as breast density reporting, that have occurred since the regulations were published in 1997." Currently the MQSA requires that breast density reporting is sent to the referring clinician, but not the patient.

At the state level, often in response to concerns from patient advocates, and in an effort to address some of the inherent challenges in screening for breast cancer in women with dense breasts, thirteen states have enacted laws requiring that women be notified of their breast density as part of standard reporting of mammography results. Similar laws are pending in 8 states, with efforts underway in additional states. The laws generally require that the mammography lay summary inform patients of their relative breast density, notify them of the association between dense breast tissue and cancer risk, and inform them of the limitations of mammography in patients with dense breast tissue and the possible benefit of additional screening tests (often specified as MRI or breast ultrasound). However, the specific reporting language, and who is responsible for the reporting, varies from state to state, and the provisions often do not include language addressing insurance coverage for any additional

screening tests. Many state laws indicate that breast density reporting categories be based on the American College of Radiology (ACR) classification scale, but some laws do not indicate a specific measurement and scoring system. The ACR classification is based on a 1-4 rating system, with type 1 indicating less than 25% fibroglandular tissue (almost entirely fat), type 2 indicating 26-50% fibroglandular tissue (scattered area of fibroglandular density), type 3 indicating 51-75% fibroglandular tissue (heterogeneously dense), and type 4 indicating more than 75% fibroglandular tissue (extremely dense).

***Responses from the medical and patient advocacy communities***

Legislative proposals at the state and federal level have elicited varying responses from professional associations and patient advocates. For example, the American College of Radiology has issued a position statement indicating that while it "is not opposed to including breast parenchymal information in the lay summary, we urge strong consideration of the benefits, possible harms and unintended consequences of doing so." ACR urges caution in considering legislative proposals, and suggests that it might be valuable to review the experience of Connecticut, the first state to enact breast density reporting requirements, to evaluate the outcomes and effects of the law.

The advocacy organization "Are You DENSE?" has led grassroots efforts in support of state and federal breast density reporting legislation, and "Susan G. Komen for the Cure" affiliates have also advocated in support of state breast density reporting requirements.

Most recently, the *Journal of the American College of Radiology* published a special issue on imaging and screening in December 2013. The issue included two articles focusing on breast density – a summary of state laws and pending legislation, as well as a commentary from the Research Advocacy Network, a patient advocacy organization focused on advancing cancer research. The commentary addressed challenges in implementation of breast density legislation across states, calling for additional research and emphasizing the importance of patient-physician conversations on this issue. It identifies variability in breast density measurement as a particular challenge, noting that breast density is currently measured using various qualitative methods, and that the quantitative ACR classification system described above (which is identified most frequently in state legislation as the recommended or required measurement) relies on the expertise of individual radiologist readers, introducing a degree of variability to how results are interpreted.

***Breast density and cancer research***

Many characteristics may be associated with an increased risk for developing breast cancer, including mammographic breast density, history of atypical breast disease, a number of factors associated with reproduction, use of hormone replacement therapy, alcohol consumption, and body weight and physical activity, although the precise roles of these factors in cancer development is not fully understood. Research on risk prediction models that have entered many of these factors have generally found that breast density may contribute most to the prediction of risk. Breast density-associated risk is of most concern in women whose breast density persists into older age, even after menopause when breast density usually decreases. Dense breast tissue and age are both significant risk factors for breast cancer; therefore, postmenopausal women who have persistent breast density, which makes it harder to detect cancer through mammography, are at a higher risk for breast cancer. Additionally, research has shown that high breast density may not increase a woman's risk of dying from breast cancer.

While mammography remains the current standard of care for breast cancer screening, NCI continues to support research on a wide variety of other technologies that may in the future serve to complement or even replace conventional mammography. These methods aim to improve sensitivity and specificity compared with screening methods currently in clinical practice. For example, Cone Beam Computed Tomography (CBCT) is currently under development for diagnosis of breast abnormalities and has a higher resolution than mammography, particularly in women with dense breasts. Another relatively new technology, Digital Breast Tomosynthesis (DBT), has shown in some studies to result in a lower recall rate than conventional mammography for women with dense breasts and may allow for more accurate viewing of dense breast tissue. In addition, ultrasound is currently used, on an as-needed basis, in conjunction with mammography, particularly for women with radiologically dense breast tissue or a high risk for developing cancer. Most ultrasound technology research is focused on increasing the resolution of

the images produced and on developing computer-aided detection programs similar to those used for conventional mammography. NCI is supporting the development and validation of 3D ultrasound technology and examining its potential for screening both high-risk women and the general population. However, at this time there is not sufficient evidence to recommend that women with high breast density receive any of these new types of screening as part of their routine breast cancer screening.

## *III. Congressional Briefings and Visits*

NIH IC Directors Met with Rep. Joe Pitts (R-PA) (2/3/14): Various NIH IC Directors, including Dr. Harold Varmus, Director, NCI, participated in a roundtable discussion on the NIH campus with Congressman Joe Pitts (R-PA), Chair of the House Energy and Commerce Committee's Subcommittee on Health. Rep. Pitts and a number of his committee and personal staff toured the NIH Clinical Center and visited a National Heart Lung and Blood Institute lab.

NIH IC Directors Met with Sen. Richard Durbin (D-IL) (2/3/14): Various NIH IC Directors, including Dr. Harold Varmus, Director, NCI, participated in a roundtable discussion on the NIH campus with Senator Richard Durbin (D-IL), Assistant Majority Leader in the Senate, and member of the Senate Appropriations Committee, Labor-HHS Subcommittee. Sen. Durbin and his staff also visited labs at the National Heart Lung and Blood Institute and the National Institute of Neurological Disorders and Stroke.

Sen. Barbara Mikulski (D-MD) Tours NCI Lab and Hosts Press Event at NIH (2/24/14): Senator Barbara Mikulski (D-MD), Chair of the Senate Appropriations Committee, visited the NIH and hosted a press event focusing on the federal workforce and budget. During her visit she toured the lab of Dr. Marston Linehan, Chief of the Urologic Oncology Branch in NCI's Center for Cancer Research. Sen. Mikulski also met with a patient participating in a clinical trial led by Dr. Linehan's research team.

## *IV. Legislation of Interest*

The following resolutions and bills were selected for inclusion in this update due to anticipated interest among the CTAC membership. More detailed information about these bills and others are available on our website under Legislative Topics: http://legislative.cancer.gov/topics

### Selected Bills With Recent Activity or Interest (113th Congress)

Consolidated Appropriations Act of 2014 (H.R. 3547/**P.L. 113-67**)

- The act contains funding for all 12 Congressional Appropriation bills, including Labor-HHS, and provides a $1 billion increase for NIH over the post-sequester funding level of FY2013 ($29.9 billion for FY2014 for NIH, including $4.92 billion for NCI).
- The Labor-HHS section of the appropriations act includes language directing each agency or operating division with research and development expenditures in excess of $100,000,000 per year to develop a Federal research public access policy to provide for free online access to peer-reviewed manuscripts supported in whole or in part by federal funds, within 12 months of publication. This effectively directs the Centers for Disease Control, the Agency for Health Research and Quality, and the Department of Education to implement a public access policy similar to NIH.
- The bill also continues existing government-wide conference and travel restrictions, specifically, executive agencies must submit detailed reports to their Inspector Generals about conferences costing over $100,000, and the head of the agencies must also report within 15 days details about any conference costing more than $20,000. All travel and conference activities must continue to be in compliance with the guidance memo issued by the Office of Management and Budget on 5/11/12.
- The bill was originally introduced by Rep. Lamar Smith (R-TX) on 11/20/13, and was amended to reflect the omnibus appropriations proposal agreed to by House and Senate Appropriators on 1/15/14. The House

passed the act by a vote of 359-67 on 1/15/14, and the Senate passed the act by a vote of 72-26 on 1/16/14, and **the President signed the bill into law on 1/17/14**.

PEPFAR Stewardship and Oversight Act of 2013 (S.1545/H.R.3177; **P.L. 113-56)**

- The bill would extend authorities related to global HIV/AIDS and promote oversight of the United States Programs. The reported version of the bill would add to the requirement for an annual report a description, globally and by country, of specific efforts to address co-infections and comorbidities of HIV/AIDS, including the number and percent of people in HIV care or treated who started tuberculosis treatment; and the number and percentage of eligible HIV positive patients starting isoniazid preventative therapy.
- The Senate Committee Report indicates that the description of efforts to limit co-morbidities should include a discussion on AIDS-related cancers, including trends with respect to cervical cancer, and efforts to address such cancers.
- The Act was introduced by Sen. Robert Menendez (D-NJ) on 9/24/13 and was reported favorably out of the Senate Committee on Foreign Relations on October 2, 2013. The Act was introduced in the House by Rep. Eliot Engel on September 25, 2013, and was referred to the House Committee on Foreign Affairs. The Act passed the Senate on 11/18/13 and the House on 11/19/13, and the **President signed it into law on 12/2/13.**

Drug Quality and Security Act (H.R. 3204; **P.L. 113-54**)

- The bill aims to clarify laws related to human drug compounding, and to strengthen the drug supply chain.
- Regarding drug compounding, the bill:
    - Distinguishes compounders engaged in traditional pharmacy practice from those making large volumes of compounded drugs without individual prescriptions.
    - Allows compounders who prefer to practice outside the scope of traditional pharmacy practice to register as outsourcing facilities. Compounders who choose to remain traditional pharmacies will continue to be primarily regulated by State Boards of Pharmacy as they are in current law.
    - Defines the FDA's role in oversight of outsourcing facilities, with these facilities subject to FDA oversight in much the same way as traditional manufacturers.
    - Gives providers and patients the option of purchasing products from outsourcing facilities that comply with FDA quality standards.
    - Requires the FDA to list FDA-regulated outsourcing facilities on its website, requires detailed labeling on compounded drugs, and prohibits false and misleading advertising.
    - Clarifies current federal law regarding pharmacy compounding by resolving the patchwork of current federal regulation and applying a uniform standard nationwide.
- Regarding a "track and trace" system for prescription drugs, the bill:
    - Replaces the current state product tracing laws with a uniform standard, in an effort to implement electronic, interoperable unit-level product tracing throughout the country over a ten year implementation period.
    - Requires, over seven years, that the major sectors of the pharmaceutical supply chain share and track key information about each drug's distribution history. Within ten years, supply chain stakeholders will be required to participate in electronic, interoperable product tracing.
    - Strengthens licensure requirements for wholesale distributors and third-party logistics providers. In addition, the bill would require the FDA to keep a database of wholesalers that will be available to the public through the FDA's website.
    - Establishes nationwide drug serial numbers, to be implemented by four years after the date of enactment.
- The Act was introduced by Rep. Fred Upton (R-MI), Chairman of the House Energy and Commerce Committee, on 9/28/13 and passed in the House by a voice vote on 9/28/13. The Senate passed H.R. 3204 on 11/18/13 and the **President signed the bill into law on 11/27/13.**

Prematurity Research Expansion and Education for Mothers who deliver Infants Early (PREEMIE) Reauthorization

Act (S. 252; **P.L. 113-55**)

While the primary bill language of the PREEMIE Reauthorization Act (Title I) does not include provisions specific to NIH, two other bills of interest, the Pediatric Research Network Act and the CHIMP Act Amendments of 2013, were added to the PREEMIE Reauthorization Act as amendments. The House passed the amended bill on 11/12/13, and the Senate passed the amended bill on 11/14/13. **The President signed the bill into law on 11/27/13.**

- The Pediatric Research Network Act (H.R. 225/S.424) was added to the PREEMIE Reauthorization Act as an amendment, and is included as Title II of the bill. The amended title is a modified version of the original bill, and indicates that the NIH Director may establish consortia and recognize existing NICHD pediatric research consortia, centers, and networks. Additionally, the final bill language no longer calls for a data coordinating center, and no longer mentions a specific number of centers or specific diseases (the bill mentions pediatric rare diseases and those related to birth defects, compared with previous references to spinal muscular atrophy, Duchenne muscular dystrophy, Down syndrome, and Fragile X).
- The CHIMP Act Amendments Act of 2013 (S.1561) was added to the PREEMIE Reauthorization Act as an amendment, and is included as Title III of the bill. The bill amends provisions the Public Health Service Act relating to the federal sanctuary system for surplus chimpanzees. Specifically, the bill provides the authority for the NIH to continue to fund the sanctuary system beyond the current $30 million cap if the Secretary of HHS determines that it would enable the NIH to operate more efficiently and economically by decreasing the overall federal cost of supporting and maintaining chimpanzees from FY 2014 through FY 2023. In addition, the bill amends a provision so that the Secretary, in consultation with the federal sanctuary Board of Directors, determines if another facility meets the standards of care in the NIH regulations instead of the Board of Directors solely making that determination.

Gabriella Miller Kids First Research Act (H.R.2019)

- This bill amends the Internal Revenue Code to eliminate taxpayer financing of political party conventions and to reprogram savings to provide for a 10-year pediatric research initiative administered through the National Institutes of Health Common Fund.
    - The bill calls for funds for political conventions currently in accounts maintained by national committees of political parties to be transferred to a fund in the Treasury to be known as the "10-Year Pediatric Research Initiative Fund." Funds would then be made available to NIH in such amounts as are provided in advance in appropriation Acts.
    - The bill authorizes appropriations to the NIH Common Fund, to be made out of the 10-Year Pediatric Research Initiative Fund, of $12.6 million per year for each fiscal year 2014-2023.
- H.R. 2019 was introduced by Rep. Gregg Harper on 5/16/13, as the Kids First Research Act, and was renamed in honor of Gabriella Miller, a 10-year-old girl from Virginia who passed away in October 2013 due to a pediatric brain tumor, Diffuse Intrinsic Pontine Glioma. This bill is related to H.R. 1724, an earlier version of the bill, also introduced by Rep. Harper (4/25/13).
- H.R. 2019 was referred to the House Energy and Commerce Committee, Subcommittee on Health, as well as the House Committees on Administration, and Ways and Means. The bill did not proceed through mark up and was not passed out of committee. **On 12/11/13, the House passed the bill under suspension of the rules, in a vote of 295-103.**
- Current Status: The bill was placed on the Senate Legislative Calendar on 1/6/14. Reports indicate that the Senate does not plan to consider the bill.

Cancer Treatment Parity Act of 2013/Cancer Drug Coverage Parity Act of 2013 (S.1879/H.R. 1801)

- The bill aims to require health insurers to provide for coverage of oral anticancer drugs on terms no less favorable than the coverage provided for anticancer medications administered by a health care provider.
    - For the Patient-administered medication, the provider can charge annual deductibles, coinsurance, copayments, as long as they do not exceed payments for anticancer medications administered by a health care provider under the plan or coverage for the same purpose.
    - The provider cannot increase in out-of-pocket costs of anticancer medications; reclassify anticancer medications benefits; or apply more restrictive limitations on prescribed oral, intravenous or injected anticancer medications.

- S. 1879 was introduced on 12/19/13 by Sen. Al Franken (D-MN) and was referred to the Committee on Health, Education, Labor, and Pensions. H.R. 1801 was introduced on 4/26/13 by Rep. Brian Higgins (D-NY), and was referred to the House Committees on Energy and Commerce (Subcommittee on Health), Ways and Means, and Education and the Workforce (Subcommittee on Health, Education, Labor, and Pensions).
- The bills include nearly the same proposals, however the Senate bill calls for provisions to apply to health plans for plan years beginning on or after January 1, 2015, whereas the House bill would apply to health plans beginning on or after January 1, 2014.
- To date H.R. 1801 has 67 cosponsors, and S. 1879 has one cosponsor, Sen. Mark Kirk (R-IL).

*Additional Information*: Rep. Higgins introduced similar bills in the 112th and 111th Congresses and they did not move out of committee. S. 1879 is the first bill in the Senate to address this issue. To date, 26 states and the District of Columbia have enacted oral chemotherapy access laws , and legislative proposals have been introduced in an additional 12 states.

Breast Density and Mammography Reporting Act of 2013 (H.R. 3404):

- The bill would amend the Mammography Quality Standards Act (MSQA) of 1992 to require mammography results to include the patient's relative breast density, and for that information to be reported to patients in their mammography results summary.
- Specifically, the summary shall convey to the patient his or her risk of developing breast cancer associated with below, above, and average levels of breast density. The summary shall also include language communicating that individuals with more dense breasts may benefit from supplemental screening tests and should talk with their physicians about any questions or concerns regarding the summary.
- The proposal includes a clause specifying that if passed, the federal bill would not preempt any state requirements regarding breast density reporting.
- The Act was introduced by Rep. Rosa DeLauro (D-CT), along with Rep. Steve Israel (D-NY), on 10/30/13 and was referred to the Committee on Energy and Commerce. To date the bill has 30 cosponsors.

*Additional Information*: Reps. DeLauro and Israel introduced a similar bill in the 112th Congress and it did not move out of committee (DeLauro also co-sponsored a similar proposal in the 111th Congress). Rep. DeLauro's announcement notes that Sen. Dianne Feinstein (D-CA) plans to introduce a companion bill in the Senate – it has not been introduced to date. Additionally, independent of this legislative proposal, the FDA had scheduled a notice of proposed rule making for a breast density reporting amendment to the MSQA for December 2013, but has yet to release any additional information.

## Selected New Bills (113th Congress)

The Protecting Children from Electronic Cigarette Advertising Act of 2014 (S. 2047)

- The Act aims to prohibit the marketing of e-cigarettes to children (under age 18), and to authorize the Federal Trade Commission (FTC) to enforce this prohibition.
- The Act permits the FTC to determine what constitutes marketing of e-cigarettes to children. The bill indicates that a violation of the prohibition would be treated as a violation of a rule defining an unfair or deceptive act or practice as described in the Federal Trade Commission Act. The FTC would also have the authority to promulgate additional rules and standards to carry out the provisions of the Act.
- The proposal would allow the FTC to work with state attorneys general to enforce the ban and to seek civil penalties. It also includes a provision indicating that the Act would not supersede any provisions of state law, except in the case of any inconsistencies between state and federal provisions.
- The bill specifies that it shall not be construed to limit or diminish the authority of the Food and Drug Administration to regulate the marketing of e-cigarettes, including to children.
- The bill was introduced by Senator Barbara Boxer (D-CA), along with colleagues Sens. Tom Harkin (D-IA), Dick Durbin (D-IL), Richard Blumenthal (D-CT), and Edward J. Markey (D-MA), on 2/26/14 and was referred to the Committee on Commerce, Science, and Transportation.

Better Care, Lower Cost Act (H.R. 3890/S. 1932)

- The bill aims to establish a Medicare "Better Care Program" to provide integrated care for Medicare beneficiaries with chronic conditions.
- Rep. Erik Paulsen (R-MN) introduced H.R. 3890, and Sen. Ron Wyden (D-OR) introduced S. 1932 on 1/15/14. The bill was referred to the House Committees on Energy and Commerce, and Ways and Means, and the Senate Committee on Finance.

Protecting Consumer Access to Generic Drugs Act of 2013 (H.R. 3709), Preserve Access to Affordable Generics Act (S. 214)

- The bills aim to prohibit the practice known as "pay-for-delay," in which brand name drug manufacturers offer patent settlements that pay generic drug manufacturers to delay bringing lower-cost generics to market.
- Among other previsions, both bills propose to amend the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 to require a brand name manufacturer and generic manufacturer to submit to the FTC any other agreements the parties enter into within 30 days of entering into an agreement related to the manufacturing, marketing, or sale of the brand name or generic drug or the exclusivity period.
- H.R. 3709 was introduced on 12/11/13 by Rep. Bobby Rush (D-IL) and was referred to the House Committees on Energy and Commerce, and the Judiciary (Subcommittees on Regulatory Reform, Commercial And Antitrust Law; and on Courts, Intellectual Property and the Internet). S. 214 was introduced by Sen. Amy Klobuchar (D-MN) on 2/4/13 and was referred to the Committee on the Judiciary Subcommittee on Antitrust, Competition Policy and Consumer Rights. The Subcommittee held a hearing on this issue on 7/23/13, "Pay-for-Delay Deals: Limiting Competition and Costing Consumers."

Breast Cancer Awareness Commemorative Coin Act of 2013 (H.R. 3680)

- The bill aims to establish a Breast Cancer Awareness Commemorative Coin by requiring the Secretary of the Treasury to mint not more than 500,000 $1 silver coins.
- The coins would be sold for a total of $11 each, the $1 face value plus a $10 surcharge. Once the cost of design and issuance of the coins is covered, half of the surcharge would be paid to the Breast Cancer Research Foundation, and half to Susan G. Komen for the Cure, to further research funded by the organizations.
- H.R. 3680 was introduced on 12/9/13 by Rep. Carolyn Maloney (D-NY) and was referred to the Committee on Financial Services.

## Selected Recent Resolutions (113th Congress)

*This section highlights resolutions introduced to raise awareness about specific diseases or issues. It is important to note that resolutions are different than bills, in that they are used to express the sentiment of one chamber (House or Senate) on an issue. As such, resolutions do no not require concurrence of the other chamber or approval by the president, and they do not have the force of law.*

### Introduced

Rare Disease Day (H.Res. 493)

- A resolution expressing support for designating February 28, 2014 as Rare Disease Day. Childhood cancers are recognized among rare diseases listed in the resolution.
- H.Res. 493 was introduced by Rep. Andre Carson (D-IN) and colleagues (including Reps. Leonard Lance, R-NJ, and Joseph Crowley, D-NY, co-chairs of the Rare Disease Caucus) on 2/27/14 and was referred to the Committee on Energy and Commerce.

National Cancer Prevention Day (H. Res. 473)

- A resolution expressing support for designating February 4, 2014 as National Cancer Prevention Day.

- H. Res. 473 was introduced by Rep. Steve Israel (D-NY) on 2/4/14 and was referred to the Committee on Energy and Commerce.

Recognizing the 50th Anniversary of the "Smoking and Health: Report of the Advisory Committee to the Surgeon General of the United States" (S.Res. 330)

- This resolution recognizes the 50th anniversary of the "Smoking and Health: Report of the Advisory Committee to the Surgeon General of the United States" and the significant progress in reducing the public health burden of tobacco use, as well as supporting an end to tobacco-related death and disease.
- S. Res. 330 was introduced by Sen. Richard Blumenthal (D-CT) on 1/13/14 and was referred to the Committee on Health, Education, Labor, and Pensions.

**Passed**

Rare Disease Day (S.Res. 368)

- A resolution expressing support for designating February 28, 2014 as Rare Disease Day. Childhood cancers are recognized among rare diseases listed in the resolution.
- H.Res. 493 was introduced by Sen. Sherrod Brown (D-OH) and was passed in the Senate by unanimous consent on 2/27/14.

National Science and Technology Week (S. Res. 329)

- This resolution expresses support for the goals and ideals of the biennial USA Science and Engineering Festival in Washington, D.C. and designates April 21 – April 27, 2014 as "National Science and Technology Week".
- S. Res. 329 was introduced by Sen. Chris Coons (D-DE) on 1/7/14 and was adopted by unanimous consent.

National Asbestos Awareness Week (S. Res. 336)

- This resolution designates the first week of April 2014 as "National Asbestos Awareness Week".
- S. Res. 336 was introduced by Sen. Max Baucus on 1/16/14 and was adopted by unanimous consent.

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# Budget Briefing for the NCI Clinical Trials Advisory Committee

John Czajkowski
NCI Deputy Director of Management
Patrick McGarey
Director, NCI Office of Budget & Finance

March 12, 2014

National Cancer Institute

# NCI FY 2014 & FY 2015 Budgets

## NCI FY 2014 Budget Summary

- $ 4.9B = NCI FY 2014 appropriation
- +$134M = NCI FY 2014 dollars, vs. FY 2013 (+2.8%)
- No NEW FY 2014 sequestration, *but* –
- FY 2014 budget only restores 53% of FY13 sequestration

## NCI FY 2015 Budget Summary

- $ 4.9B = NCI FY 2015 budget request
- +$ 7.9M = NCI FY 2015 dollars, vs. FY 2014 (+0.2%)

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# NCI Higher FY 2014 Mandatory Costs

$134M = NCI FY 2014 budget increase (+2.8%)

$ 45M = Estimate of higher NCI mandatory costs

$ 89M = Estimated balance for NCI programs (+1.9%)

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# The Big Picture – FY 2014 and beyond

## Bipartisan Budget Act of 2013 (BBA)

- Goals: Avoid another sequester, Restore some FY 2013 sequestration, Normalize FY 2014-15 budget process
- FY 2014 BBA: +$22.4B compared to FY 2013
- FY 2015 BBA: +$ 0.6B compared to FY 2014
- FY 2014 vs. FY 2015 BBA: +0.1%, i.e., essentially flat

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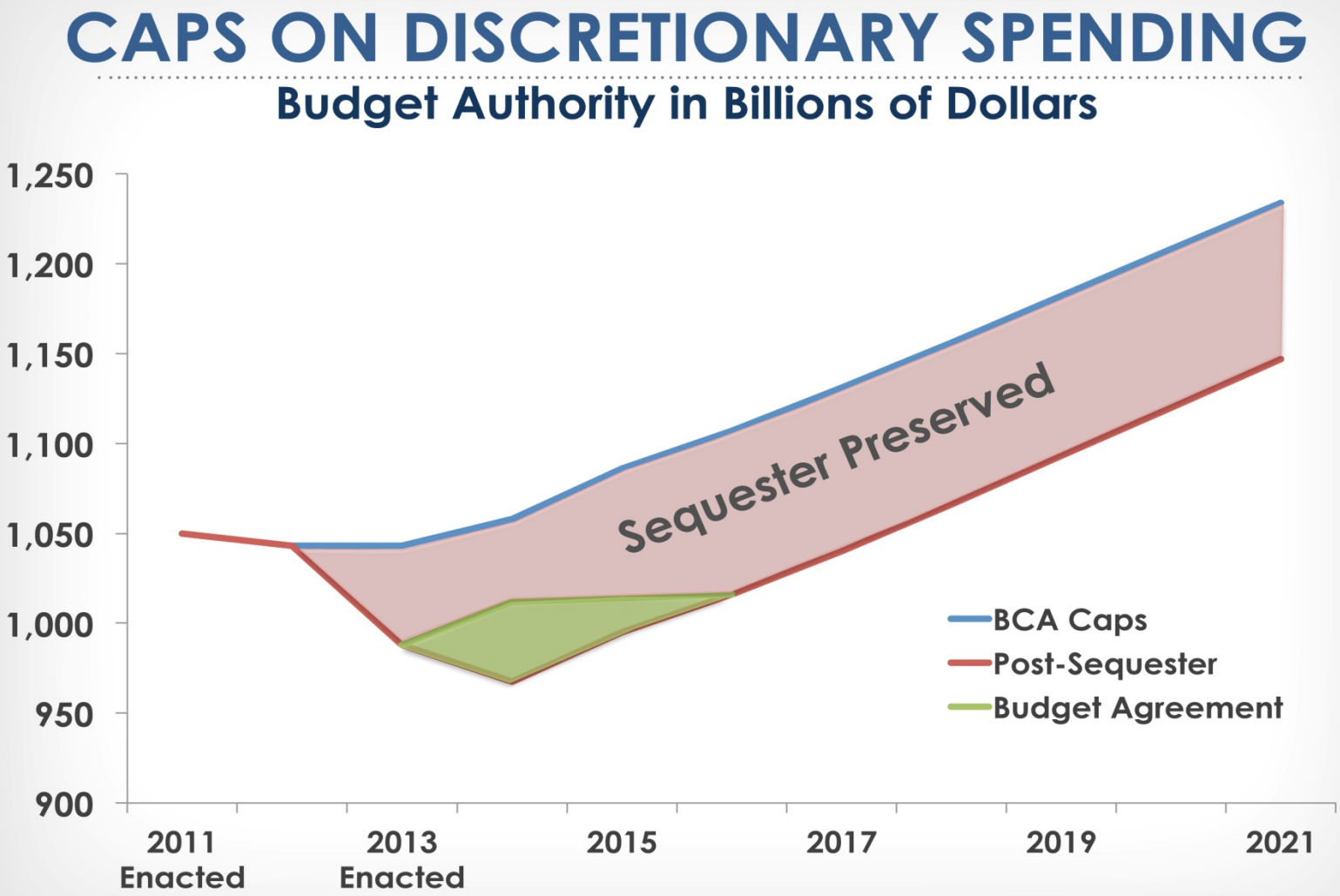
# Budget Caps, FY 2014 and Beyond




Source: CBO, HBC

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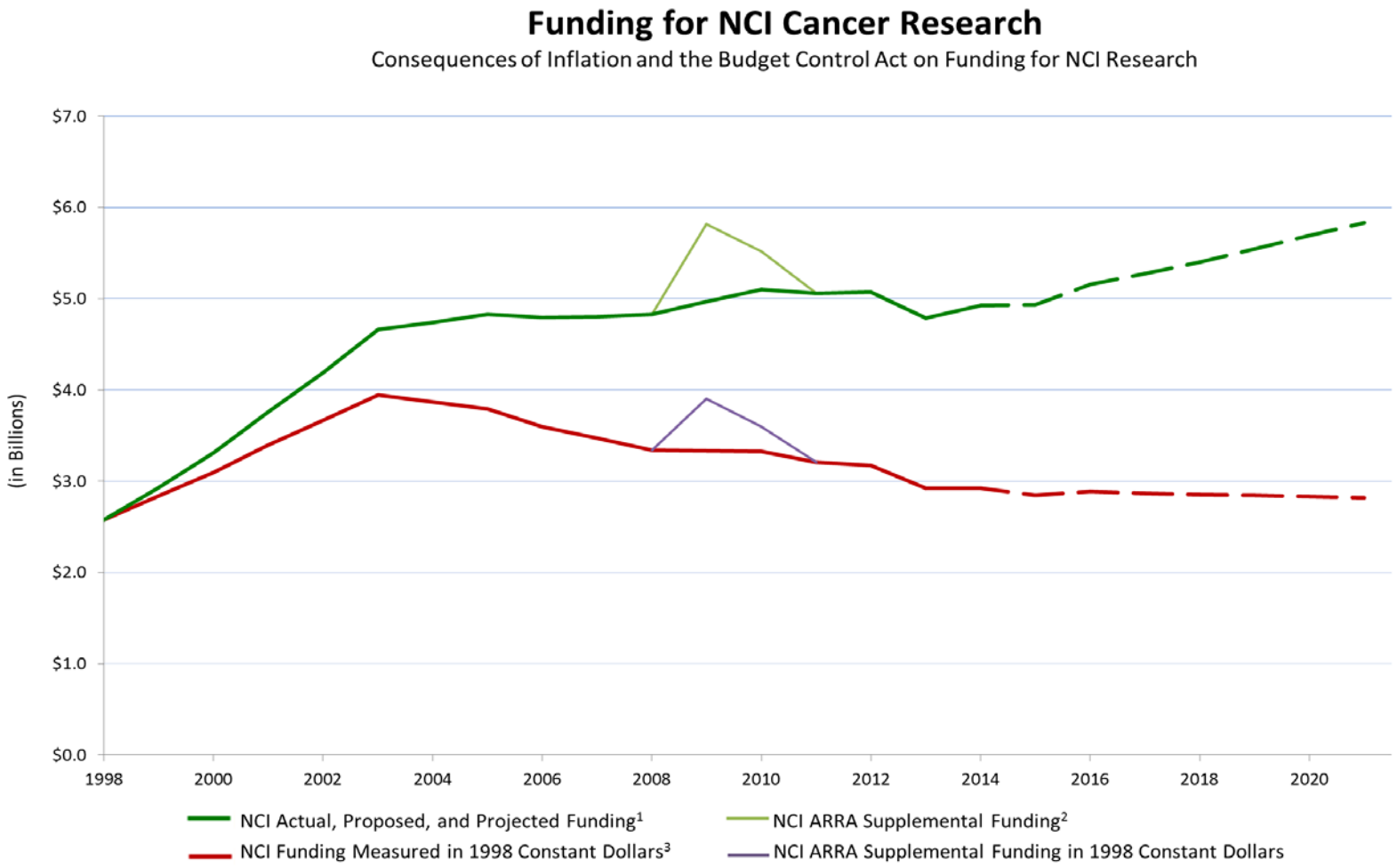
# Cancer Research Funding, March 2014 *Update*




[1]Reflects NCI actual appropriations through FY 2014, NCI proposed budget for FY 2015, and projected budgets for FY 2016 and beyond, consistent with the discretionary spending limits in the Budget Control Act of 2011, as amended by the Bipartisan Budget Act of 2013.
[2]FY 2009 includes $846 million from the American Recovery and Reinvestment Act (ARRA) of 2009. FY 2010 includes $411 million from ARRA.
[3]Reflects the impact of inflation (using the Biodmedical Research and Development Price Index ) on NCI actual, proposed, and projected funding.

2/14/2014

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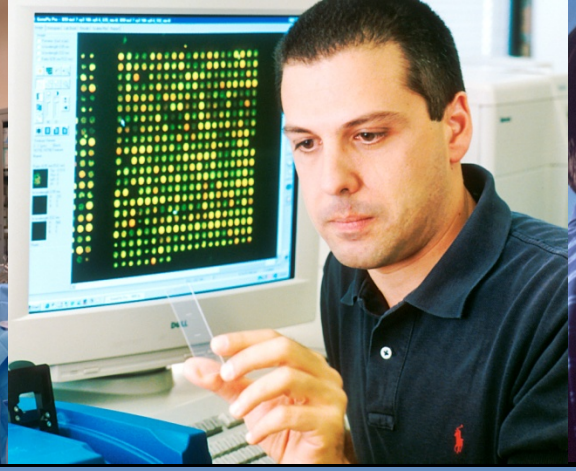
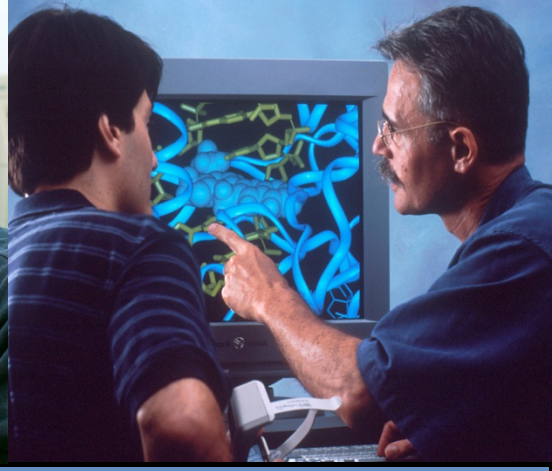
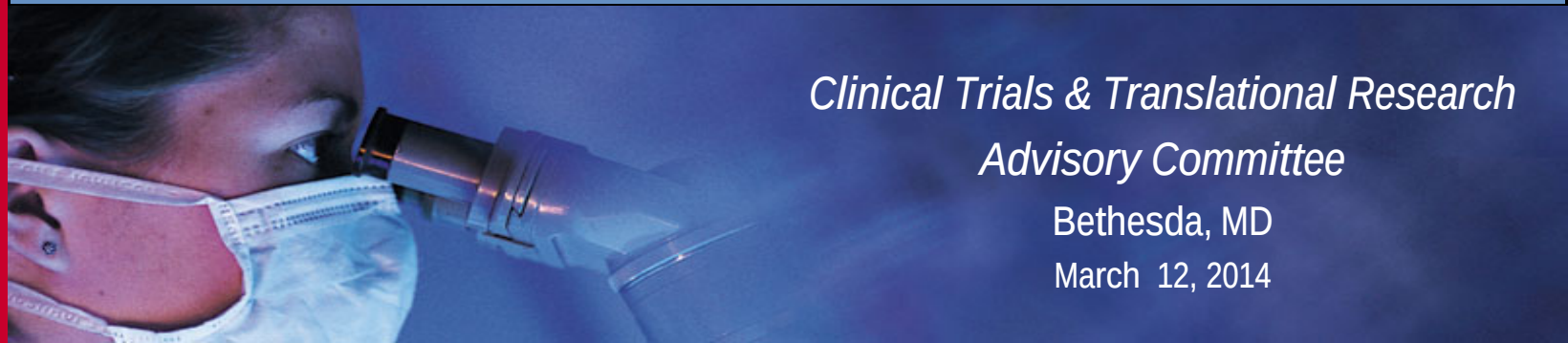



# *NCI Clinical Trials Reporting Policy*

James H. Doroshow, M.D.
Deputy Director for Clinical and Translational Research
National Cancer Institute



*Clinical Trials & Translational Research Advisory Committee*

Bethesda, MD

March 12, 2014

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# NCI Clinical Trials Reporting Policy: Premise

- Fundamental premise (ample precedent) that results of all NIH-funded research must be shared to contribute to the general body of science, and ultimately, to the public health
- Grantee/contractee institutions are expected to make the results of their activities available to the research community and to the public at large

*Problem*:

--Long lag time to publication of results, even for positive studies
--Negative studies or incomplete studies are frequently never published due to lack of journal and/or investigator interest
--Limits in FDAAA (FDA Amendment Act) legislation leave out certain studies from the requirement to publish results in clinicaltrials.gov

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# FDAAA Reporting Requirements

- Registration required for:
  - Phase 2-4 trials
  - Drug, device, or biologic
  - IND/IDE or one site in U.S.
  - Includes IND exempt studies
- Results reporting required, in general, within 12 months of the *earlier* of estimated/actual primary completion date
- Results reporting required for studies of **approved** products (or products that become approved)
- Enforcement Provisions, including
  - Withholding of NIH grant funding
  - Up to $10,000/day fines

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# FDAAA: Gaps in Results Reporting

- Phase 0 – 1 trials
- Results required ONLY for studies of APPROVED PRODUCTS
- Some surgical trials are not covered as only devices under FDA jurisdiction are subject to FDAAA
- Proposed NCI Policy applies to diagnostic, preventive, behavioral and supportive care studies, some of which may not use agents/devices under FDA jurisdiction

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# 100 Months after Completion: Two Thirds of NIH-Supported Clinical Trials Published

BMJ

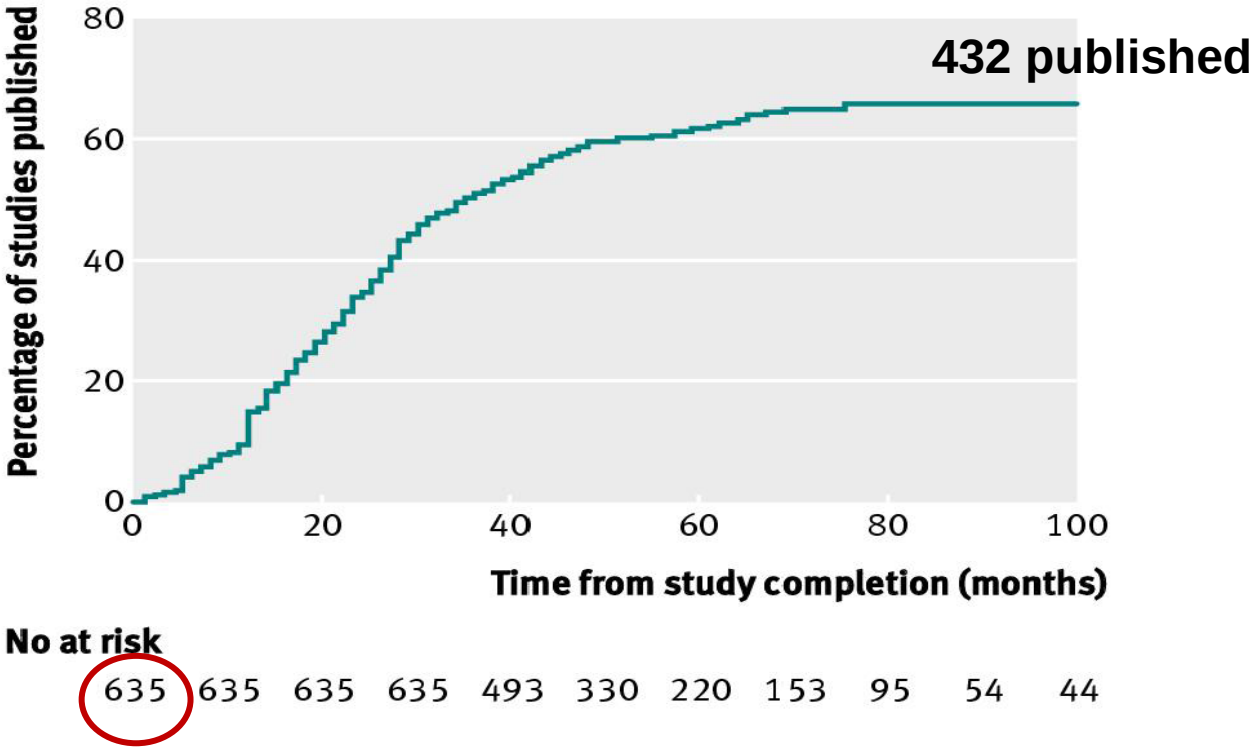
BMJ 2011;344:d7292 doi: 10.1136/bmj.d7292 (Published 3 January 2012)



BMJ 2011;344:d7292 doi

RESEARCH

**Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis**




**432 published**

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# Take Home Messages

- Fewer than half of NIH funded trials registered after September 2005 within ClinicalTrials.gov and completed by December 2008 were published in a peer reviewed biomedical journal indexed by Medline **within 30 months** of trial completion
- After a median of 51 months after study completion, a third of NIH-funded trials remained unpublished

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# Why Publish Incomplete Studies?

- Studies stopped for toxicity, poor accrual, or other reasons may still prove valuable to other researchers and patients, even if only to avoid duplication, wasted effort, or to improve knowledge of side effects

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# Proposed NCI Clinical Trials Reporting Policy

*Principle*

Rapid, public access to final trial results for investigators, clinicians, and patients is particularly important for cancer research trials because the results of such research have the potential to directly affect patient care

## Covered Trials

- All NCI-supported interventional clinical trials whether extra-mural or intramural, across all disciplines and trial phases, whether completed or not

## Excluded Studies

- Observational studies and any interventional clinical trial in which no subjects are enrolled

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# NCI-Supported: Definition

- All trials financially supported – whether in whole or in part – by NCI. In the case of NCI-designated Cancer Centers, the Policy *does not apply to the subset of trials which, although they may benefit from core support from a Center grant, are funded privately and in which the data from the trial belong to the private funder*. However, NCI-support does include those Cancer Center trials, funded at least in part by NCI, where the data resides with the academic investigator

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# When Must Trials Be Reported?

- NCI will align its policy with clinicaltrials.gov to avoid confusion
- Results are expected to be published within twelve (12) months of a trial's Primary Completion Date
  - Primary Completion Date: date final subject had final collection of data for the primary outcome. Data from incomplete trials must also be reported within 12 months of the date the last subject had data collected even if the trial does not achieve its primary aim

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# What Must Be Reported? (all results reported by arm)

- Participant Flow
  - Number Started
  - Number Completed
- Baseline Characteristics
  - Number of Participants
  - Age and Gender
- Outcome Measures
  - Summary results for primary and secondary outcome measures
  - Statistical analyses, as appropriate
- Adverse Events
  - “Serious” and “Other” by Organ System

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# Where Must Trials Be Reported?

- Final Trial Results must be reported in a publicly accessibly manner
  - Peer-reviewed scientific journal (in print or on-line)
  - On-line registration and reporting with a publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov.
  - Journals willing to publish in abbreviated format, esp. negative or incomplete trials with less rigorous peer review than full-length articles
- NCI not mandating a particular mechanism; either journal publication or registry submission acceptable; the goal must be public accessibility
  - If publication is selected, then the NIH Public Access Policy (http://publicaccess.nih.gov/) requires submission to PubMed upon acceptance; public availability no later than 12 mos. after publication

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# Compliance & Public Input

- Term of award for grants or deliverable for contracts
- NCI Program/Project Officers will enforce this policy at time of final progress report or an alternative date for larger grants to trial networks
- Non-compliance may result in funds recovery or withholding future support
- Proposed policy published in NIH Guide: NOT-CA-14-005
  - Comments were uniformly supportive
- NIH Guide Notice was shared with CTEP clinical investigator distribution list
  - Most comments were positive although one respondent was concerned about the added workload

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# Next Steps

- Input from CTAC
- Presentation to joint NCAB-BSA meeting in June 2014
- Implementation shortly thereafter

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# Report of the Specialized Programs of Research Excellence (SPORE) Program Evaluation Working Group of the National Cancer Institute Clinical Trials and Translational Research Advisory Committee

Nancy Davidson, M.D.
Working Group Chair

March 12, 2014

CTAC Meeting

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# Working Group Background

- SPORE Program Announcement – approval spring 2014 for January 2015 submissions
- Formal evaluation conducted by the IDA Science and Technology Policy Institute (STPI) as part of standard procedure for renewing Program Announcements for large programs
- NCI Clinical Trials and Translational Research Advisory Committee (CTAC) voted to form a small Working Group to provide advice on the value of the SPORE program and make a recommendation as to its future

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# Working Group Members

- Nancy Davidson (Chair)
- James Abbruzzese
- Gerold Bepler
- Deborah Collyar
- James Griffin
- Scott Lippman
- David Mankoff
- Chris Takimoto
- Louis Weiner
- George Wilding
- Cheryl Willman
- Jim Doroshow – NCI Liaison
- Jennifer Hayes – Exec. Sec.

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# Working Group Charge and Deliverable

- Charge: Provide expert input on the value of the SPORE program and make one of three recommendations
  - The SPORE Program Announcement should be re-issued with the program continuing in its current configuration (perhaps with minor modifications); or
  - The NCI should consider some substantive changes to the SPORE Program; or
  - More information is needed for the Working Group to determine if the SPORE Program should continue in its current configuration or should be substantively changed
- Deliverable: Report to CTAC responsive to the charge

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# Reference Materials Provided

- STPI 2013 SPORE Evaluation Report
  - STPI synthesis of distinctive contributions of the SPORE Program based on Report information
  - Consolidated information on SPORE Major Advances from Report
  - Consolidated data on success in achieving a “human endpoint” from Report
- Updated SPORE Funding Opportunity Announcement
- P01 Funding Opportunity Announcement

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# Conclusions on Value of SPORE Program

- Overarching conclusions
  - It remains critical for the NCI to have a funding program focused exclusively on translational research
  - The SPORE program represents a longstanding effort that has been successful in filling this niche and in which the NCI should take pride
- Transformed and revolutionized translational research
  - Creates focus on diseases
  - Promotes integration of basic science with clinical research
- Builds foundation for research in the service of patients
  - Infrastructure
  - Training individual scientists
  - Producing multidisciplinary teams
- Working Group recommends increasing program's emphasis on impact of SPORE research on patient care/clinical practice
  - Emphasis on capacity-building remains important, especially for new SPORE awards

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# Key Benefits of SPORE Program

- Catalyzes translational research at individual institutions and nationwide
  - Fosters culture of team science
  - Launches translational research careers
  - Serves as template for achieving a critical mass of translational scientists
  - Pioneered engagement of advocates in translational and clinical research
- Enhances quality of translational research at non-SPORE institutions
  - Institutions build translational capacity in order to be competitive for a SPORE award
  - SPORE participants continue in translational research after moving to a new institution
- Facilitates leveraging of funds from other sources, especially industry
  - Validation represented by a SPORE award facilitates obtaining funds from other sources
  - Especially important for funding early and late stage human testing
- Promotes creative “bottom-up” investigator-initiated translational research
  - Awardees free to choose translational goals and approaches
  - Scientific and intellectual flexibility essential to success of program
- Builds and sustains a strong translational research infrastructure
  - Biospecimen/pathology core essential to translational success
  - Builds strong individual repositories and enabling tissue banking infrastructure

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# Contributions of SPORE Program

- Overall output of SPORE program deemed exceptional
  - Speeds translational research
  - Leads to interventions and biomarkers introduced into clinical practice
- SPORE Major Advances from STPI Evaluation Report
  - Substantial, material contributions to oncology research and practice
  - Some variability in importance across disease sites
  - Therapeutic and clinical contributions sometimes more substantial than those in prevention and population science
- Other contributions
  - Leveraging substantial industry support for clinical trials of SPORE-derived interventions and biomarkers
  - Serving as nucleus for coalescing foundation-funded consortia, particularly for support of early phase trials

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# Potential NCI Actions to Enhance SPORE Program Effectiveness

- Facilitate even greater coordination with NCI clinical trials programs
  - NCI Experimental Therapeutics program (NExT)
  - Cancer Centers
  - N01/U01 early-phase trial programs
  - National Clinical Trials Network Groups
- Facilitate even greater interactions with targeted basic research initiatives
  - The Cancer Genome Atlas
  - Physical Science Oncology Centers
- Further encourage joint funding by third parties
  - Opportunities exist (e.g., NIH Foundation)
  - Promote joint funding by industry and foundations

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# SPORE Program Requirements Conclusions and Recommendations (1)

- Organizing themes for SPORE awards
  - Support for current focus on organ-specific cancers and "groups of highly related cancers"
  - Modernize, expand and make more explicit language describing "groups of highly related cancers" and provide examples (e.g., GI cancers, pediatric cancers, oncogenic signaling pathway activation, virally-induced malignancies)
- Solicitation of SPOREs in response to NCI research priorities
  - Support for promoting and including alignment in review criteria
  - Opposed to "set-aside" funding for such SPOREs
- Reaching a "human endpoint" in 5 years
  - Strong support for requirement
- Early detection, prevention, or population science project
  - Majority recommended extending requirement to all SPOREs
  - Minority votes for no requirement at all or requirement only for selected organ sites

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# SPORE Program Requirements Conclusions and Recommendations (2)

- Requirement to build collaborations
  - Strongly supported
  - Praised SPORE success in collaborations
  - PA language on collaborations should be made more explicit
- Limitations on SPOREs per organ site
  - No support for setting arbitrary limits on the number of SPOREs in each organ site
  - Distribution of SPORE awards across organ sites should be driven by the quality of the science
- Term limits for SPORE awards
  - No support for a limit to the number of consecutive 5-year renewals
  - Reasonable number of new SPORE awards in recent years
  - 50% of projects in SPORE renewal awards are new

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# SPORE Program Features Conclusions and Recommendations

- Flexibility Option
  - Strongly endorsed
  - Praised as unique and valuable feature of SPORE program
- Biospecimen/Pathology Core
  - Unanimously endorsed
  - Critical for SPORE success and a great benefit to host institutions
  - Encouraged greater integration with and leveraging of institutional resources
- Developmental Research and Career Development Programs
  - Valuable features that should be maintained
  - Funds should be combined to a single fund
  - Flexibility to fund best candidate projects independent of DRP/CDP character

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# Future of the SPORE Program

*Unanimous Recommendation*

*SPORE Program Announcement should be re-issued and the program should continue in its current configuration with minor modifications*

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# NCI Cooperative Group Phase 3 Treatment Trials

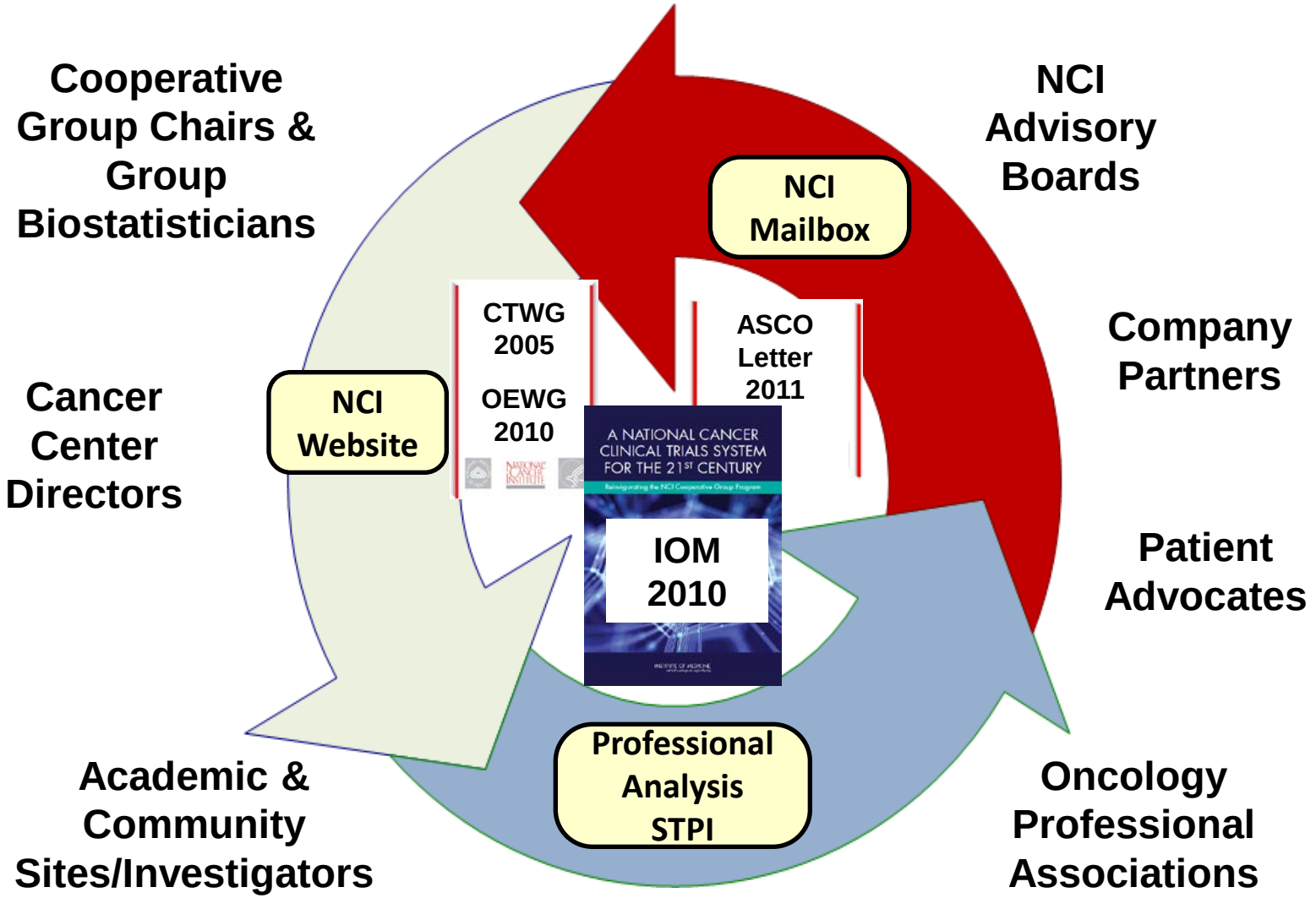
## Historical Accrual Experience of Trials Activated 2000-2010

## and

## Preliminary Assessment of the DCTD/CTEP Slow Accruing Guidelines for Phase 3 Treatment Trials

Ed Korn, PhD, DCTD Biometric Research Branch, NCI
Meg Mooney, MD, DCTD, CTEP, Clinical Investigations Branch, NCI

# Extensive Review & Stakeholder Input on Revising NCI's Late-Phase Clinical Trials System



# Consensus Goals for a Transformed System

- Improve speed & efficiency of development & conduct of trials
- Incorporate innovative science and trial design
- Improve trial prioritization, selection, support, & completion
- Ensure participation of patients & physicians in system

# Consensus Goals for a Transformed System

- Improve speed & efficiency of development & conduct of trials
  - Instituted Operational Efficiency Working Group Timelines for Protocol Development with Results Previously Reported

    *Implementation of Timeline Reforms Speeds Initiation of National Cancer Institute–Sponsored Trials, Abrams JS et al, J Natl Cancer Inst (2013) 105 (13): 954-959*

  - Now Concentrating on Activities to Support Ensuring Accrual Goals to Trials are Reached Once Trial is Opened

    *Accrual Experience of NCI Cooperative Group Phase 3 Trials Activated 2000 to 2007, Korn EL et al, J Clin Oncol (2010) 28:5197-5201*

    --------> *Updated Analysis*

# Analysis of Accrual for NCI Cooperative Group Phase 3 Trials Activated 2000-2010

N=254 Trials (activated 2000-2010 )

| | |
|---|---|
| Accrual not over | 51 |
| ≥ 90% accrued so far | 41 |
| <90% accrued so far | 10 |
| Accrual over | 203 |
| ≥ 90% accrued | 119 |
| <90% accrued | 84 |

Reasons<90%

| | |
|---|---|
| interim monitoring | 18 |
| external information | 11 |
| drug supply issues | 2 |
| unacceptable toxicity | 3 |
| achieved sufficient number of events | 1 |
| inadequate accrual rate | 53 |

# Background on Analysis

N=254 Trials (activated 2000-2010)

## Projections -- All trials

21.1% of trials will end with <90% accrual because of inadequate accrual rates

1.6% of patients will be on trials that end with <90% accrual because of inadequate accrual rates

## Projections -- Non-pediatric trials

24.4% of trials will end with <90% accrual because of inadequate accrual rates

1.8% of patients will be on trials that end with <90% accrual because of inadequate accrual rates

# Comparison Updated Analysis to Previously Published Figures

| Activated: | | |
|---|---|---|
| Years | 2000-1010 | 2000-2007 |
| | | |
| <u>All trials</u> | | |
| # of trials | 254 | 191 |
| Trials <90% accrued | 21.1% | 22.0% |
| Patients on these trials | 1.6% | 1.7% |
| | | |
| <u>Non-pediatric trials</u> | | |
| # of trials | 199 | 149 |
| Trials <90% accrued | 24.4% | 26.7% |
| Patients on these trials | 1.8% | 2.0% |

# Preliminary Analysis of Primary Reasons Trials With <90% of Targeted Accrual Closed

| | |
|---|---|
| Accrual over | 203 |
| ≥ 90% accrued | 119 |
| <90% accrued | 84 |

Reasons<90%

| | |
|---|---|
| interim monitoring | 18 |
| external information | 11 |
| drug supply issues | 2 |
| unacceptable toxicity | 3 |
| achieved sufficient number of events | 1 |
| inadequate accrual rate | 53 |

50 Adult Cancer Trials and 3 Pediatric Cancer Trials

| Primary Reason Inadequate Accrual – Closed Trials for Adult Cancer Patients (Trials Activated 2000 to 2010) | # Trials (50) | Cancer Type | % Trials with Inadequate Accrual |
|---|---|---|---|
| **Challenging Randomization: +/- Modalities** | | | **36%** |
| Observation vs Chemotx or vs Early Intervention | 3 | APL, CLL, Prostate | |
| Surgery vs RT | 1 | Prostate | |
| Surgery with ChemoRT vs ChemoRT | 1 | Gyne | |
| +/- Transplant | 1 | Hodgkins Lymphoma | |
| +/- RT | 7 | Brain, Breast, H&N, Lung (2), Pancreas, Sarcoma | |
| +/- Chemotx or ChemoRT | 4 | Breast, Gyne, Lung, (Germinoma-CNS) | |
| +/- Hepatic Infusion Catheter | 1 | CRC | |
| +/- In-patient Tx of Pleural Effusions | 1 | Lung | |

| Primary Reason Inadequate Accrual – Closed Trials for Adult & Pediatric Cancer Patients (Trials Activated 2000 to 2010) | # Trials (53) | Cancer Type | % Trials with Inadequate Accrual |
|---|---|---|---|
| **Challenging Randomization: Therapeutic Approach** | | | **15%** |
| +/- Adj Chemotx (Neoadj, Hormonal, vs Adj and/or vs an IV placebo) | **8** | **Bladder, Germ Cell, Gyne, Glioma, Prostate (3), Rectal, Renal** | |
| **Investigational to Commercial Agents Available - Competing Trials w/Potential Data Soon (*) or Change to Alternative Surgical/Technical Approach** | **9** | **Brain, CRC, Diffuse Large B-Cell Lymhoma (2), Myeloma (2), Rectal, Lung, Peds Retinoblastoma** | **17%** |
| **Site Interest in Treatment Approach Not Sufficiently High** | **8** | **Breast, CRC (3), GIST, H&N (2), Prostate** | **15%** |
| **Competing Studies (Group or Other)** | **5** | **Breast, Gyne (3), Peds ALL** | **9%** |
| **Other** | **4** | **MDS (restrictive selection tx regimen); Amyloidosis (rare cancer); Lung and Peds BMT (regulatory)** | **8%** |

***(*) AGENTS: Temozolomide (Brain), Bevacizumab (CRC and Rectal); Pemetrexed (Lung) Bortezomib, Lenalidomide, Rituximab, Thalidomide (Lymphoma, Myeloma)***

# Assessment of CTEP Slow Accrual Guidelines for NCI Cooperative Group Phase 3 Treatment Trials (4/1/2004 to 6/30/2011)

Guidelines developed in 2005.
Applied to phase 3 trials activated after April 1, 2004.

**If the accrual in Quarter 5-6 is:**

**≤ 20% of projected → STOP trial**

**< 50% and > 20% of projected → Study Team given 6 months to improve accrual**

**If the accrual in 20%<Q5-6<50% and the accrual in Quarter 8 is:**

**< 50% of projected →Amend trial to reflect actual accrual with approval of amendment based on implications of this new rate on study relevance and feasibility**

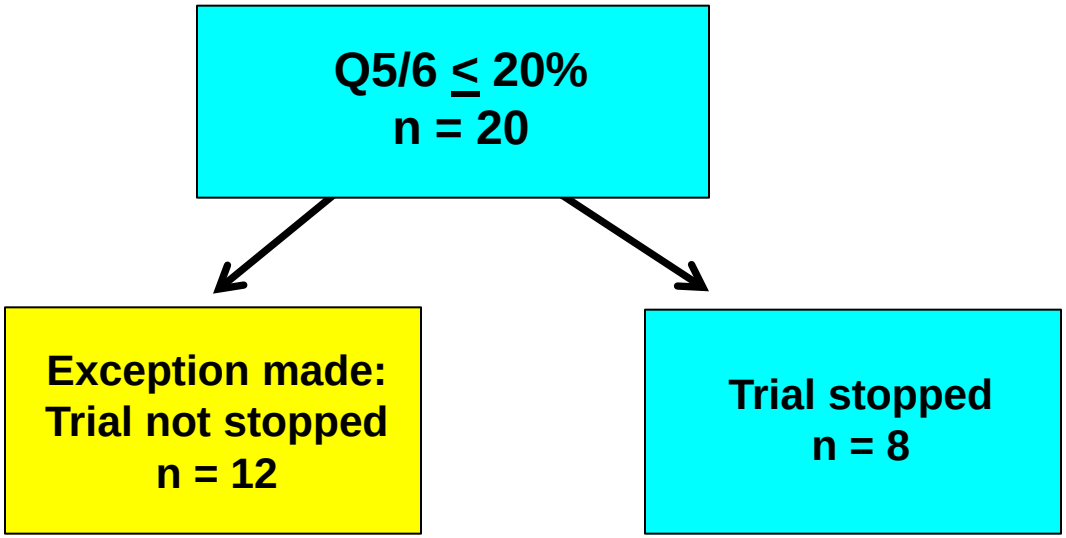
# Development of Slow Accrual Guidelines

| Quarter 5-6 results | Trials activated 1988-2001 |
|---|---|
| | |
| ≤20% of projected | 15 ( 6%) |
| 20-50% of projected | 52 ( 22%) |
| ≥50% of projected | 172 ( 72%) |
| Total | 239 (100%) |

# Assessment of Slow Accrual Guidelines (in progress)

| Quarter 5-6 results | Trials activated 1988-2001 | Trials activated 4/1/2004 - 6/30/2011 |
|---|---|---|
| Stopped before the end of Q6 | N. A. | <8> |
| ≤20% of projected | 15 ( 6%) | 20 (14%) |
| 20-50% of projected | 52 ( 22%) | 34 (23%) |
| ≥50% of projected | 172 ( 72%) | 91 (63%) |
| Total | 239 (100%) | 145 (100%) |

# Disposition of 20 trials whose Quarter 5/6 accrual was ≤ 20% of projected



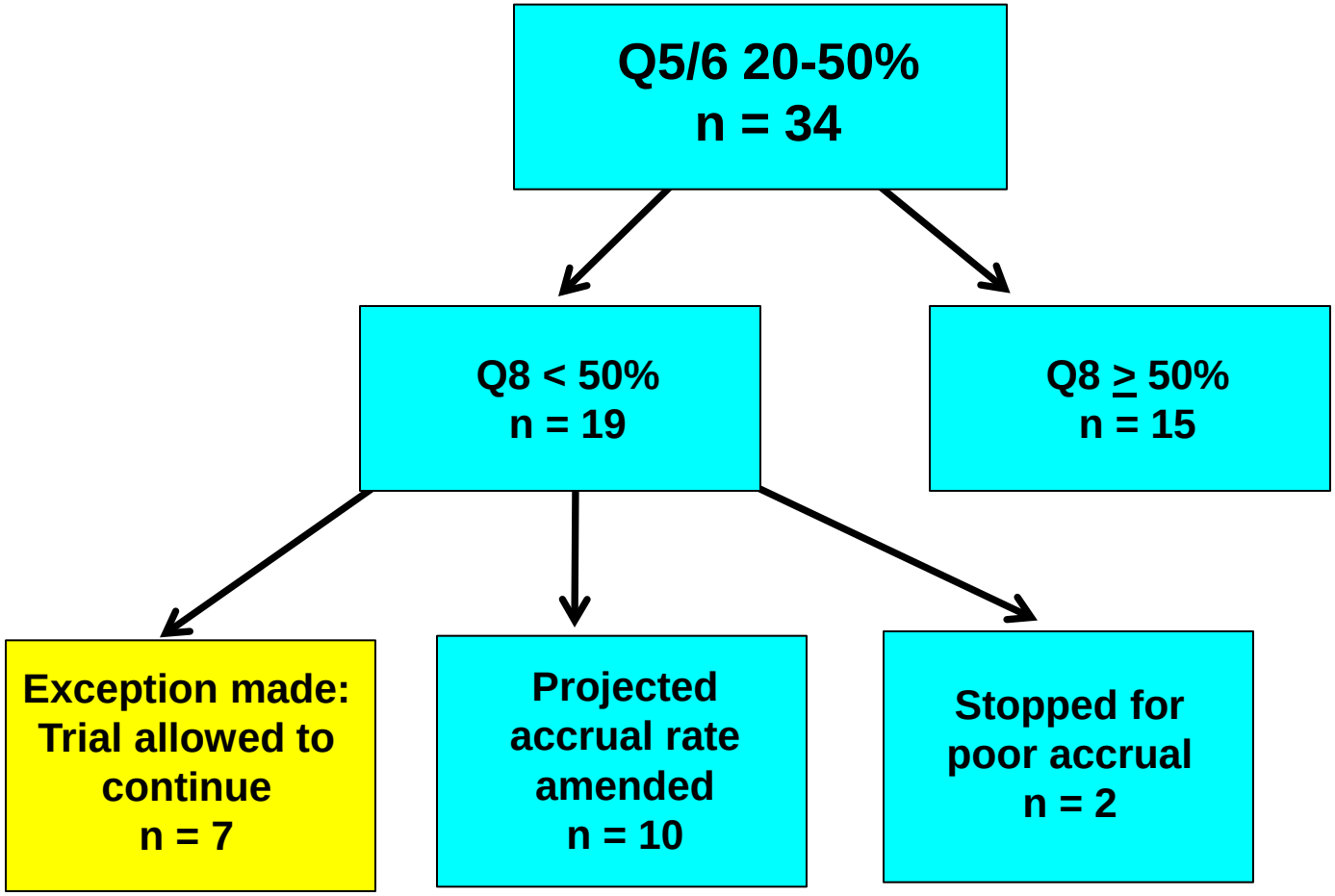
# Disposition of 12 trials whose Quarter 5/6 accrual was ≤ 20% of projected, and which were given exceptions

7 failed to achieve their accrual goals

2 succeeded

3 too early to tell (still accruing)

# Disposition of 34 trials whose Quarter 5/6 accrual was > 20% and < 50% of projected



# Disposition of 7 trials whose Quarter 5/6 accrual was > 20% and < 50% of projected, and which were given exceptions

1 closed early with drug supply issues

3 succeeded

3 too early to tell

# On-Going & Future Analyses & Activities

- Analysis on-going for reasons some trials succeeded and others did not with similar attributes
- Analysis of trial attributes for those trials that accrued well and/or better than expected
- Accrual Intervention projects for trials identified as potentially challenging with respect to accrual
- Enhancement of “feasibility” assessment for trials at concept development and during concept evaluation & improved monitoring of trials in new NCTN as well as improved projections for trials

# Major Questions to CTAC

- Should exceptions be given at Qtr 5/ Qtr 6 if accrual is < 20% of projected accrual?
- What is a reasonable percentage for trials that do not accrue well given that risk is inherent in launching any robust clinical trial program?
- Other Concerns / Questions from CTAC

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ORIGINAL REPORT

# Accrual Experience of National Cancer Institute Cooperative Group Phase III Trials Activated From 2000 to 2007

*Edward L. Korn, Boris Freidlin, Margaret Mooney, and Jeffrey S. Abrams*

From the Biometric Research Branch, Clinical Investigations Branch, and Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD.

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Corresponding author: Edward L. Korn, PhD, Biometric Research Branch, EPN-8129, National Cancer Institute, Bethesda, MD 20892; e-mail: korne@ctep.nci.nih.gov.

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## ABSTRACT

### Purpose
Recent reports have suggested that 40% or more of National Cancer Institute (NCI) –sponsored Cooperative Group phase III trials failed to achieve their accrual goals. We examine in detail the accrual experience of the Cooperative Group phase III trials.

### Patients and Methods
All Cooperative Group phase III trials activated from 2000 to 2007 were examined for their accrual experience. For trials that stopped accrual with < 90% of their accrual goal, the reasons for having < 90% accrual were documented. We focus on trials that ended with < 90% accrual because of inadequate accrual rates rather than for other reasons, such as an interim monitoring analysis by an independent data monitoring committee that stops the trial early because one treatment is clearly superior.

### Results
There were 191 trials activated from 2000 to 2007. We project that 22.0% of these trials will have < 90% accrual because of inadequate accrual rates. We project that there will be 176,627 patients eventually accrued on the 191 trials (current accrual, 154,579) and that 2,991of these patients will be on trials that have < 90% accrual because of inadequate accrual rates (1.7%). For nonpediatric cancer trials, the corresponding percentages are 26.7% and 2.0%.

### Conclusion
We find that insufficient accrual rates are not as high as previously reported and that only a small proportion of patients were enrolled on trials that ended with insufficient accrual because of an inadequate accrual rate. NCI has implemented new procedures to reduce the number of trials that fail to reach their accrual goals and to minimize the number of patients accrued on these trials.

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## INTRODUCTION

The Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) supports phase III clinical trials primarily through the NCI Clinical Trials Cooperative Group program. There are currently approximately 100 such trials actively accruing patients. Although many Cooperative Group phase III trials have led to major advances in the treatment of cancer patients,[1] a proportion of trials are never completed because they do not achieve a sufficient accrual to meet their scientific objectives. Such trials represent loss of the resources that went into designing the trials, getting them activated, and treating the patients accrued on the trials, as well as not utilizing the efforts of the participating patients. In addition, an ongoing trial may preclude opening other trials in the same disease setting that might have been successfully completed. As part of ongoing efforts to improve the efficiency of the NCI clinical trials program, we have performed an in-depth review of the accrual experience from Cooperative Group phase III trials activated from 2000 to 2007.

## PATIENTS AND METHODS

### *Trial Information*

All CTEP-supported phase III trials led by an NCI-sponsored Cooperative Group or conducted as part of an international collaboration with a Cooperative Group that were activated in the years 2000 to 2007 were identified. Trials were categorized as having accrual finished or not, with the latter category including trials that were temporarily closed to accrual. The accrual goal of the trial was taken from the latest CTEP-approved version of the trial protocol. The percent accrued for the trial was calculated as the current or final accrual divided by the accrual goal of the trial. Closed trials with < 90% accrued were considered not fully accrued. Trials not fully accrued were categorized for the reason they stopped accruing by using the

following categories: (a) external information (eg, results of another clinical trial that answered the current trial question or rendered it irrelevant), (b) formal interim monitoring of the current trial by an independent data monitoring committee (either for showing one of the trial arms superior or for futility/inefficacy of the experimental treatment arm), (c) unacceptable toxicity, (d) drug supply issues, or (e) inadequate accrual rate. Information for performing the categorization was obtained from administrative documents (eg, protocol amendments and protocol status updates), trial publications, and CTEP investigators. Trials were additionally categorized by the primary disease site, whether or not the trial involved a randomization (some pediatric phase III trials use historical controls), and whether or not the trial involved an investigational new drug agent.

### *Statistical Analyses*

Trials that were closed to accrual with < 90% of their accrual goal were considered to have insufficient accrual, with the 90% figure chosen prospectively before the analysis was begun. Considering that the statistical power of a trial is typically based on an estimated number of events that will be observed (which depends on the length of the follow-up), we believe that trials that achieve ≥ 90% of their accrual goal can be considered successfully accrued from a statistical point of view. One parameter of interest is the probability that a trial activated from 2000 to 2007 will have insufficient accrual because of an inadequate accrual rate (category (e) above). Since not all trials activated from 2000 to 2007 have completed accrual, this parameter needs to be estimated. If one estimates solely from trials that have closed to accrual, then the estimator will be subject to sampling bias. (This is the same type of bias one would observe by trying to estimate median patient survival in a clinical trial by using the median survival of only those patients who have died.) To avoid sampling bias, statistical methods for survival data that account for censored observations were used that adjust for actively accruing trials. In particular, (1) the unit of analysis is the trial, (2) "time" on study is the percentage accrued for the trial, (3) the trial is considered as having the "event of interest" if the trial stopped accruing with < 90% accrued because of inadequate accrual, (4) trials that stopped with < 90% accrual for other reasons (eg, interim monitoring) are considered a competing risk, and (5) trials that are still actively accruing are treated as censored observations. (Trials that have accrual temporarily suspended are considered active). In this framework, the parameter of interest is the crude cumulative incidence[2] evaluated at 90% percent accrued.

Other parameters of interest are a projection of the number of patients who will be accrued to trials that will have insufficient accrual because of an inadequate accrual rate and the proportion of such patients compared with the total number of patients who will be accrued to all trials. To obtain estimators of these parameters, survival methods were applied with the analyses weighted by the accrual goal for each trial (details are found in the Appendix, online only).

## RESULTS

One hundred ninety-one phase III trials were activated from 2000 to 2007 (Table 1). Figure 1 displays a histogram of the percentage accrued for the 133 trials for which accrual has finished; trials having an inadequate accrual rate are shown in gold. The estimate of the proportion of trials that have insufficient accrual because of an inadequate accrual rate is 22.0%. This estimate is remarkably similar to the naive proportion of trials that had an inadequate accrual rate (21.5%; 41 of 191), which would be an appropriate estimator if we knew that all actively accruing trials would eventually achieve at least 90% accrual. The reason for this is that practically all of the actively accruing trials are already past the point (in terms of percent accrued) at which trials that are going to stop because of inadequate accrual would have stopped (Fig 2). In particular, 85% (35 of 41) of the trials that closed for inadequate accrual rates had < 20% accrued (Fig 1), and 91% (53 of 58) of the trials still accruing already have > 20% accrued (Fig 2).

**Table 1.** Accrual Status and Reasons for < 90% Accrued in CTEP-Sponsored Phase III Trials Activated From 2000 to 2007 (191 trials)

| Status | No. of Trials |
|---|---|
| Accrual not over | 58 |
| ≥ 90% accrued so far | 9 |
| < 90% accrued so far | 49 |
| Accrual over | 133 |
| ≥ 90% accrued | 68 |
| < 90% accrued | 65 |
| Reasons for < 90% accrued | |
| Interim monitoring | 12*† |
| External information | 9* |
| Drug supply issues | 2 |
| Unacceptable toxicity | 3 |
| Inadequate accrual rate | 41 |

Abbreviation: CTEP, Cancer Therapy Evaluation Program.
*Includes two trials that had < 90% accrued because of both interim monitoring and external information.
†Two of the 12 trials were stopped for superiority monitoring; the other 10 were stopped for futility monitoring.

The estimate of the proportion of patients enrolled on trials that had insufficient accrual because of an inadequate accrual rate is 1.7%, representing a projected 2,991 patients of a projected 176,627 that will eventually be accrued to all 191 trials. This low percentage reflects the obvious point that trials stopped for inadequate accrual will tend to have only a small number of patients accrued.

When examined by primary disease site (Table 2), the pediatric cancer trials have a smaller proportion of trials with inadequate accrual rate leading to < 90% accrued than the adult cancer trials. In fact, only two of the 42 pediatric trials had < 90% accrued because of an inadequate accrual rate. For the adult cancer trials, the breast cancer trials appear to have fewer trials with inadequate accrual rates. None of the 15 phase III trials with nonrandomized designs had < 90% accrued because of an inadequate accrual rate (Table 3); these trials were all pediatric cancer trials. There is no substantial difference in the proportion of inadequately accruing

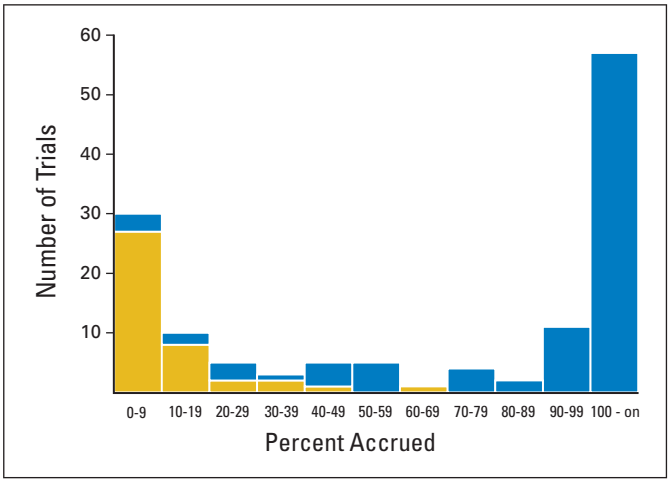


**Fig 1.** Histogram of percent accrued for 133 trials that are closed to accrual (gold indicates trials with inadequate accrual rate).

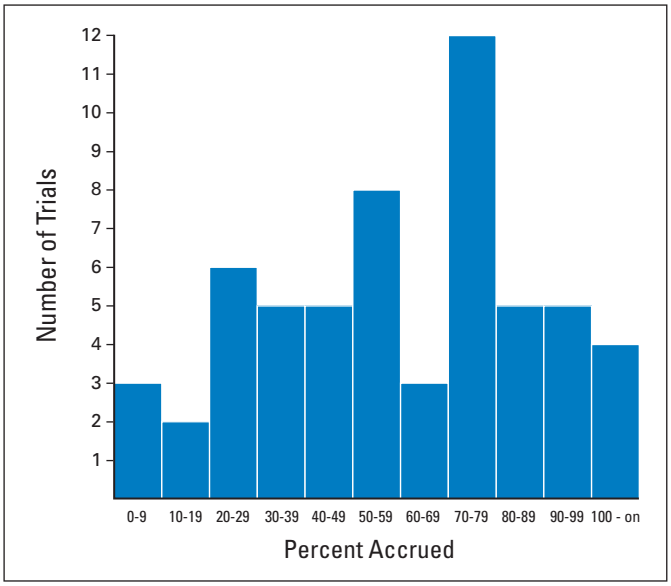


**Fig 2.** Histogram of current percent accrued for the 58 trials that are not closed to accrual.

trials depending on whether or not the trial involved an investigational new drug agent (Table 3).

Although ≥ 90% accrual was the prospectively defined cutoff for sufficient accrual, similar results are obtained by using a 95% cutoff. Using a 95% cutoff, the estimate of the proportion of trials that have insufficient accrual because of an inadequate accrual rate is 22.8% (instead of 22.0%), and the estimate of the proportion of patients enrolled on trials that had insufficient accrual because of inadequate accrual rate is 2.2% (instead of 1.7%).

## DISCUSSION

Cheng et al[3] report 49.2% (30 of 61) of CTEP-approved nonpediatric phase III trials failed to achieve at least 25% of accrual goals. Recently, the Institute of Medicine reported that 40% of CTEP-approved phase III trials failed to achieve minimum accrual goals,[4] a figure that has been repeated elsewhere.[5-7] We report here that we estimate that 28.3% of such nonpediatric trials will fail to achieve at least 90% of their accrual goals because of inadequate accrual, based on data from 149 trials (Table 2). The difference between the results can be attributed to exclusion of actively accruing trials by Cheng et al[3] (leading to sampling bias) and their inclusion, as failures to achieve accrual goals, of trials that ended for other reasons besides inadequate accrual.[4] We have chosen not to consider trials that failed to achieve at least 90% of their accrual goals because of formal interim monitoring, unacceptable toxicity, or drug supply issues as failures. This is an obvious decision for trials that closed because of interim monitoring, and one could argue for the other categories that failure to fully accrue was beyond the control of the investigators.

Overall, we estimate that 22.0% of all trials (adult and pediatric) will end with insufficient accrual because of inadequate accrual rates, and 1.7% of the total number of patients accrued on all trials will be on these trials. It is possible that a trial that ends with accrual < 90% of projected because of an inadequate accrual rate can still provide useful clinical information. For example, the Eastern Cooperative Oncology Group (ECOG) E4201 trial,[8] which closed to accrual with 74 of 332 patients accrued, demonstrated the major advance of treating locally inoperable pancreatic cancer with radiation therapy in addition to gemcitabine.[9] Another example is given by the Radiation Therapy Oncology Group (RTOG) 9813 trial, which closed to accrual with 201 of 454 patients accrued and is in follow-up. This trial, which compares temozolomide plus radiation versus nitrosourea plus radiation for

**Table 2.** Estimated Proportion of Trials That Had Insufficient Accrual Because of an Inadequate Accrual Rate and the Estimated Proportion of Patients on These Trials, by Primary Disease Site

| | Trials | | Patients | | | |
|---|---|---|---|---|---|---|
| Primary Disease Site | No. Activated | Estimated Proportion With Inadequate Accrual Rate (%)* | No. of Patients Accrued to Date | Projected No. Accrued When All Trials Are Closed*† | Projected No. on Trials With Inadequate Accrual Rate*† | Estimated Proportion on Trials With Inadequate Accrual Rate (%)* |
| Adult | | | | | | |
| Breast | 31 | 13.0 | 69,936 | 76,382 | 362 | 0.5 |
| Hematopoietic | 25 | 28.8 | 6,795 | 7,108 | 240 | 3.4 |
| GI | 18 | 28.6 | 18,437 | 20,316 | 746 | 3.7 |
| Female reproductive | 16 | 37.5 | 10,174 | 11,304 | 193 | 1.7 |
| Lung | 14 | 22.6 | 5,652 | 7,198 | 640 | 8.9 |
| Prostate | 16 | 25.0 | 8,951 | 11,204 | 150 | 1.3 |
| Other‡ | 29 | 34.9 | 10,988 | 11,470 | 523 | 4.6 |
| Subtotal | 149 | 26.7 | 130,933 | 147,742 | 2,930 | 2.0 |
| Pediatric | | | | | | |
| Nonhematopoietic | 26 | 7.7 | 6,024 | 8,845 | 25 | 0.3 |
| Hematopoietic | 16 | 0.0 | 17,622 | 19,471 | 0 | 0.0 |
| Subtotal | 42 | 4.8 | 23,646 | 28,955 | 28 | 0.1 |
| Total | 191 | 22.0 | 154,579 | 176,627 | 2,991 | 1.7 |

*These proportions and numbers are estimated using survival analysis methodology.
†Because projected numbers for subgroups are based on within-subgroup survival curves, numbers do not add up exactly to totals.
‡Includes seven head and neck cancer, four distant metastases (unspecified origin), three melanoma, three astrocytoma, three renal, three soft tissue sarcoma, three bladder, one testicular, one neuroendocrine, and one breast/colorectal cancer trials.

**Table 3.** Estimated Proportion of Trials With Insufficient Accrual Because of an Inadequate Accrual Rate and the Estimated Proportion of Patients on These Trials, by Randomization-In-Design Status and Whether or Not the Trial Involves an IND Agent

| | Trials | | Patients | | | |
|---|---|---|---|---|---|---|
| Randomization-in-Design Status | No. Activated | Estimated Proportion With Inadequate Accrual Rate (%)* | No. of Patients Accrued to Date | Projected No. of Patients Accrued When All Trials Closed*† | Projected No. on Trials With Inadequate Accrual Rate*† | Estimated Proportion on Trials With Inadequate Accrual Rate (%)* |
| Randomized design | | | | | | |
| IND agent | 60 | 18.5 | 50,947 | 59,174 | 1,073 | 1.8 |
| No IND agent | 116 | 26.7 | 100,882 | 112,716 | 1,864 | 1.7 |
| Subtotal | 176 | 23.9 | 151,829 | 172,488 | 2,983 | 1.7 |
| Nonrandomized design | 15 | 0.0 | 2,750 | 4,370 | 0 | 0.0 |
| Total | 191 | 22.0 | 154,579 | 176,627 | 2,991 | 1.7 |

Abbreviation: IND, investigational new drug.
*These proportions and numbers are estimated using survival analysis methodology.
†Because projected numbers for subgroups are based on within-subgroup survival curves, numbers do not add up exactly to totals.

treating anaplastic astrocytomas or mixed gliomas, may still provide relevant clinical information. Much more likely, trials that end early because of inadequate accrual will provide little useful clinical data. Although the number of patients involved in these trials is small (compared with the number of patients on all trials), there are still considerable resources involved in opening a trial, whether or not it accrues.

Should one aim for a clinical trials program to open only trials in which one is positive that they will accrue successfully? We would argue no, because this would preclude starting trials that address important questions but in which it is known at the start that accrual will be challenging. For example, the Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial (SPIRIT; American College of Surgeons Oncology Group [ACOSOG] Z0070), comparing radical prostatectomy versus brachytherapy in early-stage prostate cancer, accrued only 56 of a required 1,980 patients. Another example is given by the Southwest Oncology Group S0521 trial, which compared maintenance chemotherapy versus observation in patients with previously untreated low- and intermediate-risk acute promyelocytic leukemia. It accrued only 95 of a required 500 patients. Yet experts often cite the strong need for clinical trials for both these questions.

Although we believe it is important to attempt to perform important trials that may be a challenge for enrollment, it is also important to minimize the time and number of patients involved in trials that turn out to have insufficient accrual. One strategy is to examine characteristics of inadequately accrued trials to help inform trial prioritization.[10]

A second strategy is to open a trial first in a limited number of institutions to assess accrual feasibility. This strategy was used in the Surveillance Therapy Against Radical Treatment (START) trial (National Cancer Institute of Canada Clinical Trials Group [NCIC CTG] PR.11), testing radical prostatectomy or radiotherapy versus active surveillance for favorable-risk prostate cancer.

A third strategy is to stop trials early when it is apparent they will never reach their accrual goals because of inadequate accrual rates. To this end, we developed CTEP early-stopping guidelines[11] that apply to slow-accruing phase III Cooperative Group trials activated after April 1, 2004 (trials that have $<$ 20% of their projected accrual rates in quarters 5 and 6 after their activation are closed). (Twenty-six of the 41 trials that had inadequate accrual rates in Table 1 were activated before April 1, 2004.) These guidelines were based on historical data that demonstrated that trials with poor accrual in this time interval would be extremely unlikely to ever reach their accrual goals.[12] Our experience with the CTEP early-stopping guidelines will be reported when we have further follow-up of the trials activated after April 1, 2004.

A fourth strategy is to simplify the enrollment process and expand patient entry onto trials. To this end, CTEP has developed the Cancer Trials Support Unit (CTSU),[13] which allows for a larger number of institutions to enter patients into different Cooperative Group trials in an efficient manner. This strategy appears to be successful, because CTEP data (not shown) indicate that cross-Group accrual (enrollments from Groups other than the lead Group) has increased from an average of 20% in the pre-CTSU 1990s to 40% in the post-CTSU 2000s.

A fifth strategy is to simplify the data collection required for patients on trials, which may encourage physicians to participate. CTEP is working with the US Food and Drug Administration to reduce certain types of adverse event reporting, which may help in this regard.[14]

Finally, because slow development of a trial concept to a protocol ready for enrollment is associated with its ability to achieve its accrual goal,[3] CTEP, working in concert with the Cooperative Groups, developed the Central Institutional Review Board for faster protocol review[15] and has recently instituted new timelines for all phases of trial development.[16] The target timelines to move from a trial concept to a protocol ready for accrual for phase II and III Cooperative Group trials have been reduced to 7 and 10 months, respectively, a $>$ 50% reduction from current timelines. If these target timelines are achieved, then we will be able to determine whether this promising approach is indeed successful in reducing the number of trials that fail to meet their accrual goal.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

## AUTHOR CONTRIBUTIONS

**Conception and design:** Edward L. Korn, Boris Freidlin, Margaret Mooney, Jeffrey S. Abrams
**Provision of study materials or patients:** Edward L. Korn, Boris Freidlin, Margaret Mooney, Jeffrey S. Abrams

**Collection and assembly of data:** Edward L. Korn, Boris Freidlin, Margaret Mooney, Jeffrey S. Abrams
**Data analysis and interpretation:** Edward L. Korn, Boris Freidlin, Margaret Mooney, Jeffrey S. Abrams
**Manuscript writing:** Edward L. Korn, Boris Freidlin, Margaret Mooney, Jeffrey S. Abrams
**Final approval of manuscript:** Edward L. Korn, Boris Freidlin, Margaret Mooney, Jeffrey S. Abrams

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National Cancer Institute

# Community Clinical Oncology Program

# Enrollment Data Analysis Project: Trials Activated 2000 - 2010

**Lori Minasian, MD**
**Deputy Director, Division of Cancer Prevention**

**March 12, 2014**

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

# Cancer Prevention and Control Clinical Trials

Cancer Prevention Trials Considered:

- All the Large Trials (n> 2,000) have been Removed
- Smaller Trials Included

Cancer Control Trials Considered:

- Pilot Feasibility Studies
- Randomized Phase II
- Randomized Phase III
- Occasional Observational Study

CCOP Analysis Factors Complementary to CTEP Analysis:

- Same Start Dates for the Trials
- Same Criteria for Accrual Completion

# Cancer Control Trials Differ from Treatment Trials

Endpoints are not Survival, or Disease Response

- Symptom (Nausea, Neuropathy, Pain, Mucositis, etc) Response
- Incidence Cancer or Pre-neoplasia for Smaller Prevention Trials

Duration of Intervention & Follow Up Shorter

- Symptom Intervention 4-8 weeks
- Occasional Cross-over Assessment

Simpler Design

Implementation Different

- Not Always Disease Specific; Bolus Recruitment

Drug Supply & Distribution not Provided

- RBs Identify Supply, Placebo, Distribution

# 2000 – 2010 Analysis Project

**Analysis #1**

- **How Many Clinical Trials Activated between January 1, 2000 and December 31, 2010 Complete Accrual?**

Analysis #2

- How Well Do the CTEP Slow Accruing Guidelines Work to Predict CCOP Studies that Will Not Complete Accrual?

All Data is based on Protocol Activation Date

# DCP Analysis #1
# How Many Clinical Trials Activated between January 1, 2000 and December 31, 2010 Complete Accrual?

| Total Studies = 171 | No. of Trials |
|---|---|
| **Accrual Ongoing** | **11** |
| Successful Accrual: ≥ 90% accrual at the time of this analysis | **4** (37%) |
| Inadequate accrual: <90% accrual at this time of this analysis | **7** (63%) |
| **Accrual Completed or Study Closed** | **160** |
| Successful Accrual: ≥ 90% accrual at the time of study closure | **102** (60%) |
| Inadequate accrual : <90% accrual at this time of study closure | **58** (40%) |
| **Reasons for <90% Accrual at this time of analysis** | |
| Drug Supply Issues, out of our control | **14** |
| External Information (e.g., appropriate early closure; Interim monitoring for safety and closed early (unusual toxicity, and possible futility but not futile for poor accrual)) | **8** |
| Inadequate Accrual Rate | **36** |

# Results

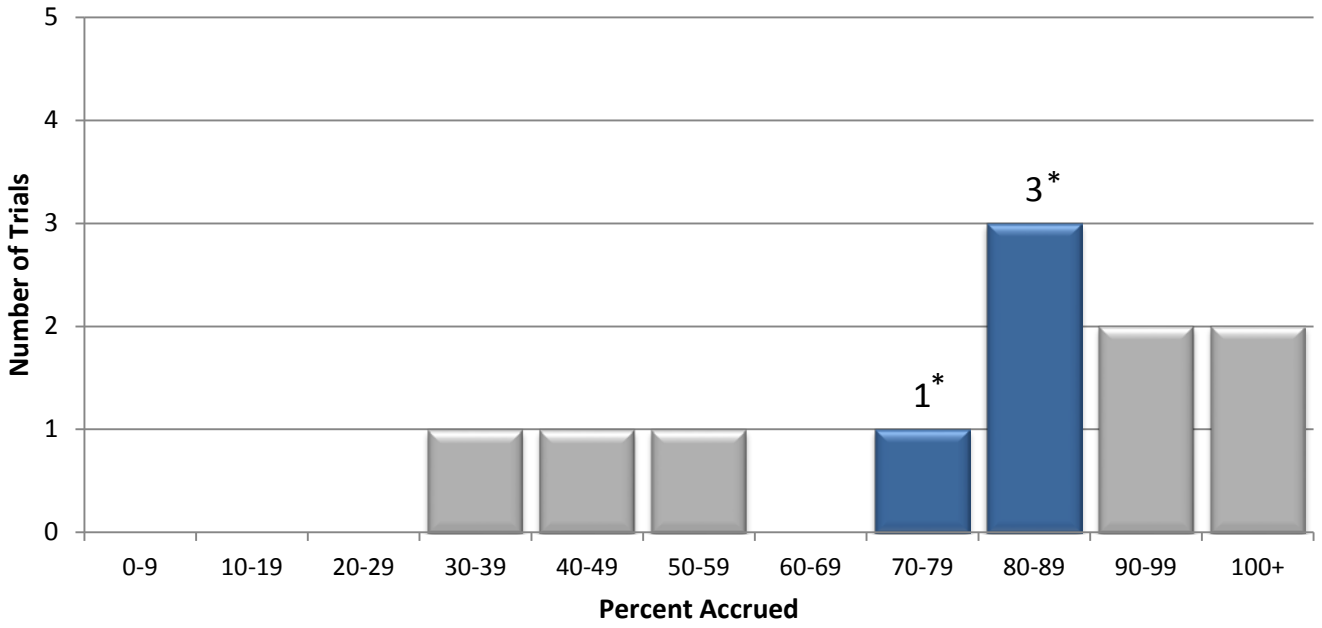
## DCP Results:

- At Least 62% (4+ 102) of Trials Complete
- **21%,** 36 of the 171 Trials Activated from 2000 to 2010 had Inadequate Accrual

## CTEP Results:

- Original Analysis
  - **21.5%**, had Inadequate Accrual
- Updated Analysis
  - **21%** had Inadequate Accrual

# DCP Analysis #1
# How Many Clinical Trials Activated between January 1, 2000 and December 31, 2010 Complete Accrual?




Histogram of current percent accrued for 11 trials that are not closed to accrual. *4 DCP projects with current accrual over 75% are anticipated to complete.

# 2000 – 2010 Analysis Project

- Analysis #1
  - How Many Clinical Trials Activated between January 1, 2000 and December 31, 2010 Complete Accrual?

- **Analysis #2**
  - **How Well Do the CTEP Slow Accruing Guidelines Work to Predict CCOP Studies that Will Not Complete Accrual?**

- All Data is based on Protocol Activation Date

# CTEP Slow Accruing Guidelines

Based Upon CTEP Data, No Trial Completed Accrual if in Quarter 5 & 6, the Accrual Rate was < 20%

Slow Accruing Guidelines:

- If Accrual Rate is < 20% → Stop Trial
- If 20 < AR < 50% → Revise Accrual Plan
  Consider Revisiting Sample Size
  Address Other Protocol Issues
- If Accrual Rate is > 50% → Continue Trial

# DCP Analysis #2
# How Well Do the CTEP Slow Accruing Guidelines Work to Predict CCOP Studies that Will Not Complete Accrual?

**Phase III Drug Intervention Trials**

| Categories | Number of Studies |
|---|---|
| If > 50% of accrual rates of the last approved protocol document prior to activation; ignore as they are on target | 18 |
| If 20-50% of accrual rates of the last approved protocol document prior to activation, this group will need to see the quarter 8 accrual rate (is that >50% or not) | 6 |
| If < 20% of accrual rates of the last approved protocol document prior to activation, they should have been closed, but probably not. | 20<br>Note: 16 of the 20 studies eventually reached its Accrual goal >90%. |
| | • 10 actually completed accrual faster than expected (e.g., planned duration based on monthly accrual goal) |
| | • 6 took longer than plan<br>  • Avg. time = 10 additional months<br>  • Med. Time of 7 additional months<br>  • Range = 3.6 – 26 months |

NOTE: Reviewed 44 of the 86 Phase III drug trials , awaiting protocol files from off-site storage.

# Next Steps

Ongoing Analysis:

- Continue to Review Trials with Respect to Slow Accruing Guidelines
- Cancer Control Studies Have Some Different Needs or Issues
- Consider Complementary Guidelines for CCOP Studies
- Studies with Behavioral Interventions, May Need Different Guidelines

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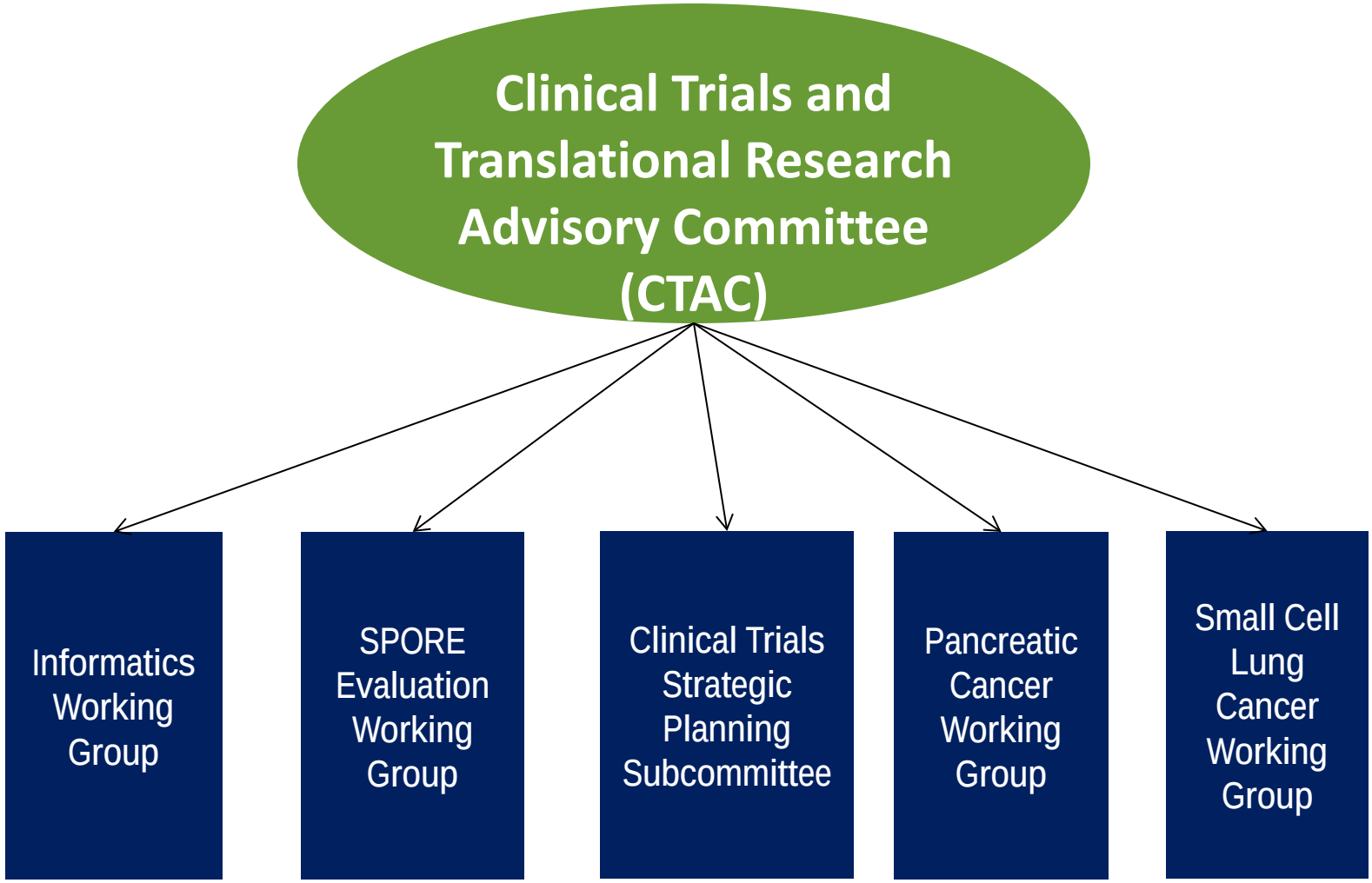
# CTAC Subcommittee/ Working Group Structure



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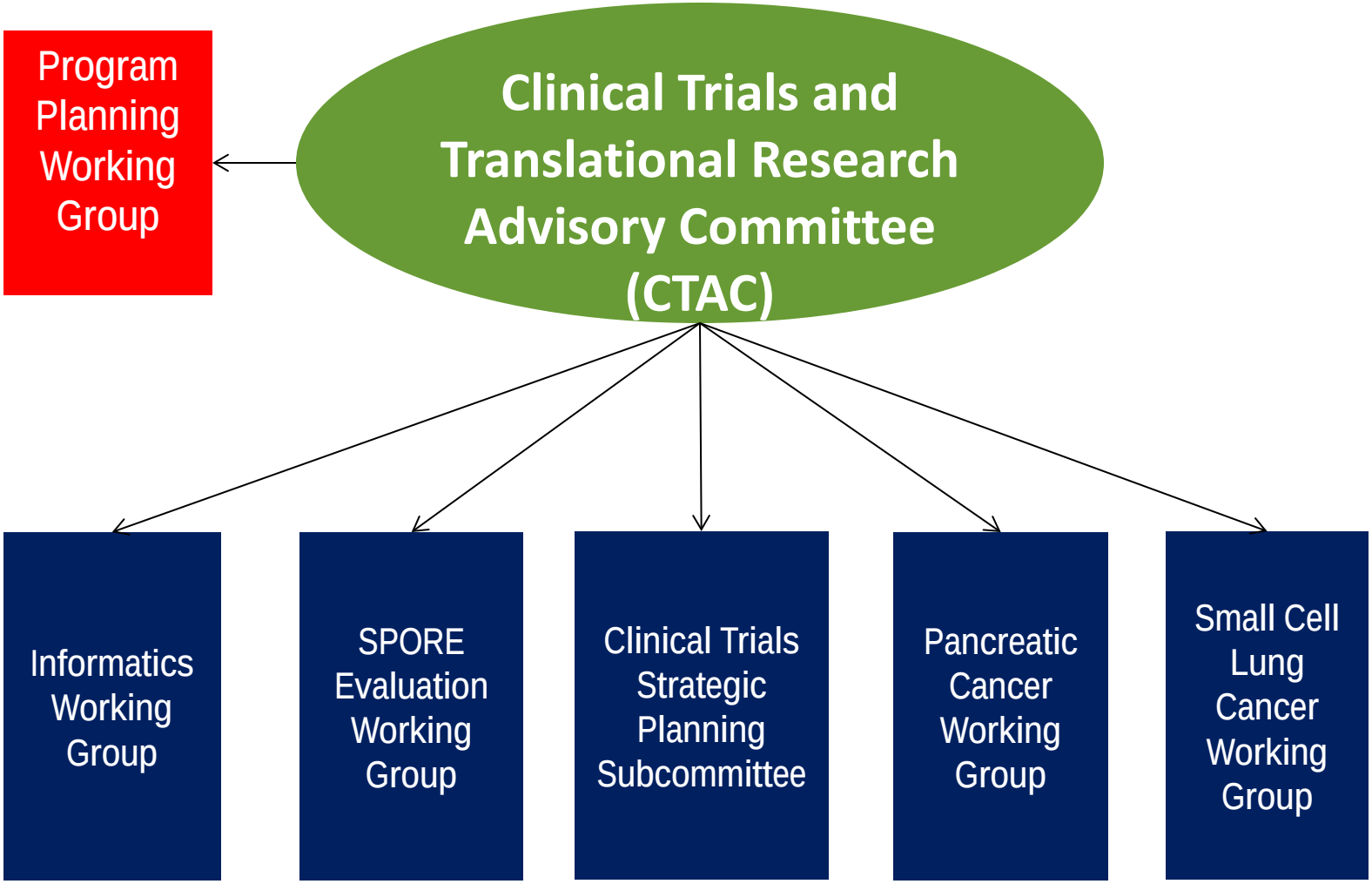

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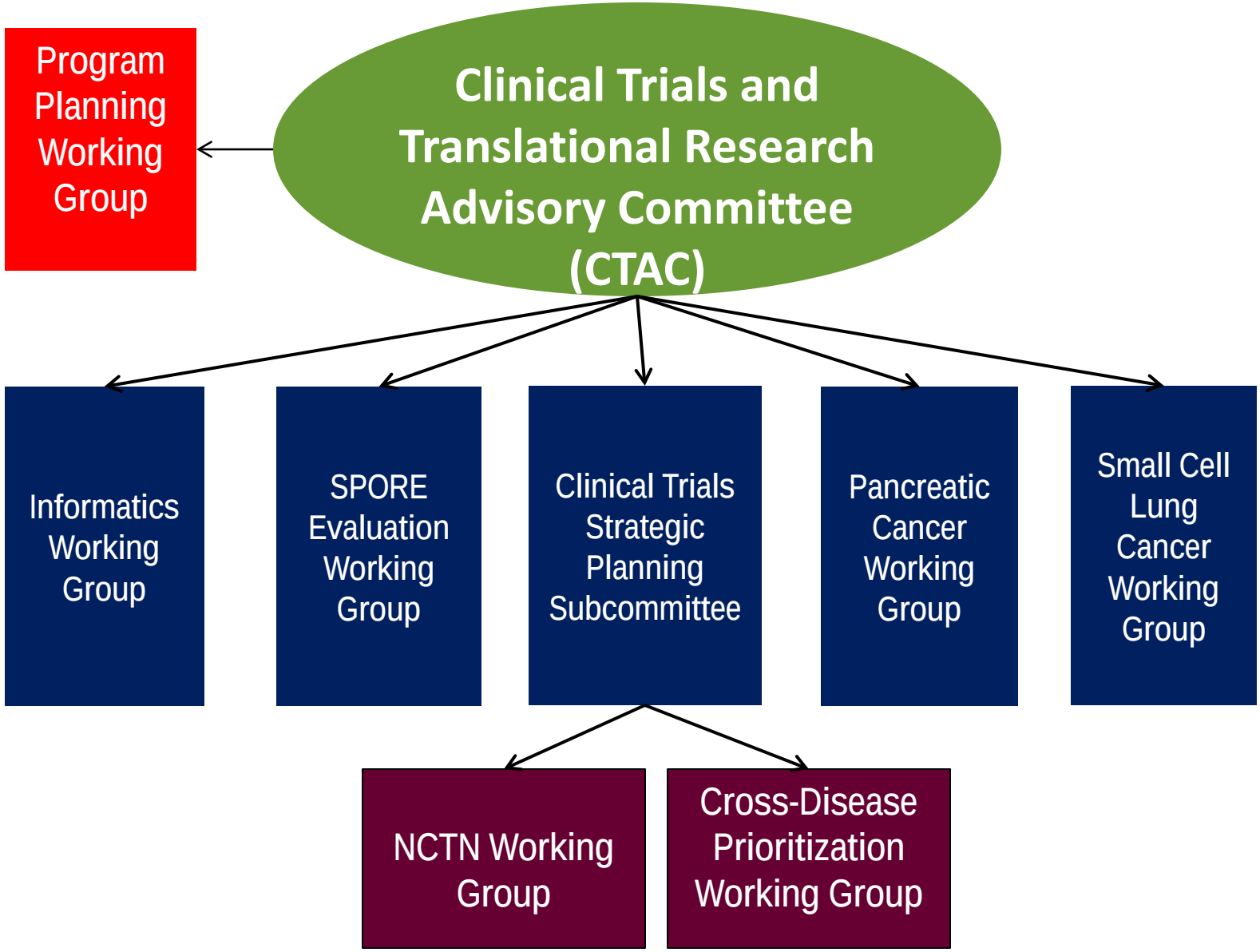

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# CTAC Program Planning Working Group

- Provide advice for the purpose of planning CTAC meetings and activities
  - Establishing priorities of topics for presentation at CTAC meetings to maximize the informational value to members
  - Continuous review of emerging issues
  - Coordination of CTAC subgroup activities
  - Assessing CTAC's progress, achievements, and implementation of recommendations

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# Members

- James Abbruzzese (Chair)
- Monica Bertagnolli
- Kevin Cullen
- Phillip Kuebler
- Scott Lippman
- Nancy Roach
- Peter Shields

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# February 2014 Meeting

- Review and comment on December 19 NCTN Working Group deliberations
- Provided input for March 26 NCTN Working Group meeting on the following topics
  - Setting disease-specific strategic priorities in advance for NCTN trials
  - Principles for guiding strategic priorities
  - Process for setting strategic priorities
- Provided input on cross-disease prioritization
  - Criteria to be used
  - Subset of trials subject to prioritization
  - Stakeholders involved in prioritization process
  - Process piloted by the Cross-Disease Prioritization Working Group