DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
44th CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC) MEETING

Summary of Meeting
March 17, 2021

Webinar

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
Summary of Meeting
March 17, 2021

The 44th meeting of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) began on Wednesday, March 17, 2021, at 12:00 p.m. The CTAC chair, Dr. Loehrer, presided.[1] The meeting was adjourned at 2:49 p.m.

Chair
Patrick J. Loehrer, Sr.

CTAC Members
Debra L. Barton
Smita Bhatia
Charles D. Blanke
Edward Chu (absent)
Janet Ellen Dancey
Nancy E. Davidson
Anjelica Q. Davis
Adam P. Dicker
Ernest T. Hawk
Michael V. Knopp
Anne-Marie R. Langevin
Seth P. Lerner
Mia Levy
Sumithra J. Mandrekar
Lynn M. Matrisian
Neal J. Meropol
Carolyn Y. Muller
Roman Perez-Soler
Raphael E. Pollock
Suresh S. Ramalingam
Steven T. Rosen
Victor M. Santana
Julie M. Vose

***Ex Officio* Members**
William L. Dahut, NCI
James H. Doroshow, NCI
Paulette S. Gray, NCI
Michael J. Kelley, U.S. Department of Veterans Affairs
Anthony Kerlavage, NCI
Julie Schneider, U.S. Food and Drug Administration (alternate for Richard Pazdur)
Xiufen Sui, Centers for Medicare & Medicaid Services

Executive Secretary
Sheila A. Prindiville, NCI

Presenters
Rick Bangs, MBA, PMP, Chair, SWOG Patient Advocate Committee
Debra L. Barton, PhD, RN, FAAN, Associate Dean for Research and Rackham Graduate Studies; Mary Lou Willard French Endowed Chair, Department of Systems, Populations, and Leadership; Professor of Nursing and Professor of Psychiatry, University of Michigan School of Nursing
Nancy E. Davidson, MD, Senior Vice President, Director, and Full Member, Clinical Research Division, Fred Hutchinson Cancer Research Center; President and Executive Director, Seattle Cancer Care Alliance; Head, Division of Medical Oncology, Department of Medicine, University of Washington
James H. Doroshow, MD, Deputy Director, Clinical and Translational Research; Director, Division of Cancer Treatment and Diagnosis, NCI
M.K. Holohan, JD, Director, Office of Government and Congressional Relations, NCI
Patrick J. Loehrer, Sr., MD, Director, Indiana University Melvin and Bren Simon Comprehensive Cancer Center; Associate Dean for Cancer Research, Indiana University School of Medicine
Norman E. Sharpless, MD, Director, NCI

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

TABLE OF CONTENTS
Wednesday, March 17, 2021

I. Call to Order and Opening Remarks

Patrick J. Loehrer, Sr., MD

Dr. Loehrer called the 44th meeting of CTAC to order and welcomed participants, including several new CTAC members: Drs. Bhatia, Lerner, Muller, Pollock, and Ramalingam. In addition, Dr. Schneider was welcomed as the U.S. Food and Drug Administration representative in place of Dr. Pazdur at this meeting.

Dr. Loehrer reviewed the confidentiality and conflict-of-interest practices required of CTAC members during their deliberations. He invited members of the public to send written comments on issues discussed during the meeting to Dr. Prindiville within 10 days of the meeting. National Institutes of Health Events Management was videocasting the meeting, and the videocast became available for viewing at https://videocast.nih.gov/watch=41220 after the meeting.

The next CTAC meeting, which will take place on Wednesday, July 14, 2021, will also be virtual.

Motion. A motion to accept the minutes of the 43rd CTAC meeting, held on November 4, 2020, was approved.

II. NCI Director's Update

Norman E. Sharpless, MD

New Presidential Administration. In spite of the ongoing public health tragedy of COVID-19 and the need for teleworking, 2020 was a productive year for cancer research and NCI; Dr. Sharpless expected 2021 to be even more productive. The new presidential administration has clearly indicated a strong interest in cancer research, as shown in comments from the President, Vice President, and First Lady, as well as a recent Oval Office discussion of progress in cancer research by Democratic and Republican members of Congress.

First Lady Jill Biden, EdD, visited NCI virtually in February. This meeting featured presentations by Worta McCaskill-Stevens, MD, MS, Chief, Community Oncology and Prevention Trials Research Group, about the NCI Community Oncology Research Program; Stephanie Goff, MD, Associate Research Physician, Surgery Branch, about her cutting-edge research on metastatic cancer; and Ligia Pinto, PhD, Director, Vaccine, Immunity and Cancer Program, Frederick National Laboratory for Cancer Research, about NCI's COVID-19–related activities. Dr. Biden and Dr. Sharpless also visited the Massey Cancer Center in Richmond, Virginia, to learn about the center's research. Cancer is one of the First Lady's top focus areas. Finally, President Joe Biden and Vice President Kamala Harris visited the National Institutes of Health (NIH) early in the year to discuss their general interest in science.

50th Anniversary of the National Cancer Act. The commemoration of the 50th anniversary of the National Cancer Act is underway, and NCI will discuss this topic throughout the year. This celebration provides an opportunity to inspire the next generation of cancer researchers and cancer research supporters. Commemoration activities will highlight progress in cancer research across the nation from basic science to translational and implementation science.

The communications materials for the anniversary commemoration are not branded with the NCI logo, so they can be used by cancer research stakeholders to advance the shared vision that nothing will stop us in our effort to end cancer suffering. Dr. Sharpless played a video summarizing accomplishments in cancer research over the last 50 years. He added that although the National Cancer Act has supported important contributions and progress in cancer research, the research community still has a long way to go to reach the goal of ending cancer suffering.

Cancer Moonshot. The Cancer Moonshot, which was given 7 years of funding from Congress beginning in fiscal year (FY) 2017, is starting its fifth year of funding. Moonshot projects are conducting research across the cancer continuum but focus heavily on translational research. Projects are designed to, for example, increase fundamental understanding of the drivers of childhood cancers and develop targeted approaches to those drivers, increase genetic counseling and screening for individuals with inherited predispositions to cancer, create new therapeutic approaches and identify biomarkers and responses to immunotherapy drugs, and engage people who have cancer more directly in research.

The Moonshot goal of expanding the pool and diversity of the cancer research workforce is being met. For example, 25 percent of extramural principal investigators with Moonshot funding are new investigators, 5 percent are early-stage investigators, and 12 percent are established investigators who have not received NCI funding before.

NCI is developing a plan to sustain the Moonshot programs after congressional funding ends in 2023.

NCI Budget. When CTAC last met in November 2020, NCI and the federal government were operating under a continuing resolution. Congress has now completed the FY 2021 appropriations process, and NCI received $6.56 billion, a $119 million increase from FY 2020. This appropriation includes $195 million for the Cancer Moonshot and $50 million for the second year of the Childhood Cancer Data Initiative (CCDI). The appropriation bill instructs NCI to spend $37.5 million to support research project grants and increase success rates for investigator-initiated research applications. Congress has clearly heard that NCI paylines are low because NCI receives so many strong applications. This is the second year in a row in which Congress has asked NCI to dedicate funds to address this problem.

In its annual budget plan and proposal for FY 2022, NCI established a goal of reaching a payline of the 15th percentile by FY 2025 (the "15 by 25" goal). NCI is setting established investigator R01 paylines at the 11th percentile in FY 2021, which is the second year in a row of increased R01 paylines. Altogether, congressional support has enabled NCI to raise the R01 payline by 35 percent since 2019, when the payline was just 8 percent. For 2 consecutive years, NCI has also raised the payline, now at the 16th percentile, for early-stage investigators.

NCI's COVID-19 Activities. NCI's expertise and resources have been central to some critical SARS-CoV-2 research at a time when the institute has maintained its focus on cancer research. NCI's COVID-19 activities include foundational serology studies through the Serological Sciences Network and research on excess mortality, digital health solutions, and COVID-19 vaccine development. In addition, NCI provides flexibility for grantees to adapt clinical trials as needed during the pandemic.

The NCI COVID-19 in Cancer Patients Study has activated 875 sites in all 50 states, the District of Columbia, Puerto Rico, and Canada. The study will enroll 2,000 patients and follow them for 2 years to determine the natural history of COVID-19 in people with cancer.

NCI's Division of Cancer Control and Population Sciences and the NIH Office of Behavioral and Social Sciences Research recently released a timely report on vaccine hesitancy and vaccine confidence. This report leverages NCI's expertise, gained through research, to better understand and address health-related misinformation online. The report has been widely shared across the Department of Health and Human Services; the National Academies of Science, Engineering, and Medicine; the National Science Foundation; the Consortium of Social Science Associations; the American Psychological Association; and many state and local public health authorities.

CCDI. The second year of funding for CCDI is beginning. In the coming year, NCI will further engage the cancer research community in this initiative, which has established three working groups:

- Childhood Cancer Data Platform Working Group: developing infrastructure to support and enhance data sharing and aggregation
- Childhood Cancer Cohort Working Group: gathering data on every child in the United States who has a cancer diagnosis from various sources, including Medicaid
- Molecular Characterization Protocol Working Group: developing a national strategy to offer clinical and research molecular characterization to every child with cancer in the United States

A steering committee is overseeing CCDI activities, and the CCDI Engagement Committee is ensuring community engagement in this important initiative. The working group and committee members have been chosen, and their charters have been finalized. The leaders of these groups have had several meetings, and the steering committee will meet later in March.

Ending Structural Racism. NIH has established the UNITE initiative to address structural racism in biomedical research with the goal of ending racial inequity. The initiative's primary goals are to support:

U Understanding stakeholder experiences through listening and learning
N New research on health disparities, minority health, and health equities
I Improving the NIH culture and structure for equity, inclusion, and excellence
T Transparency, communication, and accountability with NIH's internal and external stakeholders
E Extramural research ecosystem: changing policy, culture, and structure to promote workforce diversity

NCI shares NIH's goal of ending structural racism in biomedical research, and many UNITE working group members come from NCI. NCI has developed its own equity and inclusion program, led by the Equity Council, which Dr. Sharpless chairs. The program has five working groups that address cancer health disparities, diversity of the cancer research workforce, promotion of an inclusive and equitable NCI community, evaluation of equity activities, and communications and outreach for equity activities.

NCI Research Highlights. The Cancer Grand Challenges program, led by NCI and Cancer Research UK, funds research by multidisciplinary teams from around the world on novel topics that offer the potential to advance bold cancer research and improve outcomes for people affected by cancer. Expressions of interest in the nine 2021 cancer grand challenges will be accepted until April 22, 2021. Because of the disruptions caused by the pandemic and the new Cancer Grand Challenges effort, NCI is pausing the Provocative Questions initiative this year and will not issue a new announcement in the fall. Instead, the institute will evaluate the program and identify next steps.

A recent NCI-sponsored study showed that fecal microbiota transplants promote responses to immunotherapy with checkpoint inhibitors in patients who have melanoma and have not responded to immunotherapy before entering the study.

On March 9, 2021, the U.S. Preventive Services Task Force released its updated lung cancer screening recommendations, which now call for annual lung cancer screening with low-dose computed tomography for adults ages 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit in the past 15 years. The initial recommendation for lung cancer screening was partially based on the NCI-sponsored National Lung Screening Trial, and the task force used NCI Cancer Intervention and Surveillance Modeling Network (CISNET) modeling to identify the ages to start and

stop screening and the pack-year threshold for screening. This new recommendation could almost double the number of people who are eligible for screening, especially individuals from underrepresented populations and women, who were less likely to meet eligibility criteria using the previous guidelines. This recommendation therefore offers a way to make significant progress in reducing lung cancer mortality rates.

When Dr. Sharpless arrived at NCI, he identified increasing NCI support for chimeric antigen receptor (CAR) T-cell studies as a top priority. NCI has now created a centralized facility at the Frederick National Laboratory to manufacture CAR T cells for multicenter trials. In addition, a new core will produce vectors for the next generation of cellular immunotherapies and relieve the significant backlogs in vector design and production.

Questions and Discussion

Dr. Loehrer asked whether the meeting between members of Congress and President Biden identified congressional priorities for cancer research or was otherwise relevant to NCI's future funding or focus areas. Dr. Sharpless replied that attendees apparently expressed broad support for cancer research and discussed the President's plan to create the Advanced Research Projects Agency for Health, which will distribute funding in novel ways to address topics such as cancer research. Attendees also expressed strong support for NIH and pride in the recent funding increases for the agency.

Dr. Sharpless reported that Eric Lander, PhD, is expected to be confirmed as White House science advisor and director of the Office of Science and Technology Policy. Dr. Lander has worked closely with NCI for many years.

Dr. Davidson asked for more information on the new manufacturing facility in Frederick, Maryland, and whether institutions will need to pay for the CAR T cells and vectors produced. Dr. Doroshow said that an announcement will be distributed once this facility is ready and that the deadline for applications for vector or CAR T-cell production is in July. If an investigator has funding for a trial and submits patient material and a special emphasis panel approves the request, the facility will produce the requested materials.

Dr. Knopp asked whether NCI is addressing delays in care that have resulted from the pandemic. Dr. Sharpless replied that NCI has several activities in this area. In April 2020, Dr. Sharpless asked CISNET to study the impact of delays in care and lower rates of screening and diagnosis on breast and colon cancer care. The CISNET models showed that delayed diagnosis, screening, and treatment would lead to 10,000 excess deaths from breast cancer and colon cancer over the next decade. Similar effects are likely to occur in other types of cancer as well.

Diagnosis rates declined by more than 50 percent at the height of the pandemic, and many treatments are being delayed. As clinics resume screening, they are finding more advanced-stage cancers, demonstrating the cost of screening delays. NCI is working with various partners, including several professional societies, to address this issue. For example, NCI is explaining the importance of avoiding delays in screening, diagnosis, and treatment for cancer, and it has developed funding opportunities to identify the outcomes of these delays as well as ways to prevent them.

Pandemic-related disruptions have resulted in substantial costs for NCI. For example, NCI will need to provide cost extensions for training grants, clinical trials have had to pause accrual, and certain R01 awards will not be completed on time. NCI has not yet received funds from Congress for restart costs. The pandemic continues to be very disruptive to cancer research and cancer care.

III. Legislative Update

M.K. Holohan, JD

New Presidential Administration. At the time of this meeting, the U.S. Senate had confirmed 18 out of 23 nominees for Cabinet positions in President Joe Biden's new administration. The director of the Office of Science and Technology Policy, which requires Senate confirmation, will now also be a Cabinet position, signaling the importance of science to this President and his administration. Eric Lander, PhD, president and founding director of the Broad Institute, has been nominated for this position.

The nominee for Secretary of Health and Human Services, Xavier Becerra, was previously Attorney General of the state of California. He also served 12 terms as a Democratic member of the House of Representatives, where he was a member of the Ways and Means Committee and chaired the House Democratic Caucus and Congressional Hispanic Caucus. Secretary Becerra has been involved in youth tobacco control.

2020 Election Results. At the time of this meeting, the House of Representatives had 219 Democrats, 211 Republicans, and 5 vacant positions. The Senate is split with 48 Democrats, 2 independent senators who caucus with the Democrats, and 50 Republicans. The Vice President can break ties when necessary.

The 117th Congress breaks several records. It is the most racially and ethnically diverse Congress in history; 23 percent of voting members have racial or ethnic minority backgrounds. In addition, 27 percent of seats (a 50 percent increase over the last decade) are held by women. Ms. Holohan also listed the chairs and ranking members, including new leaders in these positions, of the House Committee on Energy and Commerce; the Senate Committee on Health, Education, Labor and Pensions; and the House Committee on Appropriations.

COVID-19 Relief Packages. Ms. Holohan reminded CTAC of the major COVID-19 relief packages signed into law between March and December 2020. President Biden recently signed the $1.9 trillion American Rescue Plan Act of 2021 into law.

Efforts to Address Lost Productivity. The Research Investment to Spark the Economy (RISE) Act would authorize almost $25 billion to support U.S. researchers affected by the pandemic, and the bill includes $10 billion for the National Institutes of Health (NIH). This bill was reintroduced in the 117th Congress and has 124 cosponsors. In the 116th Congress, the Health and Economic Recovery Omnibus Emergency Solutions (Heroes) Act, which included $3 billion for NIH, did not become law, and $5 billion in the FY 2021 House appropriations bill for NIH to offset pandemic-related costs was not part of the final appropriation.

Fiscal Year 2022 Appropriations. The appropriations process typically begins with the submission of the President's budget request to Congress, usually on the first Monday in February. After the budget request is reviewed by the appropriators and discussed at hearings, the budget legislation is written and marked up, and the spending bills are passed. With new administrations, it is understood that developing a budget request takes longer, and NCI does not anticipate a budget request from the Biden Administration until at least March or April. For this and other reasons, the FY 2022 appropriations process is unlikely to be completed by the start of the fiscal year.

Appropriators have decided to change the rules to allow earmarks (member-directed spending on specific projects), although party-specific differences in planning are occurring, and the House and Senate are taking different approaches. There is some hope that the return of earmarks that might benefit members'

states and districts could be an incentive for completing spending bills and avoiding a yearlong continuing resolution.

Other Major Funding Bills. Congress is beginning to discuss infrastructure legislation, defined very broadly. Instead of trying to pass one large package, Congress might split the bill into separate packages to move the legislation forward.

President Biden has also discussed the need to compete successfully with China in science and technology, and Senator Majority Leader Chuck Schumer (D-NY) has directed all Senate authorizing committees to draft legislation to outcompete China and create new American jobs. The centerpiece of this legislation would be the Endless Frontier Act, introduced in the 116th Congress, which would increase the budget for the National Science Foundation by $100 billion over 10 years.

As Dr. Sharpless mentioned, President Biden had convened a bipartisan meeting of members of the House of Representatives and the Senate, including many members who had led the development and passage of the 21st Century Cures Act, to discuss cancer research.

Questions and Discussion

Dr. Blanke said that many CTAC members take part in the American Society of Clinical Oncology's annual advocacy days on Capitol Hill and asked about cancer research–related legislation or issues that advocates might emphasize in these types of meetings. Ms. Holohan said that speaking with a unified voice through associations is one of the most powerful ways for biomedical researchers to communicate with Congress, and Congress appreciates hearing from researchers and patients about research advances. Ms. Holohan encouraged cancer researchers to work with their institutions and get to know their state delegations to educate them about cancer research. Researchers should emphasize issues that they believe could make a difference in their communities. One issue that advocates might discuss is telehealth, which is important for biomedical research and health care delivery systems.

Dr. Sharpless pointed out that although more funding for NCI is always appreciated, the kind of funding matters. Cancer Moonshot funding went primarily to translational research projects and could not be used for investigator-initiated research, which is one reason why NCI paylines dropped during the first years of the Moonshot. Many new drugs and devices approved by the U.S. Food and Drug Administration result from NCI-funded R01 awards. NCI supporters need to emphasize the importance of the "15 by 25" goal (raising NCI's R01 payline to the 15th percentile by 2025). Ideally, additional funding for NCI will support R01 awards for basic science research that really make a difference in cancer research progress.

Dr. Ramalingam asked Ms. Holohan whether the American Rescue Plan includes funds for NCI. Ms. Holohan explained that this act does not provide funding for NCI but does include funding for the Department of Health and Human Services, mostly for the Centers for Disease Control and Prevention and Food and Drug Administration, for vaccine delivery and speeding the approval of COVID-19 treatments.

IV. CTAC Cancer Screening Trials Working Group Report

Nancy E. Davidson, MD

After the COVID-19 pandemic began, accrual to NCI-sponsored clinical trials, including NCI National Clinical Trials Network and NCI Community Oncology Research Program trials, dropped dramatically. Although accrual rates to clinical trials have risen in recent months, these increases have not been uniform, and cancer screening trials appear to have been disproportionately affected. Decreased

accrual rates in cancer screening trials will delay the completion of these trials and potentially increase the overall cost of their conduct. In addition, some trials might be unable to answer the study questions as originally intended or, when completed, might have findings that are less relevant to contemporary practice.

In November 2020, NCI established the *ad hoc* Working Group on Cancer Screening Trials to advise the NCI director and CTAC on the real-world impact of the COVID-19 pandemic on NCI-supported screening trials. Working group members included experts in clinical trial design, biostatistics, cancer screening, breast cancer, and patient advocacy. Some working group members are also members of CTAC.

Tomosynthesis Mammographic Imaging Screening Trial (TMIST) trial. The working group was asked to initially focus on the TMIST trial.

Two-dimensional digital mammography (DM) has been the standard of care for breast cancer screening since 2005. Three-dimensional tomosynthesis mammography (TM) has been rapidly adopted since the U.S. Food and Drug Administration approved the TM device in 2012, but the overall benefit of TM to patients is unclear. Previous studies on the sensitivity of TM had mixed results, but some showed that TM might reduce screening recall rates. Data on the efficacy of TM by race or ethnicity and by breast cancer type are limited.

NCI therefore launched TMIST, a large, randomized screening trial, in July 2017 to evaluate whether TM results in a lower cumulative rate of advanced breast cancers, a surrogate marker for breast cancer mortality, than DM. The study was designed to enroll 165,000 women ages 45 to 74 who were presenting for breast cancer screening. Women are randomly assigned to receive TM or DM and are screened every year or every other year based on menopausal status and breast cancer risk factors. Blood and buccal cell specimens are collected; so far, two thirds of participants have agreed to donate specimens. In addition, when participants undergo breast biopsy, their biopsy tissues are stored for research. The women are followed for up to 8 years after study entry.

When TMIST was launched, accrual was expected to be completed by September 2020. However, in September 2020, total accrual was only about 20 percent complete; total accrual to date is approximately 41,000 women, or 25 percent of the target. One quarter of participants enrolled come from minority and underrepresented groups, and 19 percent are Black. Although accrual to TMIST has been affected by the pandemic, accrual has also been slower than expected throughout the trial.

To address this challenge, TMIST investigators proposed several modifications to the trial design, including the following:

- Reduce the sample size from 164,946 to 102,544
- Conduct a time-to-advanced-cancer assessment employing survival analysis methods instead of a binary outcome assessment
- Reduce statistical power from 90 percent to 80 percent
- Complete accrual in 2023

The trial's data safety and monitoring committee approved these changes, which must now undergo NCI scientific review.

Working Group Process. The working group met virtually several times between November 2020 and February 2021. Information was gathered through a review of the literature and presentations from TMIST study investigators, principal investigators of ongoing tomosynthesis trials in Europe, and

researchers from the Breast Cancer Surveillance Consortium mammography registry. The working group developed its recommendations and drafted its report in February and March 2021. Two sets of overarching recommendations were developed, one specific to TMIST and the other applicable to NCI cancer screening trials in general.

Working Group Recommendations. The working group's recommendations are as follows:

- Overarching Recommendation I: The TMIST trial should continue, but with modifications in a manner that allows accrual to be completed more quickly to answer the primary study question and maximize the likelihood that the results will inform patient care and advance research.

    - Specific Recommendation I-A: Establish a realistic timeline with overall and minority accrual goals, as well as strict criteria for termination of the study if these goals are not met.
    - Specific Recommendation I-B: Develop and implement a comprehensive communications and recruitment plan for TMIST that leverages the resources of the NCI Office of Communications and Public Liaison and augments the Eastern Cooperative Oncology Group (ECOG) and American College of Radiology Imaging Network (ACRIN) efforts to boost accrual.
    - Specific Recommendation I-C: Increase the rate of biospecimen collection, particularly from minority study participants, and incentivize sites to collect blood specimens at the time of the initial enrollment.
    - Specific Recommendation I-D: Ensure that data collection for the prespecified secondary outcomes is complete and that analytical and statistical plans are updated for these aims in the modified protocol.
    - Specific Recommendation I-E: Consider incorporating predictive genomic information into the definition of advanced breast cancer.

- Overarching Recommendation II: Develop a framework for the design and operations of NCI-supported cancer screening trials that incorporates slow accrual guidelines and early termination criteria.

    - Specific Recommendation II-A: Conduct a portfolio analysis of all ongoing and planned NCI-funded cancer screening trials.
    - Specific Recommendation II-B: Assess overall and minority accrual rates for all ongoing screening trials.
    - Specific Recommendation II-C: Interim analyses that assess the evolving changes in screening technology and the therapeutic landscape should be built into large screening trials.

Working Group Conclusions. The working group concluded that TMIST's randomized controlled trial design and unique characteristics, including its clinically well-annotated biorepository and diverse study population, justify its continuation in a modified manner that allows more rapid completion of accrual. The group's recommendations are designed to maximize the likelihood that TMIST will complete its accrual in a timely manner and that its results will inform patient care. The working group also hopes that these recommendations lay the groundwork for the design and operation of future large NCI-supported cancer screening trials.

Questions and Discussion

Dr. Blanke asked how the investigators can identify appropriate endpoints and how these endpoints would be used. Dr. Davidson said that the working group's charge was to provide advice to

NCI. She expected that NCI will ask the TMIST investigators to develop a plan for implementing the working group's recommendations.

Dr. Muller commented that TMIST could determine the impact of COVID-19 vaccines on screening rates and mammography findings and whether these findings change if COVID-19 becomes endemic. Dr. Davidson agreed that TMIST will have an interesting opportunity to examine the effects of COVID-19 vaccines on screening and mammography findings. Investigators conducting large trials should always survey the landscape and make adjustments as needed.

Dr. Dancey said that the reduction in sample size and statistical power is well justified but will affect the trial's ability to detect differences in effects among subgroups. This is a concern because the trial's ability to assess effects in minority populations was a key justification for its continuation. Dr. Davidson explained that the working group was not charged with proposing modifications to TMIST. Rather, the modifications were proposed by the TMIST investigators and will be reviewed by NCI. NCI and the TMIST investigators will then jointly decide how to proceed. However, the issue that Dr. Dancey raised is important for the TMIST investigators to consider. Dr. Mandrekar said that a time-to-event endpoint could be helpful with the smaller sample size, and accrual will be closely monitored, so the subgroups might be large enough for the planned analyses. Dr. Dancey said that the smaller sample size will reduce the statistical power to 80 percent, which will affect the subgroup analyses, but this concern can be addressed by targeted enrollment of key subgroups.

Dr. Levy asked about the working group's discussions of pragmatic study designs in screening trials. Dr. Davidson explained that the working group discussed the healthy tension between the information that can be provided by the gold standard of a randomized controlled trial such as TMIST and how to use real-world data for research. The working group would ultimately like to have both kinds of information available, and NCI does fund both kinds of studies. For example, NCI funds both TMIST, a randomized trial, and the Breast Cancer Surveillance Consortium, which collects real-world data. However, the working group's charge did not include making recommendations about future trial designs.

Dr. Levy asked how to advance discussions about the use of pragmatic trial approaches for screening studies in the future. Approximately 37 million women in the United States undergo breast cancer screening every year, and not learning from the experiences of each of these patients is a missed opportunity. Dr. Sharpless said that given the costs of randomized controlled trials, NCI needs to find ways to use other types of data more efficiently. NCI has funded initiatives focused on novel clinical trial designs, including pragmatic clinical trials, and on the challenging issue of how to use real-world data to guide clinical practice and regulatory decision making.

Dr. Bhatia asked Dr. Davidson to identify the barriers to accrual in TMIST (other than the pandemic) and whether the working group was charged with addressing these barriers. In addition, Dr. Hawk asked whether the working group assessed the pace of TM technology adoption by participating centers in addition to the ratio of TM to DM machines. If accrual is completed in 2023, the trials will probably continue for several more years, and participating centers might not continue offering DM for the next decade. Dr. Davidson explained that the working group was charged with addressing the future of TMIST and discussed the fact that TM use is now widespread, making it more challenging to offer women DM for screening. However, many sites do not routinely use TM for screening because it is more expensive than DM. The working group believes that the trial's diverse population, collection of biospecimens, and secondary endpoints make its timely completion important, and these strengths serve as the rationale for the working group's recommendations.

Motion. A motion carried to accept the report of the *ad hoc* Working Group on Cancer Screening Trials.

V. Translational Research Strategy Subcommittee Update

Nancy E. Davidson, MD
James H. Doroshow, MD

The mission of the CTAC *ad hoc* Translational Research Strategy Subcommittee (TRSS), which Dr. Davidson co-chairs with Chi Dang, MD, PhD, Professor, Molecular and Cellular Oncogenesis Program, The Wistar Institute Cancer Center, is to survey scientific horizons and provide broad advice to NCI advisory boards (the Board of Scientific Advisors, CTAC, and the National Cancer Advisory Board) and NCI leaders on enhancing and broadening the institute's translational research portfolio. TRSS has been active since 2019, and its members are current or former members of NCI advisory boards.

Two *ad hoc* working groups—on glioblastoma and radiation oncology—were formed under TRSS. CTAC accepted the report of the *ad hoc* Working Group on Glioblastoma in July 2019 and the report of the *ad hoc* Working Group on Radiation Oncology in November 2020. NCI has now issued a request for applications for a Glioblastoma Therapeutics Network to improve the treatment of glioblastoma multiforme in adults by developing novel therapeutic agents. The Board of Scientific Advisors has also approved a concept for a Radiation Oncology–Biology Integration Network, and NCI is preparing a request for applications.

During its January 14, 2021, meeting, the subcommittee reviewed its charge, discussed translational research opportunities in gastric and esophageal cancers, and considered how to proactively identify other translational research gaps and opportunities. The subcommittee agreed to meet quarterly in 2021 to discuss emerging translational research opportunities and present recommendations to CTAC and the NCI director twice a year. After a year, the subcommittee will review this process.

The next TRSS meeting will be on Monday, March 29, from 1:00 to 2:00 p.m. ET. At this meeting, TRSS will discuss resistance to immunotherapy. Dr. Davidson invited interested CTAC members to attend.

Proposed *Ad Hoc* Working Group on Gastric and Esophageal Cancers. Dr. Doroshow explained that survival rates for gastric and esophageal cancers are low. The fiscal year 2020 NCI appropriations language from Congress included instructions to develop a scientific framework for the prevention, diagnosis, and treatment of these cancers. NCI has completed a portfolio analysis and now seeks extramural input to help identify the most impactful translational research questions to address.

NCI therefore asked CTAC to consider forming an *ad hoc* working group of TRSS to do the following:

- Identify translational research knowledge gaps related to gastric and esophageal cancers
- Help identify the most provocative and impactful translational research questions to advance the prevention, diagnosis, and treatment of gastric and esophageal cancers
- Examine and identify the most important opportunities for application of new technologies to translational research related to gastric and esophageal cancers

Questions and Discussion

Dr. Loehrer pointed out that most cases of esophageal and gastric cancers occur in other countries and suggested that the proposed working group discuss the inclusion of international partners, especially from Asia and sub-Saharan Africa. Dr. Doroshow said that the working group was likely to consider this suggestion.

Motion. A motion carried to approve the minutes of the January 14, 2021, TRSS meeting.

Motion. A motion carried to form an *ad hoc* Working Group on Gastric and Esophageal Cancers.

VI. NCI Council of Research Advocates Clinical Trials Enrollment and Retention Working Group Update

Rick Bangs, MBA
Debra L. Barton, PhD, RN, FAAN

Dr. Barton and Mr. Bangs chaired the NCI Council of Research Advocates (NCRA) *ad hoc* Working Group on Clinical Trials Enrollment and Retention. NCRA had recently accepted this working group's report. The working group had members from foundations, cancer advocacy organizations, professional societies, academic institutions, and community cancer centers. Its charge was to identify strategies for improving patient enrollment and retention in cancer clinical trials, particularly for patients from underrepresented and minority populations. The main focus was on the financial costs of clinical trial participation, but the working group also considered the roles of researchers, clinicians, sponsors, and other health care organizations in addressing these financial burdens.

The group developed the following seven framing questions to focus their work and guide their discussions:

1. To what extent are perceived and/or actual costs a barrier to adult cancer patients and survivors enrolling in and completing clinical trials?
2. What specific perceived and/or actual costs contribute most to patients not enrolling in or completing clinical trials?
3. Does the impact of perceived and/or actual costs on clinical trial enrollment in and completion of trials vary across different underserved populations for which data are available?
4. How are the specific perceived and/or actual costs most likely to contribute to patient decisions distinct from the costs of cancer care outside the trial setting?
5. What has research shown to be effective approaches to helping adult cancer patients and survivors overcome perceived and/or actual cost barriers to participation in clinical trials?
6. Are there particular trial participation requirements that increase perceived and/or actual costs to patients and survivors?
7. What steps can researchers, clinicians, health care organizations, regulators, and policymakers take to reduce excess costs in clinical trials?

The working group conducted a literature review to identify peer-reviewed publications between 2010 and 2020 that might answer the group's seven framing questions. The literature review found 62 relevant publications, including 44 original research reports. The working group found very little evidence to address its framing questions. Therefore, many of its recommendations call for gathering the needed evidence.

The working group's recommendations are as follows:

1. Identify the types of financial costs, financial concerns, and the extent of cost barriers to clinical trial participation.
2. Develop methodology, including novel technology, to collect cost-related data for those participating in clinical trials.
3. Develop methodology to understand the role of social determinants of health in clinical trial participation in diverse populations.

4. Generate evidence to more fully understand the role of different types of payers and insurance plans as a barrier or facilitator to clinical trial participation for various populations.
5. Create and evaluate interventions aimed at reducing cost barriers to trial participation and completion, aligning decision-making stakeholders on operational details and specifications, and establishing strong partnerships across stakeholder groups.
6. Examine whether COVID-19–related adjustments to clinical trial requirements may reduce perceived and/or actual cost barriers to patient and survivor enrollment in and completion of trials.

The working group also suggested that NCI central institutional review boards and grantees distinguish between potentially coercive incentives and justifiable reimbursement. In addition, the working group suggested that NCI implement recommendations from CTAC's Strategic Planning Working Group to reduce trial complexity and cost and to decentralize trial activities.

Questions and Discussion

Dr. Dicker asked whether the working group discussed the distinctions between intervention trials and other types of trials, as well as between trials sponsored by NCI and those sponsored by pharmaceutical companies. Ann M. Geiger, PhD, MPH, the working group's executive secretary, explained that the group was asked to focus on NCI-supported trials, so it did not discuss trials sponsored by pharmaceutical companies. Dr. Barton added that the working group hopes that as NCI implements these recommendations, other funders will recognize their utility and implement them as well.

Dr. Vose reported that private insurance policies in her state have clauses that prevent patients from participating in clinical trials, even if these trials are studying over-the-counter medications. She asked how to overcome this barrier. Dr. Barton replied that as evidence is gathered on payer systems, the cost factors that affect clinical trial participation will be identified, and these findings are likely to have policy implications. Policies would need to be changed to overcome these barriers, and data will be needed to guide these policy efforts. The working group was disappointed by the limited evidence available to make progress in several areas.

Dr. Loehrer said that investigators do not consider the costs of standard-of-care services to patients or the fact that many patients, especially those at safety net hospitals, cannot afford these costs. This report is important and timely.

Dr. Ramalingam asked whether the working group considered consent form language, particularly language about who is responsible for expenses for research-related injury or treatment for complications. Dr. Barton and Mr. Bangs reported that the working group did not discuss consent forms.

Dr. Hawk suggested that NCI start collecting the needed data by developing case report forms for use in NCI's ongoing clinical trials. Dr. Barton said that the working group discussed this type of approach because no one wants to wait years to collect the evidence needed to make progress. The report does identify some steps that could be completed sooner. The articles that the working group reviewed were not about research studies; rather, most were descriptions of experiences at cancer centers with patient navigation and other patient support programs. These cancer centers probably collect data on these efforts, and one place to start is with people who are already collecting useful information. Mr. Bangs said that some centers are providing financial navigation services and that a landscape analysis of these activities would be valuable.

Mr. Bangs reported that he was surprised to find no information on patients' out-of-pocket costs for cancer care, including travel and other indirect costs. Dr. Levy offered to share the findings of her

quantitative patient burden studies on such factors as commute time, commute distance, time off from work to obtain cancer care, and other associated costs.

Dr. Loehrer suggested involving health economists and health policy experts in NCI's clinical trial networks.

VII. Ongoing and New Business

Patrick J. Loehrer, Sr., MD

Dr. Doroshow explained that a substantial number of people will be needed to help NCI implement the recommendations developed by the CTAC *ad hoc* Strategic Planning Working Group to move NCI toward its 2030 vision. NCI may therefore ask CTAC members to identify colleagues who have appropriate expertise and to volunteer themselves to participate in working groups to address certain issues.

Dr. Doroshow announced that the Board of Scientific Advisors recently approved a concept for a new clinical scientist R50 grant program. This program will provide 5-year, renewable awards for up to 40 percent effort to 20 to 30 established clinical investigators who do not lead R01 or P01 grant programs but who oversee clinical protocol review and monitoring systems, lead disease groups, and accrue patients to clinical trials. Dr. Prindiville added that NCI aims to publish this announcement in approximately 6 months, and awards are expected to begin in 2022.

Dr. Santana asked whether CTAC will be updated on the implementation of the recommendations from the *ad hoc* Cancer Screening Trials Working Group and the progress of the Tomosynthesis Mammographic Imaging Screening Trial (TMIST). Dr. Prindiville replied that she and her colleagues keep track of the implementation of recommendations from CTAC working groups, including the recommendations on TMIST, and arrange presentations on NCI's progress in implementing recommendations. Dr. Davidson confirmed that CTAC has received these sorts of updates over the years. Once decisions about TMIST are made, the public will be informed. Dr. Davidson hoped that NCI will develop guidelines for managing screening trials in the future, just as it did for therapeutic trials.

Dr. Loehrer noted that the CTAC *ad hoc* Strategic Planning Working Group has spent about a year and a half developing a strategic plan that includes approximately 15 recommendations. High-priority recommendations focus on streamlining clinical trials, including through more efficient use of telehealth. The working group also called for evaluating lessons learned from the COVID-19 pandemic, loosening restrictions on enrolling patients with comorbidities, and designing trials to focus on underserved populations.

Dr. Doroshow welcomed the new CTAC members and thanked them in advance for bringing new energy to the work that they will be asked to do for NCI.

VIII. Adjournment

Patrick J. Loehrer, Sr., MD

There being no further business, the 44th meeting of CTAC was adjourned at 2:49 p.m. on Wednesday, March 17, 2021.

_____

Date Patrick J. Loehrer, Sr., MD, Chair

_____

Date Sheila A. Prindiville, MD, MPH, Executive Secretary

March 2021

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
Clinical Trials and Translational Research Advisory Committee

CHAIR

Patrick J. Loehrer, Sr., MD 2021
Director
Indiana University
Melvin and Bren Simon Comprehensive Cancer Center
Associate Dean for Cancer Research
Indiana University School of Medicine
Indianapolis, Indiana

MEMBERS

Debra L. Barton, PhD, RN, FAAN 2021
Associate Dean for Research and Rackham Graduate Studies
Mary Lou Willard French Endowed Chair
Department of Systems, Populations, and Leadership
Professor of Nursing
Professor of Psychiatry
University of Michigan School of Nursing
Ann Arbor, Michigan

Smita Bhatia, MD, MPH* 2025
Vice Chair of Outcomes for Pediatrics
Professor
Division of Hematology/Oncology
Department of Pediatrics
University of Alabama at Birmingham
Birmingham, Alabama

Charles D. Blanke, MD 2024
Chair
SWOG Cancer Research Network
Professor
Knight Cancer Institute
Oregon Health and Sciences University
Portland, Oregon

Edward Chu, MD* 2025
Director
Albert Einstein Cancer Center
Carol and Roger Einiger Professor of Cancer Medicine
Department of Medicine
Albert Einstein College of Medicine
Bronx, New York

Janet Ellen Dancey, MD, FRCPC 2021
Professor
Department of Oncology
Queen's University
Director, Canadian Cancer Trials Group
Kingston, Ontario
Canada

Nancy E. Davidson, MD (BSC) 2022
Senior Vice President, Director, and Full Member
Clinical Research Division
Fred Hutchinson Cancer Research Center
President and Executive Director
Seattle Cancer Care Alliance
Head
Division of Medical Oncology
Department of Medicine
University of Washington
Seattle, Washington

Anjelica Q. Davis, MPA (NCRA) 2021
President
Fight Colorectal Cancer
Springfield, Missouri

Adam P. Dicker, MD, PhD 2024
Professor and Chair
Department of Radiation Oncology
Sidney Kimmel Cancer Center
Thomas Jefferson University
Philadelphia, Pennsylvania

Ernest T. Hawk, MD **2024**
Vice President and Head
Division of Cancer Prevention and Population Sciences
T. Boone Pickens Distinguished Chair for Early Prevention of Cancer
The University of Texas MD Anderson Cancer Center
Houston, Texas

Michael V. Knopp, MD **2023**
Professor of Radiology
Department of Radiology
Novartis Chair of Imaging Research
The Ohio State University
Columbus, Ohio

Anne-Marie R. Langevin, MD **2021**
Greehey Distinguished Chair in Pediatric Oncology
Department of Pediatrics Hematology/Oncology
The University of Texas Health Science Center at San Antonio
San Antonio, Texas

Seth P. Lerner, MD, FACS **2025**
Vice Chair for Faculty Affairs
Beth and Dave Swalm Chair in Urologic Oncology
Professor
Scott Department of Urology
Baylor College of Medicine
Houston, Texas

Mia Levy, MD, PhD **2024**
Director
Rush University Cancer Center
System Vice President
Rush System for Health
Chicago, Illinois

Sumithra J. Mandrekar, PhD **2024**
Professor of Biostatistics and Oncology
Associate Director
Biostatistics Shared Resource
Mayo Clinic College of Medicine and Science
Rochester, Minnesota

Lynn M. Matrisian, PhD, MBA **2021**
Chief Science Officer
Pancreatic Cancer Action Network
Washington, DC

Neal J. Meropol, MD **2021**
Vice President and Head of Medical and Scientific Affairs
Flatiron Health
New York, New York

Carolyn Y. Muller, MD, FACOG **2025**
Associate Director of Clinical Research
The Judy Putman Dirks Endowed Professor in Gynecologic Cancer Care
Department of Obstetrics and Gynecology
The University of New Mexico Health Sciences Center
Albuquerque, New Mexico

Roman Perez-Soler, MD (BSC) **2021**
Chairman
Department of Oncology
Montefiore Medical Center
Deputy Director
Albert Einstein Cancer Center
Director
Division of Medical Oncology
Albert Einstein College of Medicine
Bronx, New York

Raphael E. Pollock, MD, PhD, FACS* **2025**
Kathleen Wellenreiter Klotz Chair in Cancer Research
Director
The Ohio State University Comprehensive Cancer Center
Columbus, Ohio

Suresh S. Ramalingam, MD, FASCO* **2025**
Deputy Director
Winship Cancer Institute of Emory University
Roberto C. Goizueta Distinguished Chair for Cancer Research
Assistant Dean for Cancer Research
Department of Hematology and Medical Oncology
Emory University School of Medicine
Atlanta, Georgia

Steven T. Rosen, MD, FACP **2021**
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, California

Victor M. Santana, MD **2023**
Associate Director for Clinical Research
Vice President, Clinical Trials Administration
St. Jude Children's Research Hospital
Memphis, Tennessee

Julie M. Vose, MD **2023**
Neumann M. and Mildred E. Harris Professor
Chief
Division of Oncology/Hematology
Department of Internal Medicine
University of Nebraska Medical Center
Omaha, Nebraska

***Ex Officio* Members**

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

James H. Doroshow, MD
Deputy Director
Clinical and Translational Research
Director
Division of Cancer Treatment and Diagnosis
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Paulette S. Gray, PhD
Director
Division of Extramural Activities
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Michael J. Kelley, MD, FACP
National Program Director for Oncology
Veterans Health Administration
Department of Veterans Affairs
Durham, North Carolina

Anthony Kerlavage, PhD
Director
Center for Biomedical Informatics and Information Technology
Office of the Director
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Richard Pazdur, MD, FACP
Director
Oncology Center of Excellence
U.S. Food and Drug Administration
Silver Spring, Maryland

Xiufen Sui, MD, MS
Biostatistician
Center for Clinical Standards and Quality
Center for Medicare & Medicaid Innovation
Baltimore, Maryland

Executive Secretary

Sheila A. Prindiville, MD, MPH
Director
Coordinating Center for Clinical Trials
Office of the Director
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

***pending appointment**