DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
33rd CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC) MEETING

Summary of Meeting
July 12, 2017

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

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
BETHESDA, MD
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The 33rd meeting of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) was held on Wednesday, July 12, at 8:04 a.m. in Conference Room 10, C Wing, Sixth Floor, Building 31, on the National Institutes of Health main campus in Bethesda, Maryland. The CTAC chair, Dr. Nancy E. Davidson, presided.[1] The meeting was adjourned at 2:01 p.m.

Chair
Nancy E. Davidson

CTAC Members
David F. Arons
Susan M. Blaney (absent)
Walter J. Curran, Jr.
David M. Gershenson
Michael L. LeBlanc (absent)
Patrick J. Loehrer, Sr.
David A. Mankoff
Edith P. Mitchell
Nikhil C. Munshi
Augusto C. Ochoa
Gloria M. Petersen
Louis M. Weiner

***Ad Hoc* Members**
Debra Barton
Janet Ellen Dancey
Timothy Eberlein
Howard Fingert
Paul A. Godley
Anne Marie Langevin
Lynn M. Matrisian (absent)
Neal J. Meropol
Roman Perez-Soler
Steven T. Rosen
Dan Theodorescu

***Ex Officio* Members**
William Dahut, NCI
James H. Doroshow, NCI
Paulette S. Gray, NCI
Xuifen Sui, Centers for Medicare & Medicaid Services
Michael J. Kelley, U.S. Department of Veterans Affairs
Warren A. Kibbe, NCI
Richard Pazdur, U.S. Food and Drug Administration (absent)

Executive Secretary
Sheila A. Prindiville, NCI

Presenters
Jeffrey S. Abrams, MD, Associate Director, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, NCI
Matt Boron, RPh, Associate Branch Chief, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, NCI
Nancy E. Davidson, MD, Director, University of Pittsburgh Cancer Institute
James H. Doroshow, MD, Deputy Director for Clinical and Translational Research, NCI
Ann Geiger, PhD, MPH, Deputy Associate Director, Healthcare Delivery Research Program, Division of Cancer Control & Population Sciences, NCI

[1]A roster of CTAC members and their affiliations is included as an appendix.

Douglas R. Lowy, MD, Acting Director, NCI
Holly Massett, PhD, Senior Behavioral Science Analyst, Clinical Trials Operations and Informatics Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, NCI
Worta McCaskill-Stevens, MD, MS, Community Oncology and Prevention Trials Research Group, Division of Cancer Prevention, NCI
Grace Mishkin, MPH, Public Health Analyst, Clinical Investigations Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, NCI
Michael Montello, PharmD, MBA, Branch Chief, Clinical Trials Operations and Informatics Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, NCI
Margaret Mooney, MD, MBA, Chief, Clinical Investigations Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, NCI
Rocio Paul, MSHS, CCRP, RAC, Associate Branch Chief, Clinical Trials Monitoring Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, NCI
M. K. Holohan, JD, Director, Office of Government and Congressional Relations, Office of the Director, NCI
Nita Seibel, MD, Head, Pediatric Solid Tumor Therapeutics, Clinical Investigations Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, NCI

TABLE OF CONTENTS
WEDNESDAY, JULY 12, 2017

I. Call to Order and Opening Remarks

Nancy E. Davidson, MD

Dr. Davidson called the 33rd meeting of CTAC to order and welcomed participants to the meeting. She introduced new ad hoc CTAC members Dr. Rosen and Dr. Meropol.

Dr. Davidson reviewed the confidentiality and conflict-of-interest practices required of CTAC members during their deliberations. She invited members of the public to send written comments on issues discussed during the meeting to Dr. Prindiville within 10 days of the meeting. She also announced that the National Institutes of Health Events Management was videocasting the meeting and that the videocast would be available for viewing following the meeting at http://videocast.nih.gov.

Motion. A motion to accept the minutes of the 32nd CTAC meeting held on March 8, 2017, was approved unanimously.

II. NCI Acting Director's Update

Douglas R. Lowy, MD

Dr. Lowy began by noting that NCI's budget increased in fiscal year (FY) 2016, and in May, Congress included a substantial increase for FY 2017. The 21st Century Cures Act provided an additional $300 million for the Beau Biden Cancer Moonshot, which is intended to identify and fund research areas that are ready for acceleration. NCI believes that many of the research areas targeted by the Moonshot are ready for acceleration because of the groundwork laid by long-term NCI support from the regular appropriation. Most of NCI's activities will continue to be supported by the regular appropriation. Between FY 2014 and FY 2016, NCI has increased the total number of R01s and R35s. The number of people receiving awards has also increased. About one in five R01s and R21s is awarded to new and early-stage investigators.

Activities Supported with Regular Appropriation. Research supported by NCI's regular appropriation includes training the next generation of researchers, investigator-initiated research, most clinical trials and cancer cohorts, the Precision Medicine Initiative (PMI) for Oncology, and the RAS Initiative. Dr. Lowy noted that these programs largely do not overlap with the Cancer Moonshot. He reported that the K08 and K23 awards for physician scientists have been combined into one award and that the award criteria have been expanded in order to increase the flexibility of the program and to attract high-quality applicants.

New initiatives supported by the regular appropriation include the initiative on genomic analysis of breast cancer in African-ancestry populations, which will improve understanding of breast cancer in black women by using biospecimens from multiple cohort studies; the National Cryo-Electron Microscopy Facility at the Frederick National Laboratory; and the Tomosynthesis Mammographic Imaging Screening Trial (TMIST), in collaboration with ECOG-ACRIN, which is comparing the rate of advanced breast cancer in women undergoing tomosynthesis plus digital mammography compared to digital mammography alone. TMIST will clarify the role of tomosynthesis and may lead to a change in screening recommendations for women of normal risk.

Cancer Moonshot. The initial goals of the Cancer Moonshot include: accelerating progress in cancer prevention, screening, treatment, and understanding cancer-related drivers and resistance mechanisms, from cutting-edge research to achieving wider uptake of the standard of care; encouraging greater cooperation and collaboration within and between academia, government, and the private sector; and enhancing data sharing. Enthusiasm for the Cancer Moonshot has continued under the new

administration. Congress authorized $300 million for both FY 2017 and FY 2018, $400 million for FY 2019, and then about $200 million per year for four additional years.

In response to the Cancer Moonshot, the NCI created a Blue Ribbon Panel that identified major scientific opportunities poised for acceleration and made recommendations related to cross-cutting research areas. The full report of the Cancer Moonshot's Blue Ribbon Panel can be found on the NCI website. Starting in FY 2017, NCI is implementing seven of the 10 recommendations. Dr. Lowy highlighted the single-dose HPV efficacy trial, which is expected to start immunizing the first subjects next month in Costa Rica. The goal is to determine whether a single dose of the vaccine confers long-term protection in adolescent girls. In collaboration with the Bill & Melinda Gates Foundation, companion immunogenicity trials are being conducted in the U.S. and Tanzania. If the results are positive, vaccinating with a single dose could save money and increase vaccine uptake.

Cancer Moonshot Implementation Teams include staff from NCI and other institutes. Each team is working to implement a particular Blue Ribbon Panel recommendation. NCI is also holding workshops on topics such as cancer-prone syndromes and pre-clinical lesions. The Board of Scientific Advisors (BSA) has issued recommendations for initiatives to be pursued as part of the Cancer Moonshot. Soon, Requests for Applications (RFAs) that relate to these recommendations will be issued.

The Cancer Moonshot will also result in collaborations with other institutes and agencies, private philanthropy, biotech, other countries, and international donors. One example is the International Cancer Proteogenome Consortium, a group that includes 18 institutions from 11 countries. The members are studying cancer by using genomics and proteomics, following standard operating procedures developed by the NCI Clinical Proteomics Program and publicly sharing their data through the NCI proteomics website.

New Director. The President plans to name Norman E. Sharpless, MD, as the director of NCI. Dr. Sharpless is the director of the University of North Carolina Lineberger Comprehensive Cancer Center. Dr. Lowy looks forward to working with him on a smooth and seamless transfer.

Questions and Discussion

Dr. Davidson commended Dr. Lowy for his service as acting director, which began in 2015. His tenure included the start of the Cancer Moonshot and the passage of the 21st Century Cures Act. He has been an advocate for outstanding science and for researchers and patients. He has also published about 20 papers during that time. Dr. Davidson led CTAC and the other attendees in a round of applause to thank Dr. Lowy.

Dr. Mitchell also thanked Dr. Lowy for his work and particularly noted his support for health disparities research, including a plenary session for the National Medical Association that was very well received. She asked how disparities topics are being included in the Cancer Moonshot recommendations and the projects based on them. Dr. Lowy responded that he believes that all funding opportunity announcements (FOAs) will explicitly include disparities and that some FOAs will deal directly with disparities.

III. Deputy Director's Report

James H. Doroshow, MD

Dr. Doroshow began by thanking Dr. Lowy for the 7 years they have worked together. He then provided updates on several ongoing and new initiatives.

NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) Trial. The first stage of accrual for NCI-MATCH has been completed, years ahead of schedule. As of June 18, 2017, 6,398 patients have been enrolled with tumor samples. About half of the 25 treatment arms have finished their accrual. About one-quarter of the arms are well on their way. The remaining arms are focused on rare lesions. The assay success rate has been high, and the median assay turnaround time was 16 days, remarkable for a national study. Toxicity has been acceptable. In the next 6 to 8 months, patient response information will become available.

Much of the enrollment for NCI-MATCH has been done by community physicians in the heartland; the states with the highest enrollment per 1 million people are in the upper Midwest and Oklahoma. By absolute numbers, the most patients were accrued in California, followed by Minnesota. In Minnesota, cancer centers organized a statewide initiative to facilitate enrollment.

Rare Variant Initiative. Even with 6,000 patient tumors sequenced, several arms of NCI-MATCH are not expected to fill. Through the Rare Variant Initiative, patients tested at certain CLIA-certified, non-MATCH labs will be notified by their doctors that they may be eligible to participate. Dr. Doroshow emphasized the value of being able to find patients with these rare mutations anywhere in the population.

Patient-Derived Models Repository (PDMR). After 3 years processing and characterizing biopsies and surgical specimens collected by NCI-designated Cancer Centers and NCI Community Oncology Research Program (NCORP) sites, the repository is open for business. From 100 well-characterized models, the repository can now provide solid tumor fragments, RNA, DNA, and protein lysate to extramural scientists at a very reasonable price. Another 300 models are far along in the pipeline. The goal is to reach 1,000 models.

NCI Virtual Drug Formulary. The process of negotiating access to investigational agents for clinical trials is cumbersome for individual investigators and even more so when multiple agents are involved. The Virtual Drug Formulary was established earlier this year, in collaboration with a large number of pharmaceutical companies, to remove this roadblock to precision medicine trials for investigators at NCI-Designated Cancer Centers. The formulary currently includes seven companies and 26 drugs—more than the goal. Dr. Doroshow encouraged CTAC members to share information about the formulary with their preclinical colleagues.

Cancer Clinical Investigator Team Leadership Awards. These awards recognize and support outstanding clinical investigators at NCI-Designated Cancer Centers who are actively engaged in NCI-funded collaborative clinical trials. The work they do in mentoring, serving on committees, and other such activities is not often recognized. The awards are for $60,000 a year for 2 years and are intended to give awardees the flexibility in their schedules to focus on clinical investigation and to retain them at academic medical centers. Of the more than 100 recipients to date, more than 90 percent are still on the faculties of the same cancer center where they were initially identified. The awards are intended for mid-level assistant professors or early-level associate professors, who are at the highest risk of leaving academia. Dr. Doroshow read the names of the awardees and their research areas; CTAC members recognized the awardees with a round of applause. The 2017 recipients are:

- Ajjai Alva, M.D., M.S., University of Michigan Comprehensive Cancer Center
- Lisa Barroilhet, M.D., University of Wisconsin Carbone Cancer Center
- Ursa Brown-Glaberman, M.D., University of New Mexico Comprehensive Cancer Center
- Shira Dinner, M.D., Robert H. Lurie Comprehensive Cancer Center, Northwestern University

- Jean Hoffman-Censits, M.D., Sidney Kimmel Cancer Center, Thomas Jefferson University
- Kevin Kalinsky, M.D., M.S., Herbert Irving Comprehensive Cancer Center, Columbia University
- Christopher Lieu, M.D., University of Colorado Comprehensive Cancer Center
- Rahul Parikh, M.D., Ph.D., University of Pittsburgh Cancer Institute
- Eric Roeland, M.D., Moores Cancer Center, University of California, San Diego
- April Salama, M.D., Duke Cancer Institute, Duke University Medical Center

Questions and Discussion

Dr. Davidson asked the cost of a patient-derived xenograft. Dr. Doroshow replied that the cost is $250.

Dr. Rosen asked whether NCI is partnering with The Jackson Laboratory. Dr. Doroshow responded that The Jackson Laboratory is providing a series of its models with funding from a supplement associated with the Precision Medicine Initiative (PMI).

Dr. Munshi noted that fewer than 1,000 of the 6,000 patients who were screened for NCI-MATCH have been or will be assigned to an arm. He asked whether the data collected from all of the other patients can be used in future studies. Dr. Doroshow explained that the goal has always been to put the genomic data in the NCI Genomic Data Commons. Dr. Kibbe added that, when the analysis of individual arms is completed, the data from those arms will be released. However, the patients who did not go on an arm would be eligible for an arm if they have a recurrence, so it is not clear how long NCI should wait before releasing their data.

Dr. Langevin asked whether the report for the Rare Variant Initiative sent from Foundation Medicine includes the patient's eligibility for NCI-MATCH. Dr. Doroshow explained that the report will notify the person who ordered the test that the patient might be eligible for an arm of the trial. Dr. Abrams added that the report will include information on how to make a referral to a participating physician.

Dr. Ochoa asked about expanding the Cancer Clinical Investigator Team Leadership Awards beyond NCI-Designated Cancer Centers, since the majority of patients are seen elsewhere. He suggested opening it up, for example, to active NCORP sites. Dr. Doroshow said that this has been considered but that funding is an issue. Dr. Davidson noted that the awards have been successful at keeping people in cancer centers doing research and congratulated Dr. Doroshow on the program's success.

Dr. Mankoff asked whether the virtual formulary makes material transfer and intellectual property components unnecessary. Dr. Doroshow said that the agreements expand the agreements already in place with the companies through the Cancer Therapy Evaluation Program (CTEP), and do not change the intellectual property issues.

Dr. Davidson asked whether NCI-MATCH will accrue indefinitely. Dr. Doroshow said it will continue to accrue as long as it continues to make progress toward the completion of the Rare Variant Initiative arms. The initiative will show whether it is possible to get a reasonable rate of accrual by looking for mutations in patients throughout the country. Dr. Lowy noted that Congress has strongly supported the PMI in oncology. That support made it possible to increase the number of patients from 3,000 to 6,000 and to go forward with the pediatric version of NCI-MATCH.

IV. Legislative Update

M. K. Holohan, JD

Appropriations Update—FY 2017. Congress passed an omnibus appropriations bill, which was signed into law on May 5. The bill included a substantial increase for NIH for the second year in a row. The approximately $2 billion increase included a $174 million increase in NCI's regular appropriation plus $352 million from the 21st Century Cures Act.

Budget Process for FY 2018. Ms. Holohan reminded CTAC members that the first step in the budget process is for the White House Office of Management and Budget to coordinate with federal agencies to formulate the budget request. Then Congressional appropriations subcommittees consider the requests. This is where the FY 2018 process is now. Both the House and the Senate subcommittees were very supportive of NIH during their hearings held on May 17 and June 22, respectively. Dr. Lowy was at both sessions and answered questions from the appropriators about immunotherapy and childhood cancers.

Congressional Support. There is strong bipartisan support for NIH and NCI—particularly for biomedical research and cancer research. Ms. Holohan shared information about and photographs of NIH's appropriations hearings and several Congressional visits to NIH that highlight appropriators' interest in understanding what the investment in biomedical research yields and what it means for patients and families. She noted that one recent visit included nine Senate appropriators, including two who aren't on the NIH appropriations subcommittee—a truly unusual occurrence.

Outlook for FY 2018. It is important that Congress pass a budget deal for FY 2018, because the budget caps set in place by the Budget Control Act of 2011 (BCA) are back in place for FY 2018 unless Congress passes new legislation to raise the caps, as occurred in 2013 (the Bipartisan Budget Act of 2013 raised the budget caps for FY 2016 and FY 2017). Ms. Holohan noted that there is bipartisan support for raising the budget caps and that all funding proposals currently on the table, including the President's budget request and the Congressional Appropriations bills for FY 2018, exceed the level of the BCA's FY 2018 budget caps. Possible paths forward include a 12-bill omnibus, a continuing resolution (CR) that would maintain current funding levels across all bills, and a combination of a CR with "minibus" bills that allow funding increases for a few agencies but cap others at FY 2017 levels.

Questions and Discussion

Dr. Davidson asked about the deadline to address the debt ceiling. Ms. Holohan said the Secretary of the Treasury would like it to happen before August but could take extraordinary measures to extend the date until September or maybe October.

Mr. Arons asked whether attempts to reform the Patient Protection and Affordable Care Act (ACA) would affect the requirement that some health insurance plans cover the routine medical costs associated with participation in clinical trials. Ms. Holohan said there has been no discussion at this level of detail.

Dr. Weiner noted that the proposed 18 percent budget cut is alarming, and asked whether there was a non-legislative way that the administration could make that happen. Ms. Holohan said that while the executive branch can affect specific aspects of operational budgets, the Secretary's authority to transfer funds is set by appropriations law, and Congress pays close attention. The budget for NCI, for example, is a line item in the bill. Dr. Weiner asked about actions like the hiring freeze. Ms. Holohan agreed that this is something the executive branch can do.

Dr. Petersen asked how members of Congress think about cancer research across agencies—for example, whether funding levels for cancer research through the Department of Defense budget affect funding for NIH. Ms. Holohan said that the appropriations bill for Defense and the bill for Labor-HHS (where NIH gets funding) are considered by separate committees.

Dr. Fingert noted that Ms. Holohan had shared examples of members of Congress being impressed by interactions with patients with long-term benefits from cancer research. He asked whether there are other ways to show the return on investment, such as the business value of having quality research and quality pharmaceuticals. Ms. Holohan said some members are very interested in economic arguments regarding investment in cancer research and what improvements in outcomes can mean to the economy. Dr. Lowy said that it is widely believed that federal investment in biomedical research stimulates the economy. Also, a high percentage of the products that industry develops are based on discoveries made through NIH-supported research, and most of the people who work in industry were trained through NIH-supported research.

Dr. Munshi asked whether cuts would affect the Cancer Moonshot funding. Ms. Holohan explained that the Moonshot funding is from a mandatory funding bill. However, Congress could choose to decrease the amount of money coming from the regular appropriation to compensate. Dr. Lowy said that if the NCI budget were to remain flat for the 7 years of the Moonshot, its purchasing power would decrease by about 25 percent.

V. Implementation of the National Clinical Trials Network (NCTN) External Evaluation Working Group Recommendations

Margaret Mooney, MD, MBA

As a follow-up to the NCTN External Evaluation Working Group report that was presented during the March webinar, Dr. Mooney presented NCI's plans for implementing the working group's recommendations.

Structure of the NCTN. The NCTN began in 2014 with a 5-year project period. Now, NCI is evaluating the first 2½ to 3 years of the program to determine whether the RFAs associated with the NCTN should be reissued.

The NCTN's objectives are to provide essential infrastructure for NCI phase II and phase III multi-site trials; launch trials rapidly and complete accrual on schedule; promote user-friendly, harmonized processes and encourage collaborations; and enhance the trial portfolio, focusing on innovative science, precision medicine, and questions not addressed by industry.

In 2014, 10 Cooperative Groups were consolidated into five U.S. groups—one pediatric group and four groups focused on adult cancer. Coordination with NCORP, which is overseen by the Division of Cancer Prevention, was enhanced. Also, centralized infrastructure, including the central institutional review board (CIRB) and core services for radiation therapy and imaging, was strengthened. New components, such as 30 lead academic sites, have augmented the network's scientific and accrual potential.

Currently, the NCTN has a diverse mix of trials, including large precision medicine trials and trials on rare cancers and rare subsets of common cancers along with trials in special patient populations, such as the elderly, adolescents, or HIV-positive people. The NCTN also conducts studies through public–private partnerships and reports outcomes that result in new drug indications and changes in the standard of care. Accrual has increased from 17,000 in the first year of the NCTN to more than 20,000 in the third year, which is similar to accrual in the three years before launch of the NCTN.

Recommendations for Change. Dr. Mooney noted that the NCTN goal statement has been revised to reflect the NCTN External Evaluation Working Group's recommendation to include references to NCTN earlier-phase trials that require a national catchment area for accrual and trials of single modalities, such as radiotherapy or surgery, or a combination of those modalities with novel agents. Many of the working group's other recommendations were focused on ensuring that the NCTN complements rather than duplicates research efforts in the private sector while maintaining a high rate of cross-group accrual and coordination across the program. The recommendations also emphasized the need to share best practices across the network.

At the recommendation of the NCI Board of Scientific Advisors (BSA), NCI changed the NCTN's project period from 5 years to 6 years to allow the investigators more time to conduct and analyze large trials. CTEP requested an additional $20 million per year in the NCTN budget to compensate for funds lost due to the 2013 budget sequester. These funds would be used to support patient accrual.

In terms of the NCTN's competitive renewal timeline, the goal is to reissue the FOAs in late September to mid-October with a receipt date in January 2018 and peer review in the spring or early summer of 2018. The National Cancer Advisory Board review is planned for October 2018, with new awards to be made on March 1, 2019.

Dr. Mooney thanked the NCTN External Evaluation Working Group for its recommendations and the whole of CTAC for its support.

Questions and Discussion

Dr. Loehrer asked how many trials have been completed versus how many have been opened and whether the NCTN could reduce the total number of trials and increase per-patient capitation. Dr. Mooney explained that the NCTN has slow accrual guidelines to monitor enrollment and terminate trials that likely won't complete accrual. Of the phase III trials that were initiated in the first 32 months of the NCTN, all but one have exceeded accrual benchmarks.

Dr. Munshi asked whether there is a cap to overall accrual through the NCTN. Dr. Mooney said that the amount of funding has always constrained accrual. Because many of the 22,000 patients enrolled on NCTN clinical trials may go through only the screening portion of a study and not the actual intervention phase of the trial, the data management associated with their accrual is not as costly as it was in the past, which made it possible to increase the per-case capitation rate. If the additional $20 million requested is not available, the NCTN will need to consider how the reduced budget affects the trials that can be conducted.

Dr. Fingert noted that trial results are one element of success and that ECOG-ACRIN will be donating data sets to Project Data Sphere. The Food and Drug Administration (FDA) is encouraging the pharmaceutical industry to invest in data quality. Dr. Fingert asked whether the NCTN is looking at metrics on whether the data are reliable. Dr. Mooney said that all phase III trials completed with primary outcome data published on or after January 1, 2015, are contributing their data to the NCTN/NCORP Data Archive and that the data also go into Project Data Sphere. Making data available to the public leads to value for all kinds of research questions related to oncology.

Dr. Rosen asked whether the NCTN should focus solely on studies that would not be done through industry. Dr. Mooney said that that is one of the goals. For example, when ipilimumab was first evaluated as an adjuvant therapy for resected high-risk melanoma in a clinical trial, a dose of 10 mg per kilogram was used. ECOG-ACRIN mounted a phase III trial (E1609) to compare a dose of 3 mg per

kilogram as well as a dose of 10 mg per kilogram against a standard control arm, since toxicity of the agent is dose-dependent—something that might not have been done by other sponsors.

VI. Timeliness for Activation of CTEP Network Trials

Grace Mishkin, MPH

In 2010, the Operational Efficiency Working Group (OEWG) recommended that CTEP set target dates and absolute deadlines for the amount of time from approval of the study concept to study activation. During this session, Ms. Mishkin, a public health analyst in the Clinical Investigations Branch at CTEP, reviewed the data on time to study activation before and after introduction of the OEWG target dates.

Review of OEWG Report Goals and Timelines. The OEWG was established to identify barriers to timely trial activation and solutions to improve timelines moving forward. The working group's other objective, which was not part of Ms. Mishkin's presentation, was to improve trial accrual timelines. Starting in 2012, the target for phase I and II trials was changed to 210 days for activities that were under NCI and extramural control, with an absolute deadline of 450 days for a trial to be activated. External activities not under NCI or extramural control included negotiations with industry, FDA approval, and institutional review board (IRB) approval. In terms of phase III trials, the target was 300 days with a deadline of 540 days.

For comparison of progress, the trial activation process is broken into key stages:

1. LOI/Concept Approval, which starts with the OEWG start date and ends when the LOI or concept is approved.
2. Protocol Authoring, which is typically out of NCI's control, starts when the concept is approved, and ends when the investigator submits the protocol to NCI for review.
3. Protocol Development, which starts when NCI receives the protocol and ends when the protocol is approved.
4. Protocol Approval and Activation, which includes any amendments or delays after a protocol is approved until the study is activated.

CTEP tracks steps and activities within these stages.

Comparison of Reviews and Timelines Pre- and Post-OEWG. The key question guiding the analysis was how trial timelines now compare to the timelines before the OEWG goals were implemented. Shortening the activation process was the goal of the timelines. To understand that, Ms. Mishkin and her CTEP colleagues analyzed the timeline data for trials that were activated between July 2012 and June 2017. They broke the 5 years into two groups: trials activated July 2012 to June 2014, which was after the OEWG report but largely before the launch of the NCTN and the Experimental Therapeutics Clinical Trials Network (ETCTN); and trials activated July 2014 to June 2017. They analyzed data on 372 protocols activated in that 5-year period and compared them to the information from the March 2010 OEWG report about timelines for earlier protocols. Most of the trials were phase II trials; the next most common were phase I trials.

The number of trials that take more than 2 years to activate has decreased compared to the pre-OEWG data. In the pre-OEWG era, 23 percent of trials took more than 2 years to activate; for studies that were activated in July 2014 to June 2017, that number was only 4 percent. A similar change was observed for phase III trials. For phase II trials, the median time for each of the timeline stages generally decreased for trials activated July 2012 to June 2014, with the exception of protocol authoring. Compared to the 2012 to 2014 trials, the median time for each stage increased for the 2014 to 2017 trials, with the

exception of the activation stage. However, the median overall days to activation was largely unchanged between the two post-OEWG time periods. A similar trend was seen for phase III trials, with a particularly large drop in the median number of days for protocol review and a drop in the overall days to protocol activation for protocols activated July 2014 to June 2017. The number of revisions has not declined for phase II or III trials, and in the most recent period, there were more trials with three or more revisions than before.

In-Depth Look at Recent Trials. Ms. Mishkin shared a closer look at the trials that were activated between July 2014 and June 2017, the most recent period analyzed. Across phases and types of organizations, the median time to activation was very close to the deadline. The time to activation varied widely. One NIH Clinical Center trial was activated in less than 200 days, because the protocol was received only 8 days after the concept was approved. Overall, 77 percent of trials were activated within their original deadline. The consortia were the most likely to have their trials activated within the timeline, with 89 percent. Overall, 42 percent of trials were activated between 96 and 100 percent of their absolute deadline. Most of the faster trials were not short in any particular stage. Where they were long in one stage, they made up for it in another. This could show that the deadlines are set at about the right places, or it could be that the system is set up such that people are working to the deadline.

Common reasons that protocols are given extensions (which means they missed their original deadline) include:

- Another study component being added or a change to the design
- A delay in drug dosing decisions or production
- NCI resource issues (e.g., when NCI-MATCH was going through the CIRB, it took up so much of the IRB's resources that other protocols were delayed)
- Precision medicine study coordination
- Regulatory decisions, such as whether to try for registration
- Administrative issues at the lead organization
- A combination of factors

Because there are many valid delays, it can be difficult to make a decision to terminate protocols. CTEP has been trying to communicate the possibility of termination to the study team earlier in the process.

Ms. Mishkin noted two possible sources of bias in the analysis: trials withdrawn before activation and grouping by the trial activation date rather than the OEWG start date. However, she did not believe that these affected the results.

Next Steps and Questions for CTAC. Different reasons for delays are expected based on trial design and lead organization. For example, the consortia and the NCTN have centralized offices, while the ETCTN does not. Many of the delays for ETCTN trials seem to be due in part to a lack of protocol development support, so CTEP is developing a support mechanism and will evaluate its impact. Ms. Mishkin concluded by noting that the data showed a strong tendency to work toward the absolute deadline rather than the target. She asked CTAC for advice on whether the absolute deadline should be shortened and whether any other analyses would be useful.

Questions and Discussion

Dr. Meropol noted the tremendous progress in shortening timelines. He said he thinks that study teams are working to the absolute deadline and that it should be shortened, with a focus on the protocol

development phase (from protocol receipt to approval). He suggested taking a closer look at the data on that phase.

Dr. Gershenson asked whether international trials were included in the analysis. Ms. Mishkin said that individual trials may have had international participation, but the analysis was limited to trials that were led by a domestic organization, and the activation date is when the trial was activated domestically. International participation can cause a delay. Dr. Gershenson asked whether steps are being taken to help with the delay. Dr. Mooney said the problem is primarily with international partners that are not full members of the group and when there are regulatory issues (for example, if drugs cannot be shipped to their country). CTEP asks groups to identify problems early so they can be addressed, including whether it makes sense to proceed with the international collaboration. CTEP also tries to give a timeline for activation of the international sites. This work is just beginning.

Dr. Mankoff noted that the protocol development time seemed to have gotten longer and that the number of protocols that had three or more reviews seemed to have increased. He asked whether this indicated a problem with how reviews are done or how protocols are written. Ms. Mishkin said that some of the earlier data came from before the implementation of the CIRB, so some changes that were not previously recorded would now be counted as revisions. The revision process can be improved. For example, recommended changes are being interpreted as required, which is causing more delay.

Dr. Fingert said it would be useful to know who is responsible for the delays. He also noted that the consortia did better, so it would be good to have more detail about those protocols. Perhaps best practices could be shared with the other types of lead organizations.

Dr. Munshi noted that much of the discussion was about the absolute deadline, while a very large percentage of studies are outside of the shorter target range. If the idea is to shorten the timelines, the change should be made to the absolute deadline, not the target date, and not too many exceptions should be given.

Dr. Loehrer suggested doing a detailed analysis of one study, finding out exactly when it is held up. He asked how a protocol can have six revisions. Ms. Mishkin said that most of those are cases where there are new trial components or new drug information requiring revisions. Dr. Massett has analyzed the ETCTN trials and found that protocol authoring was a key concern because of difficulties in making sure that required edits were incorporated and that recommendations and requirements were communicated clearly.

Dr. Dancey said, as a leader of an NCTN group, that she thinks there may be capacity issues that are affecting timelines. The increasing complexity of trials with drugs and biomarkers means that more people are involved in advising and writing sections of the protocols, which makes writing slower. Because of this increased complexity, many existing templates cannot be used. Changing the timeline will challenge the system and could lead to better processes and tools. Ms. Mishkin said this complexity is why the focus is on early-phase trials, and she agreed that this is often an issue of resources and capacity.

Mr. Arons asked whether the analysis included time to start by disease or cancer type. Ms. Mishkin said there are too few protocols for each to do a strong analysis, and no clear differences emerged. Mr. Arons asked whether it was possible to tell what delays were in NCI's control and what were not. Ms. Mishkin said this is difficult to do, because so many things happen in parallel.

Dr. Doroshow mentioned that the idea to set absolute deadlines came from industry colleagues. He asked whether Dr. Fingert knew the current industry standards for time to activating a phase II or III

trial. Dr. Fingert said that a group from Tufts University has been studying this and may have a publication. He agreed that complexity slows the process.

Dr. Davidson invited any committee members with other thoughts to send them to Ms. Mishkin.

VII. CTEP Regulatory Operations Enhancements

Jeffrey S. Abrams, MD
Matt Boron, RPh
Holly Massett, PhD
Michael Montello, PharmD, MBA
Rocio Paul, MSHS, CCRP, RAC

Dr. Abrams introduced a series of short talks about various regulatory enhancements. CTEP has cooperative research and development agreements with more than 50 different companies and therefore needs to meet modern-day regulatory, auditing, and IRB requirements. In recent years, CTEP has been given new funds to redevelop its computer systems, which were developed in the 1990s. These changes are expected to help the investigator community.

Clinical Oncology Research Enterprise (CORE). Dr. Montello introduced CORE, the IT infrastructure to support NCI's extramural research portfolio, patient safety, and regulatory compliance. CORE combines many systems to address evolving, complex science. The IT infrastructure had to be modernized in order to support that and to enable future changes. The overhaul has also emphasized improving data quality and control.

CORE supports CTEP, other NCI staff, and the extramural community in the domains of information security, study administration and logistics, clinical data capture and reporting, correlative study data, regulatory monitoring and reporting, and data quality and control. CORE supports the clinical trial process end to end, from research planning and study concept to analysis, with the hope of leading to new therapies. The system aims to reuse information so that research staff do not have to reenter it. The system includes several data quality tools that can transfer information to other systems for study monitoring, serious adverse event (SAE) review, review of the FDA Amendments Act of 2007, or submission to clinicaltrials.gov. The clinical trial data can also be connected to correlative science data.

CTEP Adverse Event Reporting System (CTEP-AERS)/Rave Integration. The goal is to promote serious and routine safety reporting into a single harmonized process by integrating CTEP-AERS and Medidata Rave. This will reduce both overreporting and underreporting of SAEs; improve timeliness of adverse event (AE) reporting; create a single source for AE data; eliminate the need for reconciliation, the most labor-intensive process of clinical trials; and reduce the administrative burden on the entire oncology research community.

Before CTEP-AERs was redeveloped, SAEs and AEs were entered by different people into different reporting systems, leading to conflicting data. Now, a nurse who is entering an AE will start in Medidata Rave (the clinical data management system). If the AE is identified as an SAE, the system will direct the nurse to CTEP-AERS. The data is entered once; no reconciliation is required. This was piloted in 2016 with limited functionality and has now been released for new NCI-held investigational new drug (IND) studies as of mid-March. Its use is required for new NCI IND studies activated after July 1, 2017. For now, the system is focused on CTEP-held INDs; but in the first quarter of 2018, the intent is to expand its capabilities to support other types of research.

Auditing and Monitoring. Ms. Paul started by explaining the difference between auditing, which is typically retrospective; and central monitoring, which is continuous. A subset of patients is

selected for auditing, while monitoring can include all patients or a subset of patients. Auditing covers a comprehensive list of data points, while central monitoring covers selected critical data points that are prospectively defined in the protocol's monitoring plan.

The NCI auditing program has been in place for many years. The Audit Information System has been in place since 1999 and is well established. Now CTEP is developing three new areas related to data quality and control:

- Target Source Data Verification. This tool was created to record source data verification by auditors in Rave.
- Central Monitoring Portal. This is a place for each site to upload redacted source documents for the patients and data that are selected for review. It informs the site and lead organization as to what has been reviewed, what is pending, and whether there are any discrepancies with the data submitted to Rave by case report form.
- Data Quality Portal. This is in the early stages of development. It will allow access to a variety of data by form, protocol, site, and lead organization. In the future, it will be used to measure timeliness of submission by sites, conduct trend analysis of aggregated data, and assess site performance.

Registration and Credential Repository (RCR) and Delegation of Tasks Log (DTL). Mr. Boron gave an overview of two new IT applications that are being developed to handle investigator registration and delegation of tasks. RCR allows for identification of people; DTL defines what they can do at the site level. RCR is expected in August or September, while DTL is expected by July 31.

The current system for registering investigators is paper-based; the RCR provides an online registration application with the capacity for an electronic signature. It will help centralize data collection and storage. It allows clear identification of members of the study team and definition of people by registration types, which will be used to control access to clinical trial activities through the DTL. The RCR will also allow verification of good clinical practice and human subjects training and will integrate several forms that are currently filed on paper. People will register through the NCI Identity and Access Management (IAM) application, which establishes a unique identifier and provides electronic signature credentials. Any documents and training certificates can be easily shared with authorized entities.

The DTL will identify protocol-specific research tasks and who can do them. It will also maintain a complete audit trail of people and tasks across the life of the protocol. The protocol-specific DTL will be developed in collaboration between the lead organization and NCI. It will be piloted for protocols seeking regulatory approval.

Benefits of this new RCR/DTL process include enabling compliance with FDA investigator and sub-investigator data collection requirements; leveraging data capture across multiple NCI applications to make sure only qualified investigators are participating; controlling protocol-specific research tasks; decreasing the burden on investigators through the use of a single NCI-specific registration packet; and increasing accuracy, efficiency, and coordination between NCI and sites.

Questions and Discussion

Dr. Fingert asked whether central monitoring allows researchers to follow patients to look for safety concerns that emerge only after the studies are completed. Ms. Paul said the systems could be adapted for a post-study registry.

Dr. Mankoff expressed enthusiasm for handling delegation logs electronically. He asked whether FDA has endorsed the process. Mr. Boron said that CTEP is working with FDA and has had ongoing discussions. Dr. Mankoff asked whether this might be exported outside of NCI-directed trials. Dr. Montello said that for now, this is only for NCI trials, based on discussions with the FDA.

Dr. Langevin noted that there will be a learning curve for site staff and that there could be issues with the local computer systems. Dr. Montello agreed, but he said that harmonizing all of the functions in one system should make it easier for institutions to coordinate, since there is now one standardized package for almost the entire NCI.

Leading the Way: NCI's CIRB for Multisite Research. The talks continued with Dr. Massett presenting on NCI's CIRB.

NIH will require use of a single IRB for NIH-funded multisite research as of January 25, 2018. The goal is to streamline the review of multisite trials by eliminating redundant review and relieving administrative burdens without diminishing human subject protections. Public comments on the policy have reflected support from individual researchers, professional societies, and patient advocacy organizations, who believe it will streamline the process. There are concerns, particularly among academic institutions, IRBs, and organizations representing them, that the policy will decrease the quality and expertise of review, hamper coordination, discourage multisite research, and decrease the influence of local context. The need for data on experiences using a single IRB was clear.

NCI's CIRB has existed since 2001. From 2001 to 2012, NCI had a "facilitated review" model that was a partnership between local IRBs and the CIRB. By 2011, its use had plateaued, with adoption by about 45 percent of sites. In 2013, NCI switched to an "independent" model, in which the CIRB is the sole IRB of record, responsible for the local context considerations; the local IRB is not involved. The independent NCI CIRB was accredited in December 2012 and formally launched in January 2013.

Dr. Massett reviewed the key CIRB processes and analyzed trial and site data from 2013 to 2016 for the four networks that use the CIRB: the NCTN, the ETCTN, NCORP, and the Phase 0/I/II Cancer Prevention Consortia.

The CIRB has four boards: Adult Late Phase, Pediatric, Adult Early Phase, and Cancer Prevention and Control (CPC). The CIRB ensures high-quality reviews by including people with oncology expertise and knowledgeable lay members, screening members for conflict of interest, and providing orientation and training to members. It was re-accredited in 2015 by the Association for the Accreditation of Human Research Protection Programs. A routine FDA inspection in 2015 found no infractions.

The CIRB has a systematic approach to addressing local context, because it works with more than 2,000 sites. It uses a series of worksheets that collect information including state and local laws, conflict of interest policies, boilerplate language for the consent forms, and descriptions of study participants and vulnerable populations. The CIRB has a sophisticated communications process and aims to be transparent. It uses an online system, IRBManager, which is password-protected and integrated with other NCI clinical trials systems. A public-facing CIRB website, www.ncicirb.org, was recently revised and provides information for all CIRB stakeholders.

By 2017, 81 percent of NCI's 2,228 sites were enrolled in the CIRB. There was a 52 percent increase in the number of studies covered by the CIRB from 2013 to 2017, with 538 studies in the CIRB system at the end of 2016. The Adult Late Phase and Adult Early Phase Boards do the initial review of about 20 trials a year, taking a median of 39 (Adult Late Phase) or 54 (Adult Early Phase) days from

submission to approval. The Pediatric Board has about 10 initial reviews per year; the CPC Board, which was set up most recently, in 2015, has had 13 initial reviews per year and has taken a median of 87 days. The boards also conduct continuing reviews and amendment reviews, with the largest number carried out by the Adult Late Phase Board. In 2013, slightly fewer than 70 percent of studies at the sites enrolled in the CIRB were activated with the CIRB; in 2016, it was 96 percent.

For the 2 years in which many studies were still activated through a local IRB, Dr. Massett and Sharon Hampp, JD, RN, head of CIRB Strategy and Operations, compared the time it took for the local IRBs and CIRB to respond to major protocol amendments. Eight trials that used local IRBs were closed for major amendments, and it took 18 to 73 days to reopen the studies; CIRB sites can implement amendment changes within 24 to 48 hours.

The CIRB helpdesk responds to 6,000 to 7,000 requests annually. In 2017, the resolution time is an average of 3.4 days. The top reason for contacting the helpdesk is the local context review process. In a member satisfaction survey for NCTN key personnel and leadership, 84 percent said that the CIRB met or exceeded their expectations. Only 2 percent said that it needed significant improvement. The ETCTN satisfaction survey found that a majority were satisfied.

Lessons learned are that CIRBs:

- Require a commitment of resources
- Require carefully developed processes to manage local context issues, timelines, and conflicts of interest
- Must have the ability to communicate easily with multiple stakeholders (e.g., principal investigators, board members, clinical performance sites), which the NCI CIRB does through the website, helpdesk, and IT systems
- Can achieve widespread adoption and high satisfaction at a national level.

Dr. Massett and Ms. Hampp are in the process of writing up the data and welcomed input.

Questions and Discussion

Dr. Loehrer asked whether it would be possible to circulate the satisfaction survey to users of local IRBs. Dr. Massett said it could be done.

Dr. Fingert noted that many people do not have access to the Internet, and he wondered whether the CIRB could connect its work to efforts to expand Internet access to more people. Dr. Massett agreed that this would be good to have, but she said the CIRB's influence is limited outside of its own stakeholders.

Dr. Mankoff asked how the CIRB interacts with other local committees, such as the radiation safety committees and regulatory committees for INDs. Ms. Hampp said there is a lot of communication between the CIRB operations office and the local IRBs, trying to determine how to make the local context less of a burden for the local IRBs and how to coordinate what information is needed. Dr. Mankoff suggested applying this approach to other approval-related processes that are not IRB issues.

Dr. Langevin said her institution's experience is that using a CIRB streamlines the process, but with the local implementation of billing, coverage analysis, and so on, the amount of time to initially activate a study is about the same. However, the CIRB saves time on annual reviews and amendments. Dr. Massett agreed, adding that based on a survey of ETCTN study activation, CTEP is piloting approaches to address the other issues.

Dr. Davidson thanked Dr. Massett for the presentation. Dr. Davidson mentioned that it took a great deal of effort for a site to become a member of the CIRB. However, she discovered that the extra effort was worthwhile. She encouraged Dr. Massett to publish the data in advance of the more general adoption of single IRBs in 2018.

VIII. NCORP Updates and Renewal Plans

Worta McCaskill-Stevens, MD

Overview of NCORP. NCORP launched in 2014 as a consolidation of two existing programs, the NCI community cancer centers and the legacy Community Clinical Oncology Program (CCOP) and minority-based CCOP network. NCORP is a community-based research network designed to bring state-of-the-art trials and studies to individuals in their own communities. NCORP develops and conducts clinical trials in cancer prevention, symptom science, cancer screening, and post-treatment surveillance and also conducts quality of life studies embedded in treatment trials. NCORP accrues patients to NCTN treatment and imaging trials, conducts cancer care delivery research, and studies cancer disparities. Since 2014, NCORP has added about 600 new investigators, for a total of 4,025, and more than 120 components or subcomponents. It has a total of 46 community sites, 12 of which represent minorities and underserved populations. Seven research bases develop the concepts and conduct the trials for the program; five are NCTN groups, and the other two are the University of Rochester and Wake Forest University.

Dr. McCaskill-Stevens shared the following snapshots of NCORP:

- NCORP has a strong portfolio of symptom research, including an integrated biomarkers program, which allows investigators to pursue the mechanisms of cancer treatment side effects.
- NCORP is a major contributor of tumor tissue and blood samples to the pre-clinical patient-derived models program in the Precision Medicine Initiative.
- For NCI-MATCH, 44 percent of screenings came from NCORP.
- Having a CIRB has been very important for the success of NCORP.
- NCORP is reinvigorating cancer prevention research.
- The Cancer Moonshot regional committees had representation from the community through NCORP.

External Program Evaluation. Before the renewal of NCORP could occur, NCI required an external evaluation to assess scientific contributions and determine whether the program should be reissued and, if so, whether any changes were needed. The evaluation committee, chaired by Robin Zon, MD, from South Bend, Indiana, met recently. Dr. McCaskill-Stevens expects to share the outcome of the review at the next CTAC meeting. The expected timeline has the new FOAs being issued in March 2018, with applications due in June and awards made in August 2019.

Highlights of NCORP Research Activities. Dr. McCaskill-Stevens shared additional information on TMIST. Tomosynthesis is an x-ray technique that better visualizes dense breasts compared to standard digital mammography. Preliminary evidence suggests increased sensitivity and lower recall rates following tomosynthesis. In addition to clinical outcomes and genetic markers, the study is looking at diagnostic performance. TMIST is also collecting benign, premalignant, and malignant tissue, blood, and buccal samples for a biorepository. The trial was activated on July 6, 2017, and more than 100 sites have committed to participate.

The New-Onset Diabetes (NOD) Cohort Study is a collaboration with the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. People ages 50 to 85 with an elevated risk of pancreatic ductal adenocarcinoma (PDAC) often are diagnosed with that cancer soon after developing diabetes. The goals of the NOD Cohort Study are to identify and follow a large cohort of such individuals, develop a biorepository, clinically validate promising biomarkers of PDAC, and develop an early-detection protocol for sporadic PDAC. This study came from the Early Detection Research Group in the Division of Cancer Prevention (DCP), which is using NCORP as a resource to find participants. The cohort will have 10,000 new onset diabetes patients, 6,000 of whom are expected to come from NCORP. The estimated number of PDAC cases is 85 over a 3-year follow-up.

The Early-Onset Malignancy Initiative (EOMI) builds on the knowledge that some underrepresented populations have early onset of particular cancers (younger than 45 to 55 years, depending on the cancer type). Using prospective, clinically annotated, genomic data from newly diagnosed patients, EOMI will try to discover mechanisms for early-onset cancer; determine whether there is genetic variation between and among populations and demographic groups; identify rare genetic variants; identify lifestyle, environmental exposures, and behavioral risk factors that affect outcomes; and use the information to better understand risk factors, treatment options, and prognosis. EOMI is enrolling patients who are newly diagnosed with early-onset breast, colorectal, liver, multiple myeloma, prostate, or renal cancer in African-American, Caucasian, Hispanic, and Native American populations. (Renal cancer is being studied only in Native Americans.)

Cancer Prevention Steering Committee. In November 2015, DCP convened cancer prevention research experts and stakeholders to discuss the current state of cancer prevention research, identify key prevention research priorities for NCI, and identify studies that could be conducted within NCORP. Following an internal review of the cancer prevention research portfolio, they realized that a Cancer Prevention Steering Committee, which would offer consistent, rigorous, scientific reviews of cancer prevention research, was needed. Currently, possible members are being vetted, and the plan is to establish the committee soon.

Questions and Discussion

Dr. Petersen clarified for CTAC members that participation in the pancreatic diabetes screening cohort terminates after 2 or 3 years; it is not an endless cohort and is relatively inexpensive. This cohort could change the practice of medicine by identifying early cases of pancreatic cancer. Dr. Davidson said that CTAC looks forward to hearing from Dr. McCaskill-Stevens again in November.

IX. Cancer Care Delivery Research (CCDR) Portfolio

Ann Geiger, PhD, MPH

The goal of this session was to identify key policy challenges that affect the delivery of cancer care and clinical research, to describe NCI's research portfolio in this area, and to think about NCORP as a vehicle for CCDR.

Policy Challenges. The cost of health insurance and the amount that workers are contributing to their insurance premiums have increased much faster over the last few decades than earnings or inflation, which economists believe is unsustainable. Cancer care reimbursement has become more patient-centered, which includes things besides clinical outcomes, rather than reimbursing for the volume of procedures. Clinicians are expected to coordinate many kinds of treatment over a longer period, because survival has increased. The population is aging with more comorbidities. The buying power of research dollars has gone down.

Affordable Healthcare Act (ACA) of 2017. As of July 5, the House and Senate versions of their proposed respective repeals to the ACA included keeping provisions related to allowing young people to remain covered by their parents' insurance through age 26; the coverage of 10 essential benefits, including several types of cancer screening; and most of the Medicare adjustments enacted to date. Subsidies for insurance premiums are expected to change, likely resulting in the cost of insurance increasing for older adults and decreasing for younger adults. A possible solution to concerns about premium increases, offered by Senator Ted Cruz, would be to allow plans that do not cover all 10 essential benefits. Both bills would repeal the employer mandate, small business subsidies, and the individual mandate. The Democrats are particularly opposed to provisions that would turn Medicaid into a block grant program. From a health policy perspective, that provision would be an interesting development, because states would be able to apply for innovation funds to develop new approaches to providing care. Successful state-level innovations have led to changes at the federal level.

The Oncology Care Model (OCM). This payment model, from the Center for Medicare & Medicaid Innovation (CMMI) and the Centers for Medicare & Medicaid Services (CMS), is about improving care coordination to improve quality and decrease cost. About 3,000 oncologists at 200 practices have agreed to participate, reaching about 150,000 beneficiaries, with the partnership of 16 private insurers. The model bases payment on episodes which cover all oncology care for 6 months after initiation of either oral or intravenous chemotherapy (costs of actual chemotherapy agents are not included). Participating practices receive their usual fee-for-service payments plus two forms of incentive: $160 per beneficiary per month and additional payments based on performance on certain quality metrics. The practices are required to offer patient navigation, a care plan, 24/7 access to a clinician who can access medical records, use of therapies consistent with national guidelines, data-driven continuous quality improvement, and use of a certified electronic health record (EHR). CMMI is evaluating the OCM by both quantitative and qualitative methods, looking at the effect on beneficiaries' clinical and quality of life outcomes. It is also trying to compare changes over time in practices that participate and practices that do not.

CMS data may be useful for researchers who want to do long-term follow-up for health conditions requiring medical treatment, estimation of direct costs of health care utilization, and assessment of representativeness of trial enrollees. The OCM evaluation data probably will not be released until the evaluation is finished, and even then, Dr. Geiger predicts that they may not be very useful for NCI, because only a small proportion of trial participants will have received care at an OCM practice.

Healthcare Delivery Research Program. Given this policy context, NCI decided to take an active role in building the evidence base for how to deliver cancer care. In January 2015, the NCI Division of Cancer Control and Population Sciences formed a new program that focuses on health care delivery research. The program has three branches: Outcomes, which focuses on evaluating and improving the patient experience; Health Systems and Interventions, which observes and intervenes on provider behavior and context; and Healthcare Assessment, which assesses utilization, access, diffusion, and population-based outcomes. While health services research has often focused on the patient, the field needs to also pay attention to clinicians and the environments in which they practice.

Dr. Geiger shared some examples of the work in the CCDR grant portfolio:

- Participation in lung cancer screening and nodule management
- Reduction of diagnostic error
- Use of the EHR to measure and improve prostate cancer care
- Technology diffusion in cancer: variation, outcomes, and cost

The program is working to draw new investigators. Implementation science is also of interest, as is the symptom management research recommendations from the Cancer Moonshot and the 21st Century Cures Act. Dr. Geiger also shared some of the current funding opportunity announcements:

- Linking the Provider Recommendation to Adolescent HPV Vaccine Uptake
- Reducing Over-Screening for Breast, Cervical, and Colorectal Cancers Among Older Adults
- Surgical Disparities Research
- Oral Anticancer Agents: Utilization, Adherence, and Health Care Delivery
- Intervening with Cancer Caregivers to Improve Patient Health Outcomes and Optimize Healthcare Utilization
- End-of-Life and Palliative Needs of Adolescents and Young Adults (AYA) with Serious Illnesses

The program is also interested in financial toxicity. More than just bankruptcy or losing their homes, financial pressure may increase patient and family stress and reduce survival. (But good coping skills can dampen the impact.) Research has shown that young people with cancer are three to five times more likely to declare bankruptcy than others of their age, and people who declare bankruptcy are more likely to die in the next 5 years than those who do not.

NCORP as a Vehicle for CCDR. The goal is to make NCORP the premier infrastructure for doing clinical trials of health care delivery-based interventions. Dr. Geiger hopes that this can be a venue for studying changes to care that improve clinical outcomes, enhance patient experiences, and optimize value. For example, the group is trying to understand community sites' ability to do biomarker testing of common solid cancers in a way that is consistent with NCTN guidelines. She also highlighted a study about documentation and delivery of guideline-consistent treatment in adolescents and young adults with leukemia. Other studies focus on long-term assessment of financial toxicity for people with colon or rectal cancer or blood cancers. She cited a study of the effect of standing orders on use of colony-stimulating factor in neutropenic patients as the kind of potentially practice-changing study that can be conducted by NCORP and as an example of implementation science.

How to Engage Clinicians. A recent Cancer Care Delivery Research Steering Committee (CCDR SC) meeting suggested new directions for research in care coordination and practice change, including clinician behavior and the use of technology to monitor and treat patients with various symptoms. NCI funds many studies that develop decision aids, but those may not be widely adopted, even when the evidence of their benefit is strong. Engaging clinicians in framing the research questions of interest to them is crucial, but it has been challenging to engage both clinicians and researchers in this process.

Questions and Discussion

Dr. Davidson asked Dr. Godley, who chairs the CCDR SC, to share his perspective. Dr. Godley emphasized three points from the last two presentations:

- There are major changes in the delivery models and infrastructure that affect the quality and efficiency of cancer care, and cancer care is likely to get more complicated. The CCDR field is studying this.
- NCI was visionary for developing a dedicated program to evaluate cancer care delivery. It is important that the research is being done at NCORP sites, which reflect practice in the general population.

- The approved concepts represent key areas of care delivery that were not covered by other parts of NCI.

Dr. Perez-Soler said that he represents a site that is part of both NCORP and the Oncology Care Model and that he would like to engage young investigators in CCDR. However, he does not know where to find mentors. Dr. Geiger said that each NCORP research base has a CCDR committee that includes people who are eminent in the field, and she offered to help him identify a few possibilities.

Dr. Langevin mentioned RVUs (relative value units, a measure of physician productivity used by CMS) and said that CCDR investigators need protected time and an incentive to do research. Dr. Geiger agreed that protected time for research is important.

Dr. Meropol noted that there are few investigators who do health services research. In terms of framing questions, he suggested talking to hospital administrators and analysts involved in the OCM who, although not scientists, are very interested in the details of health care delivery and cancer and the outcomes associated with the OCM. First, Dr. Geiger said that there has been more outreach to behavioral scientists and intervention scientists. Second, the program is very interested in engaging administrators and operations people, but doing so is very difficult. It may be easier through NCORP, since the practices are smaller. The Wake Forest University research base has surveyed sites on their practices, including patient demographics and doctors' specialties, which led to creation of relationships with administrators. One of the challenges is that administrators tend to think in 3- to 6-month timeframes, while for research, it is necessary to think about what the problems will be in 5 years.

Dr. Loehrer returned to the issue of needing more people who are trained in health services research. He suggested partnering with NCI-Designated Cancer Centers to get trainees interested in this research. Dr. Geiger said there has been thought about how to do this and that new programs may begin in the next few years.

Dr. Arons asked whether the program is carrying out or supporting research on access to cancer care or trial participation. Dr. Geiger said that the NIH Office of the Director issued a notice suggesting that some health economics research that would be required to answer these questions may be outside the purview of NIH. However, the program is funding a limited portfolio of related research—for example, comparing access and health outcomes in states where Medicaid was or was not expanded.

X. NCI-COG Pediatric MATCH Trial

Nita Seibel, MD

This trial is being carried out in collaboration with the Children's Oncology Group (COG). Dr. Seibel is co-chair of the trial, along with Will Parsons, MD, PhD, of COG.

Overview of Pediatric MATCH. Pediatric MATCH is a precision medicine clinical trial for children and adolescents ages 1 to 21 with refractory and recurrent solid tumors. This includes central nervous system tumors, non-Hodgkin lymphoma, and histiocytoses. About 200 to 300 patients are expected to be screened per year, for a total of 1,000 patients. The hypothesis is that by identifying genetic changes affecting pathways of interest in refractory and recurrent pediatric cancer, the researchers will be able to deliver targeted anticancer therapy that produces a clinically meaningful objective response rate.

The same genetic platform as in adult MATCH will be used, although it is a newer version with testing for more than 160 genes. For adults, the match rate is between 20 percent and 25 percent. For children, it is expected to be 10 percent or less. The number of pediatric tumors that have mutations is

lower than the number of tumors for adults, and pediatric tumors have different types of mutations. For example, in a study of 240 high-risk neuroblastoma patients, only a few patients had identifiable mutations; and of those, only the *ALK* mutation could be targeted.

Patients who meet the eligibility criteria for a given treatment arm can be enrolled on the arm and stay on the treatment as long as they have a response or stable disease. If they develop progressive disease and, at the time the tumor was analyzed, another actionable mutation was identified, they can be enrolled on a second arm that targets this mutation.

The trial incorporates nine classes of therapeutic agents and will probably be activated with five or six. The goal is to enroll at least 20 patients per arm. If there are three responses or more, this will be considered of interest, and the arm can be expanded to include additional patients.

Target and Agent Prioritization (TAP) Committee. The levels of evidence for Pediatric MATCH are the same as for adult MATCH, for both target selection and drugs. The TAP Committee, led by Katherine Janeway, MD, included members from COG, NCI, FDA, and adult MATCH. The committee's charge was to prioritize the most relevant molecular targets and corresponding agents to recommend for inclusion on the study. The committee started with a list of high-priority targets and agents; performed a detailed assessment of each target/agent pair and assigned a priority score; presented the target/agent pair to the committee, which voted; and forwarded it to be reviewed by MATCH leadership. Then pharmaceutical partners were engaged to determine availability of agents in a particular class. The process was published in the *Journal of the National Cancer Institute* in February 2017.

Workflow. A patient's biopsy is sent to Nationwide Children's Hospital, the site of the COG Biopathology lab. The lab conducts quality control and extracts nucleic acids, which are sent to either MD Anderson Cancer Center or the Molecular Characterization Laboratory at the Frederick National Laboratory for Cancer Research for genetic analysis. Specimens on slides will be sent to MD Anderson for immunohistochemistry. The results will be entered in the software platform MATCHBox for matching with an agent; a report will go to the treating pediatric oncologist after review by the Pediatric MATCH verification team.

Design Features. Dr. Seibel shared the following design features of Pediatric MATCH:

- The biopsy must be obtained from tissue post-relapse to be sure that the current tumor genome is analyzed. (Diagnostic biopsies from brainstem glioma patients are allowed.)
- The vast majority of patients are not expected to match a treatment arm and may be enrolled in other COG studies or Pediatric Brain Tumor Consortium studies.
- Not all agents will have been tested in children beforehand. Agents with an adult recommended phase II dose (with detailed pharmacokinetics, review of toxicity, and input from the pharmaceutical company) are being included.
- The primary endpoint is response rate (tumor regression).
- Patients who do not have the biomarker may be enrolled on select arms when there is demonstrated activity of the agent and equivocal data for needing the biomarker.
- For enrolled patients, germline DNA is being analyzed because research has found that 8 percent to 10 percent of pediatric patients with solid tumors have a cancer susceptibility mutation. The germline DNA report will be sent to the treating oncologist.

Challenges in Development of Pediatric MATCH. There have been many challenges to developing this trial, which Dr. Seibel shared:

- Deciding on risk determination with FDA

- Establishing the analytical performance of assays on pediatric tissue
- Incorporating germline testing and validation into the workflow
- Developing a process for sharing germline results with the referring pediatric oncologist and eventually with the family
- Incorporating Nationwide Children's Hospital into the workflow
- Building MATCHBox for Pediatric MATCH
- Adjusting processes to meet New York State laboratory regulations
- Educating and engaging advocates in the process
- Managing families' expectations
- Coordinating with adult MATCH, which was very busy toward the end
- Managing the pediatric CIRB's workload

Dr. Seibel concluded by reminding everyone of all the work that went into planning Pediatric MATCH and that adult MATCH couldn't just be superimposed for pediatrics. She offered to return in a year or so to update CTAC on the progress of Pediatric MATCH.

Questions and Discussion

Dr. Davidson asked when Pediatric MATCH was opening. Dr. Seibel said the hope was to open the week after the meeting—as soon as the pediatric CIRB signs off on the arms.

Dr. Mankoff shared his experience with imaging in NCI-MATCH, currently led by Susanna Lee, MD, PhD, in collaboration with Keith T. Flaherty, MD, the MATCH principal investigator. The images are a rich repository for the field of radiomics and radiogenomics. Dr. Mankoff suggested contacting Dr. Lee and Dr. Flaherty. Dr. Seibel said there have been discussions with COG about doing this. Dr. Mankoff said that capturing the images is helpful even without being able to connect them directly to the biopsy and that it takes little extra effort to build a repository.

Dr. Arons congratulated Dr. Seibel on progress; this trial is important to the pediatric oncology community, including patients, parents, and advocacy groups. He asked whether NCI could connect with childhood cancer advocacy coalitions before a press release is issued so that they can be ready to support the study and the announcement. Dr. Kibbe and Dr. Seibel said that the advocacy groups would be informed about the press release.

Dr. Langevin noted that there is an overlap between NCI-MATCH and Pediatric MATCH for ages 18 to 21. She asked whether the investigator will be informed if someone does not match on Pediatric MATCH but matches an adult MATCH arm. Dr. Seibel said they are working with adult MATCH on the possibility of enrolling patients as young as 12 on the adult arms.

Dr. Fingert suggested looking into transcriptional modulation agents or transcriptional controls for the patients who do not match to an arm, such as those being worked on by Syros Pharmaceuticals, Inc., which he does not have an interest in. Dr. Seibel thanked him for the suggestion. The TAP Committee is continuing to evaluate new agents and targets and can consider this.

XI. Ongoing and New Business

Nancy E. Davidson, MD

Dr. Davidson acknowledged Dr. Kibbe, who is leaving NIH for a position at Duke University. She thanked him for his service at NCI, and the attendees thanked him with a round of applause.

The next in-person meeting of CTAC is November 1, 2017. Dr. Prindiville listed the current CTAC working groups:

- Progress in PDAC Research
- Progress in Small Cell Lung Cancer (SCLC) Research
- Clinical Trials Informatics
- Clinical Trials Strategic Assessment (in the process of forming)

Dr. Prindiville reminded members that the PDAC and SCLC working groups were formed under the auspices of CTAC in response to the Recalcitrant Cancer Research Act of 2012 to assess research progress and identify new scientific opportunities. She referred members to their binders, which contained lists of the grants awarded in response to the FOAs that resulted from the recommendations of these working groups. In 2018, the extramural community will be coming together again to assess the progress in PDAC and SCLC. The Clinical Trials Informatics Working Group has been active over the last year and is expected to report out in November. The Clinical Trials Strategic Assessment Working Group will be looking at steering committee portfolios and the priorities for NCTN and NCORP trials.

Dr. Prindiville asked CTAC members to respond promptly when they are contacted about travel in August or September, because the beginning of the fiscal year can be a difficult time to arrange travel.

Dr. Petersen asked whether Dr. Sharpless will be joining the meeting. Dr. Davidson said that he will be encouraged to join and that she imagines that he will make it a priority to visit all of his advisory groups early in his term. Dr. Doroshow is expected to continue as deputy director.

Dr. Fingert made a suggestion related to core competencies for investigators outside the U.S. who take part in trials. Dr. Davidson said this would be discussed in a meeting to be held after this meeting closed.

XII. Adjournment

Nancy E. Davidson, MD

There being no further business, the 33rd meeting of CTAC was adjourned at 2:01 p.m. on Wednesday, July 12, 2017.

Appendix

National Institutes of Health
National Cancer Institute
Clinical Trials and Translational Research Advisory Committee

CHAIR

Nancy E. Davidson, MD **2018**
Senior Vice President, Director and Full Member
Clinical Research Division
Fred Hutchinson Cancer Research Center President
& Executive Director
Seattle Cancer Care Alliance Head
Department of Medicine
Division of Medical Oncology
University of Washington
Seattle, WA

MEMBERS

David F. Arons, JD (NCRA) **2016**
Chief Executive Officer
National Brain Tumor Society
Watertown, MA

Susan M. Blaney, MD **2019**
Vice President for Clinical and Translational Research
Vice Chair for Research
Department of Pediatrics
Baylor College of Medicine
Texas Children's Hospital
Houston, TX

Walter J. Curran, Jr., MD, PhD **2019**
Executive Director
Winship Cancer Institute of Emory University
Atlanta, GA

David M. Gershenson, MD **2020**
Professor of Gynecology
Department of Gynecologic Oncology and Reproductive Medicine
Division of Surgery
University of Texas MD Anderson Cancer Center
Houston, TX

Michael L. LeBlanc, PhD **2019**
Member
Fred Hutchinson Cancer Research Center
Research Professor
Department of Biostatistics
University of Washington
Seattle, WA

Patrick J. Loehrer, Sr., MD **2020**
Director
Melvin and Bren Simon Cancer Center
Associate Dean for Cancer Research
Indiana University School of Medicine
Indianapolis, IN

David A. Mankoff, MD, PhD **2019**
Gerd Muehllehner Professor of Radiology
Chief of Nuclear Medicine and Clinical Molecular Imaging
Perelman School of Medicine
University of Pennsylvania
Philadelphia, PA

Edith P. Mitchell, MD **2016**
Associate Director for Diversity and Minority Programs
Sidney Kimmel Cancer Center
Clinical Professor of Medicine and Medical Oncology
Thomas Jefferson University
Philadelphia, PA

Nikhil C. Munshi, MD **2016**
Associate Director
Jerome Lipper Multiple Myeloma Center
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
Boston, MA

Augusto C. Ochoa, MD **2018**
Director
Stanley S. Scott Cancer Center
Professor
Department of Pediatrics
Louisiana State University Health Sciences Center
New Orleans, LA

Gloria M. Petersen, PhD **2019**
Deputy Director, Mayo Clinic Cancer Center
Professor of Epidemiology
Department of Health Sciences Research
Mayo Clinic College of Medicine
Rochester, MN

Louis M. Weiner, MD **2017**
Director
Lombardi Comprehensive Cancer Center
Francis L. and Charlotte G. Gragnani Chair
Department of Oncology
Georgetown University Medical Center
Washington, DC

***Ex Officio* Members**

William L. Dahut, MD
Scientific Director of Clinical Research
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Bethesda, MD

James H. Doroshow, MD
Deputy Director
Clinical and Translational Research
Director, Division of Cancer Treatment and Diagnosis
National Cancer Institute
National Institutes of Health
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Paulette S. Gray, PhD
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U.S. Department of Veterans Affairs
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National Institutes of Health
Bethesda, MD

Richard Pazdur, MD, FACP
Director
Office of Hematology and Oncology Products
U.S. Food and Drug Administration
Silver Spring, MD

***Ad Hoc* Members**

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University of Michigan School of Nursing
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Bixby Professor and Chairman
Department of Surgery
Washington University School of Medicine in St. Louis
St. Louis, MO

Howard Fingert, MD, FACP
Senior Medical Director
Oncology Clinical Research
Millennium, The Takeda Oncology Research Company
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Deputy Director
Albert Einstein Cancer Center
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Provost & Chief Scientific Officer
Director
Comprehensive Cancer Center and Beckman Research Institute
Irell & Manella Cancer Center Director's Distinguished Chair
Comprehensive Cancer Center
City of Hope
Duarte, CA

Dan Theodorescu, MD, PhD
Professor and Director
Department of Pharmacology and Urology
University of Colorado Comprehensive Cancer Center
Aurora, CO

Executive Secretary

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