# DEPARTMENT OF HEALTH AND HUMAN SERVICES
# NATIONAL INSTITUTES OF HEALTH
# NATIONAL CANCER INSTITUTE
# 46TH CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC) MEETING

## Summary of Meeting
## November 10, 2021

**Webinar**

**CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE**
**Summary of Meeting**
**November 10, 2021**

The 46th meeting of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) was convened on Wednesday, November 10, 2021, at 11:02 a.m. The acting CTAC chair, Dr. Meropol, presided.[1] The meeting was adjourned at 3:00 p.m.

**Chair**
Neal J. Meropol

**CTAC Members**
Debra L. Barton (absent)
Smita Bhatia
Charles D. Blanke
Edward Chu
Nancy E. Davidson
Anjelica Q. Davis
Adam P. Dicker
Ernest T. Hawk
Michael V. Knopp
Seth P. Lerner (absent)
Mia Levy
Sumithra J. Mandrekar
Carolyn Y. Muller
Raphael E. Pollock
Suresh S. Ramalingam
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 Veteran Affairs
Anthony Kerlavage, NCI
Julie Schneider, U.S. Food and Drug Administration (alternate for Richard Pazdur)
Xiufen Sui, Centers for Medicare and Medicaid Services

**Designated Federal Official**
Sheila A. Prindiville, NCI

**Presenters**
Vishal Bhatnagar, MD, Associate Director, Oncology Patient Outcomes, Oncology Center of Excellence, U.S. Food and Drug Administration
Andrea M. Denicoff, RN, MS, Head, NCTN Clinical Trials Operations, Cancer Therapy Evaluation Program, NCI
James H. Doroshow, MD, Deputy Director, Clinical and Translational Research; Director, Division of Cancer Treatment and Diagnosis, NCI
Amylou C. Dueck, PhD, Consultant-level Biostatistician, Associate Professor of Biostatistics, Mayo Clinic, Scottsdale, AZ
M.K. Holohan, JD, Office of Government and Congressional Relations, Office of the Director, NCI

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

Paul G. Kluetz, MD, Deputy Director, Oncology Center of Excellence, U.S. Food and Drug Administration

Neal J. Meropol, MD, Vice President of Research Oncology; Scientific and Clinical Lead, Clinical Research, Flatiron Health

Lori Minasian, MD, FACP, Deputy Director, Division of Cancer Prevention, NCI

Norman E. Sharpless, MD, Director, NCI

Nastaran Zahir, PhD, Chief, Cancer Training Branch, Center for Cancer Training, NCI

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## I. Call to Order and Opening Remarks

*Neal. J. Meropol, MD*

Dr. Meropol called the 46th meeting of CTAC to order at 11:02 a.m. He recognized Dr. Chu, who was attending his first CTAC meeting, and Dr. Schneider, who was representing the U.S. Food and Drug Administration (FDA) in place of Richard Pazdur, MD, at this meeting.

Dr. Meropol 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=42665 after the meeting.

The next CTAC meeting, which will take place on March 16, 2022, is currently expected to be virtual.

**Motion.** A motion to accept the minutes of the 45th CTAC meeting, held on July 14, 2021, was approved.

## II. NCI Director's Update

*Norman E. Sharpless, MD*

**NCI Appropriations.** In 2021, NCI's base budget appropriation is $6,635 million. Its 2023 budget recommendation to Congress is $7,550 million, which would allow NCI to meet its goal of increasing the payline for investigator-initiated research to 15 percent by 2025.

**NCI Research Investments**. Three-quarters of NCI's funding is allocated for extramural research, including research project grants (RPG), which are the largest part of the budget (43 percent of the total dollars spent), research and development contracts (13 percent), Specialized Programs of Research Excellence (SPORES) (9 percent), and other research grants (8 percent). Intramural research accounts for 17 percent of the total dollars spent.

**Clinical Trial Oversight**. A presentation at the 2021 Congress of the European Society for Medical Oncology (ESMO) reported that, over the last forty years, NCI National Clinical Trials Network (NCTN) trials added 14 million years of life to cancer patients based on analysis of 163 randomized phase III clinical trials (30.9 percent of all NCTN trials).

The 2020 report from CTAC's Strategic Planning Working Group identified 15 recommendations and three operational initiatives to enable NCI to develop flexible, faster, simpler, less expensive, high-impact clinical trials that seamlessly integrate with clinical practice. NCI is currently working on the implementation of several of the working group's recommendations.

A new NCI working group focusing on gastric and esophageal cancers has been formed under CTAC and will discuss how NCI can make progress in these diseases. The group will be holding its first meeting in December 2021.

**NCI Initiatives**. The Childhood Cancer Data Initiative (CCDI) has made significant progress on several projects, including the CCDI Childhood Cancer Data Platform that will link data from multiple children's hospitals and cancer institutions with community-based and NCI-supported childhood data resources; the National Childhood Cancer Registry that will link data from various registries to identify and follow every child diagnosed with cancer in the U.S.; and a national strategy that will provide detailed clinical and molecular information to every child with cancer.

Since 2017, NCI has invested nearly $1 billion of *Cancer Moonshot* funding, supporting over 240 research projects. The Dual Anti-*CTLA-4* & Anti-*PD-1* blockade in Rare Tumors (DART) trial, launched in 2017 by the SWOG Cancer Research Network, illustrates a successful basket trial framework that can be helpful in researching rare cancers, a topic of immense Congressional interest. DART is a platform for multiple small phase II trials, such as a recent successful trial for angiosarcoma. Dr. Sharpless also presented new results from the PHOENIX phase III clinical trial in which NCI researchers added targeted therapy (Ibrutinib) to standard chemotherapy, improving survival for some younger people with diffuse large B-cell lymphoma who have specific molecularly defined subsets.

**NCI's SARS-CoV-2 Serology Activities.** In 2020, NCI received an additional $1 million appropriation for serology research on SARS-CoV-2. The funds supported collaborative studies with other Department of Health & Human Services (HHS) agencies such as the U.S. Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC), and the National Institute of Allergy and Infectious Diseases (NIAID). This work has included antibody test performance evaluation, development of a COVID-19 Seroprevalence Studies Hub (SeroHub), development of a standard reference serum which has been shared with other countries, and the ongoing NCI COVID-19 in Cancer Patients Study (NCCAPS) which is currently enrolling participants. Additionally, NCI created a Serological Sciences Network for COVID-19 (SeroNet) to bring together different institutions conducting research to understand immunity to SARS-CoV-2 infection.

**Equity and Inclusion.** NCI has five working groups addressing equity and inclusion issues. Two initial efforts are emerging from their work. One is the Connecting Underrepresented Populations to Clinical Trials (CUSP2CT) funding opportunity announcement (FOA) to implement and evaluate multi-level and culturally tailored outreach and education interventions to increase referral of racial/ethnic minority populations to NCI-supported clinical trials. The second is the NIH Faculty Institutional Recruitment for Sustainable Transformation (FIRST), an NIH Common Fund initiative administered by NCI in collaboration with the National Institute on Minority Health and Health Disparities (NIMHD). The program has recently announced its first cohort of seven institutions that will promote faculty diversity and recruitment of early-career faculty who have a demonstrated commitment to inclusive excellence.

**Cancer Diagnostic Devices**. On September 17, 2021, NCI formalized arrangements for the creation of the Cancer Diagnostic Devices Interagency Task Force with the Health Research and Services Administration and the FDA. The task force will coordinate scientific and programmatic collaborations, as well as regulatory and technical challenges to translation and implementation of cancer screening and diagnostic devices, particularly for rural and underserved communities.

**U.S.-U.K. Bilateral Cancer Summit**. Last spring, Prime Minister of the United Kingdom (U.K.), Boris Johnson, and President Joseph Biden agreed to hold a U.S.-U.K. bilateral cancer summit. There will be a scientific summit in November 2021, followed by leadership summit in the spring of 2022.

**Updates to NCI Training Programs**. New developments include increased flexibility for surgeon-scientists under the K08 career development program; changes to stimulate greater inclusion and innovation within the T32 grant program for institutional research training; and development of a new Early-Stage Surgeon-Scientist Program to encourage surgeon-scientists to pursue careers in cancer research.

**Staff Changes**. Robert T. Croyle, PhD, Director, NCI Division of Cancer Control and Population Sciences, will retire in December 2021. Katrina Goddard, PhD, Kaiser Permanente Center for Health Research, will become the new director.

**Questions and Discussion**

Dr. Meropol asked if there has been an assessment of the financial investment in NCTN studies leading to an increase in life years for cancer patients. Dr. Blanke responded that an analysis was conducted for a subset of a SWOG trials and revealed an investment of $125 per year of life.

## III. Legislative Update

*M.K. Holohan, JD*

Ms. Holohan explained that the federal government is funded via a continuing resolution through December 3, 2021. Congress has been busy with the infrastructure bill and Build Back Better program, delaying attention to the budget.

**Infrastructure and Legislative Climate.** On November 5, 2021, the U.S. House of Representatives passed the infrastructure bill with bipartisan support; the bill will go to the President's office to be signed into law. The upward of $1 trillion bill includes improvements to the nation's physical infrastructure, high-speed internet access, and environmental remediation.

**Reconciliation.** The $1.75 trillion Build Back Better social infrastructure reconciliation bill underwent a procedural vote on November 6, 2021, and was cleared 221-213. Senate Democrats removed funding for the Advanced Research Projects Agency for Health (ARPA-H) from the reconciliation package; Senate leaders indicated that they remain supportive of the proposal.

**FY2022 Budget and Appropriations**. The President's FY2022 budget included $52 billion for NIH (a $9 billion increase, including $6.5 billion for ARPA-H) and $6.73 billion for NCI (a $174 million increase). The House of Representatives passed its budget during the summer of 2021. It included $49.4 billion for NIH (a $6.5 billion increase, with $3 billion for ARPA-H) and $6.99 billion for NCI (an increase of $434 million). The Democratic majority in the Senate released a draft budget on October 18, 2021, that proposed $47.9 billion for NIH (a $5 billion increase, with $2.4 billion for ARPA-H) and $6.77 billion for NCI (an increase of $212 million).

Passage of the draft 21st Century Cures 2.0 bill is unclear at this time. In addition, there are several proposals in Congress to make permanent changes in support of telehealth flexibilities that were temporarily put in place at the beginning of the pandemic.

**Questions and Discussion**.

Dr. Davidson inquired if there was any information about the search for a new NIH director. There is no definitive information at this time.

## IV. Clinician Scientist Awards

*Nastaran Zahir, PhD*
*James H. Doroshow, MD*

**Early-stage Surgeon Scientist Program.** Dr. Zahir indicated that the purpose of the NCI Early-Stage Surgeon Scientist Program (ESSP) is to support and train early-stage surgeon scientists conducting cancer-related research and to accelerate their progress to an independent surgeon-scientist career. Surgeon scientists face many challenges to participating in clinical research, including hospital requirements for procedure-based revenue and the surgical training paradigm, which does not allow time for research until late in their training. The 5-year program will support three cohorts of 12 participants, staggered a year apart, through administrative supplements to an NCI-designated Cancer Center Support Grant (P30) or a Comprehensive Partnerships to Advance Cancer Health Equity (CPACHE; U54) program grant. There will be a mentoring committee established for each participant and NCI will provide quarterly symposia on topics such as grant writing, content area mentoring, scientific methods curriculum, and more. The annual budget

limit is $125,000 direct costs to cover 6 calendar months effort and other allowable costs, including support for research training activities and travel.

Eligible candidates must be a U.S.-licensed surgeon scientist with active surgical duties at an eligible institution, within the first 1-3 years of tenure-track academic appointment, and conducting research on cancer-related basic or translational science. The ESSP candidate must be nominated by the program's center director based on the candidate's qualifications, interests, accomplishments, motivation, and plans to pursue a career as a surgeon scientist with a focus on cancer-related research.

**Clinician Scientist Research Award (R50).** Dr. Doroshow provided an overview of the Clinician Scientist Research Award, noting that it allows outstanding clinical investigators at academic institutions to carry out activities that are critical to the success of NCI clinical trials, such as accruing patients, developing national trials, and providing leadership for the clinical trials infrastructure of institutions. The R50 award provides a career path and the critically necessary stable salary support for clinician scientists who want to focus on the design and conduct of NCI-funded clinical trials but who do not seek independent research funding. To be eligible for the R50 award, candidates must be clinician scientists who have a clinical degree, possess active licensure, and are actively practicing in an oncology clinical setting. Individuals with a PhD or other doctoral degree in clinical disciplines with direct patient contact are also eligible. Applicants can apply for 20 to 40 percent effort, with a maximum NCI funding cap of 50 percent. Any academic institution that carries out significant NCI-funded clinical trial activity is eligible.

**Reimagining the Cancer Clinical Investigator Team Leadership Award (CCITLA) Discussion.** Dr. Doroshow described the CCITLA and asked the committee to advise on where best to (re)position it in the clinician scientist support continuum. Other current NCI support mechanisms for clinician scientists include: K12, K08, and ESSP for early-stage scientists; the R50 award for mid-career scientists; and the R50 and P30 Development Funds (DF) for senior faculty. The CCITLA has straddled the end of the early and mid-career stages, but NCI is considering repositioning its placement to better complement the new Clinical Scientist Research Award (R50). Since 2009, NCI has funded 8 to 12 new awards annually at $60,000 per year for 2 years; the award is non-renewable. Awardees must spend at least 15 percent effort on research. To date, 96 percent of recipients who have completed an award are still in academic clinical research positions.

Eligibility for a CCITLA award is limited to physicians or oncology nurses, clinical psychologists, or similarly qualified clinicians with a doctoral degree who are currently practicing in the oncology setting and board certified or equivalent. They must also be a full-time faculty member with potential for leadership of the cancer center's clinical trials infrastructure activities and engaged in conducting NCI-funded cancer clinical trials.

**Questions and Discussion**

In response to a question from Dr. Hawk related to the ESSP, Dr. Zahir confirmed that the definition of "basic or translational science" is inclusive of research in all areas of cancer research. Dr. Mueller inquired about the tenure track requirement, noting that it may be a bit challenging for women surgeons as many centers have "flex" type tracks that allows the tenure clock to be set later. Dr. Zahir replied that the center director is encouraged to reach out to NCI to inquire about eligibility; the Institute aims to provide as much flexibility as possible. Dr. Levy noted that it is difficult for surgeons to carve out 2 days per week for research; she recommended keeping the requirement flexible at 1-2 days.

Dr. Meropol invited Dr. Ramalingam, a former CCITLA awardee, to share his perspective on the program. Dr. Ramalingam recommended setting up CCITLA as a program for which first- or second-year faculty members were eligible and who could subsequently become eligible for an R50. Dr. Vose also voiced support for earlier eligibility, noting that there are few opportunities for research support during Years 2-6 in a clinician scientist's career.

Dr. Chu proposed that the award be increased to support 2 days per week of protected time because 1 day is insufficient for junior faculty to meet with basic and translational research investigators to integrate these research questions into clinical trials. Dr. Vose commented that having more protected time would be desirable but would have to be supported.

Dr. Doroshow asked about the level of accomplishment needed by applicants. Dr. Chu responded that determination of qualifications should be up to the institution that must make a compelling case for why its nominee should be funded. Dr. Santana proposed that another criterion for qualification be evidence that the candidate is seeking additional academic training in clinical trials (e.g., a master's in clinical research) to demonstrate commitment to becoming an academic clinical researcher.

Dr. Meropol asked how institutions could demonstrate commitment to mentoring in their applications. Dr. Chu commented that his institution has formed a mentoring committee of four to five faculty members for each new translational/clinician scientist it has hired. Of these committee members, one to two must be involved in the young scientist's research and the others can provide career guidance. Dr. Blanke highlighted the role that cooperative groups could play, (e.g., young investigators could join working groups within cooperative groups). If their home institution doesn't have a mentor with experience in the awardee's specialty, the mentor could come from the cooperative group. Dr. Knopp echoed this comment, noting that awardee's alignment with one of the National Clinical Trials Network (NCTN) groups and his or her integration into clear development efforts (e.g., bringing the awardee onto disease committees) would be an enormous enabling factor. It would provide not only institutional but also community mentoring. In the chat, Drs. Muller and Levy concurred with the community mentorship approach. Dr. Muller noted that the leadership goals should focus on the process of trials and disease-specific working group leadership. Awardees could participate on voting committees, national trial development, task forces, etc., so that they learn process as well as trial design. She suggested that it would be helpful if NCI can advise the NCTN groups that all clinical trials and concepts should have a mentor/mentee partnership; this suggestion was endorsed by both Dr. Levy and Dr. Hawk. Dr. Levy recommended that the program include funding for awardees to travel to cooperative group meetings.

Dr. Bhatia asked what success would look like for a CCITLA awardee. Dr. Doroshow responded that the issue is keeping clinician scientists engaged and flourishing in an academic career. Dr. Blanke agreed, commenting favorably on the role that cooperative groups could play.

Dr. Davidson asked if there should be a solicitation for one cohort of individuals from underrepresented groups, similar to the FIRST program. Dr. Minasian inquired if there are implicit biases that should be avoided in terms of criteria for selection. Dr. Doroshow responded that a cohort of underrepresented individuals is a very interesting idea that NCI should consider.

Dr. Mandrekar asked if biostatisticians who participate in NCTN studies would be eligible to apply. Dr. Prindiville stated that the current eligibility requirement is for a clinical degree so biostatisticians would not be eligible. Drs. Minasian and Mandrekar voiced support for including biostatisticians. Dr. Santana also expressed support, suggesting that biostatisticians could show commitment to academic clinical research training as an alternative to traditional training.

Dr. Ramalingam commented on the potential 2 to 6-year eligibility period, noting the review criteria should reflect the fact that potential candidates who've been working for 6 years would have a more expansive portfolio than someone at the beginning of his or her career.

## V. CTAC Strategic Planning Working Group: Update on Implementation of Recommendations

*James H. Doroshow, MD*

Dr. Doroshow updated CTAC members on the progress toward the implementation of the CTAC Strategic Planning Workgroup (SPWG) recommendations. The recommendations NCI selected for initial implementation fall into three focus areas, as described below.

**Streamlining Clinical Trials**. The first recommendation under streamlining clinical trials was to limit clinical trial data collection in late phase trials to essential data elements, as the logistical complexity and data collection burden of NCI clinical trials increase costs and disincentivize site participation. Progress on this recommendation includes an analysis of recent National Clinical Trials Network (NCTN) phase III protocols, currently underway, to gain an understanding of the current extent of data collection, and the convening of an expert group in early 2022 to review findings and provide guidance on ways to limit data collection.

There were also two recommendations around using electronic health records (EHRs) to support clinical trials. The first was to engage EHR and Clinical Trial Management System (CTMS) vendors to create mechanisms for automatically integrating study-specific documents into local implementations of their products. The second recommendation was to resolve the logistical and data quality challenges of extracting clinical trial data from electronic health records. Progress made on the use of EHRs in clinical trials includes NCI funding administrative supplements to P30 Cancer Center Support Grants to develop approaches to automatically integrate study-specific documents into local CTMS and EHR systems and gathering information on internal and external initiatives addressing EHR study builds and/or data extraction. NCI anticipates a presentation to CTAC in March 2022 summarizing its findings and implications.

**Decentralizing Clinical Trials**. Two recommendations toward decentralizing some aspects of clinical trials are being addressed. The first is to identify study procedures modified due to COVID-19 to be performed locally or remotely that can be adopted as standard clinical trial practice to increase trial efficiency and patient convenience. In response, NCI's Cancer Therapy Evaluation Program (CTEP) is assessing which trial procedure modifications due to the pandemic can be continued. Staff is currently planning interviews with a sample of NCI clinical trials stakeholders to probe costs/benefits of the modified procedures, internal and external obstacles to their continuation, and steps required to enable continuation. The second recommendation was to expand the use of telehealth in clinical trials because its convenience can improve clinical trial access. In support of this recommendation, NCI has conducted a survey of National Community Oncology Research Program (NCORP) sites on telemedicine use during the pandemic as well as community sentiment about continuation. Data on state-level licensing and reimbursement policies along with the status of national physician and nurse cross-state licensing compacts is being reviewed. Pilot studies will be needed in a carefully chosen setting where licensing and reimbursement policy are permissive to evaluate the potential to enhance participation by rural and underserved populations.

**Increasing Patient Access to Trials.** Two recommendations addressed increasing patient access to trials. The first was to broaden eligibility criteria to address distinctive medical problems experienced by minority and underserved patients, as higher rates of chronic comorbidities limit their participation. Progress on this recommendation includes CTEP implementation of American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (Friends) recommendations for broadening eligibility criteria for trials, which is already underway, and consideration of pilot studies to further broaden eligibility criteria. The second recommendation was to address the distinctive medical problems experienced by minority and underserved patients during cancer treatment because clinical trials often do not adequately address their treatment needs. Progress on this recommendation includes the development of the Connecting Underrepresented Populations to Clinical Trials (CUSP2CT) program, designed to implement and evaluate outreach and education interventions to increase referral of racial/ethnic populations to NCI-supported

clinical trials. In addition, discussions are planned with NCORP Minority/Underserved (M/U) sites to explore cancer care delivery research (CCDR) studies in safety-net settings and clinical studies addressing aspects of cancer treatment that are of specific concern for minority and underserved patients.

Dr. Doroshow also touched briefly on emerging issues in the oncology workforce. The first is staff attrition during the COVID-19 pandemic. NCI plans to assess the extent of the problem through a survey of NCI-designated cancer centers. Secondly, in order to inform workforce and training discussions, NCI plans to collect data on the demographic breadth of its investigator workforce.

Finally, Dr. Doroshow announced that NCI is seeking CTAC members to serve as "champions" for each CTAC Strategic Planning Working Group recommendation currently in active implementation. He then explained that Ms. Denicoff would describe NCI's progress on the SPWG recommendation to expand eligibility criteria.

**CTEP Analysis of NCTN Adoption of ASCO-Friends Eligibility Criteria**
*Andrea M. Denicoff, RN, MS*

In 2017, ASCO/Friends published broadened eligibility criteria to include patients with brain metastases, prior and concurrent malignancies, HIV infection, organ dysfunction, and younger than age 18 years. In 2018, NCI created protocol template language based on the ASCO/Friends guidance. In 2021, NCI assessed eligibility criteria in 122 protocols first approved by CTEP between November 1, 2018, and April 30, 2020, to determine compliance with the new guidance. In the analysis, eligibility criteria were abstracted from protocols and compared with the NCI template language and the ASCO/Friends guidelines. All criteria were reviewed by two or more NCI clinicians and two information specialists. Protocols with a pediatric focus or in malignancies not primarily seen in adults were not relevant for the lower age criterion analysis. Of the 122 protocols assessed, 71 percent were early phase trials and 84 percent had an Investigational New Drug (IND) collaboration with an industry partner. The majority (104 trials) were adult trials. NCTN was the lead organization in 69 of the trials, NCI's Experimental Therapeutics Clinical Trials Network (ETCTN) was the lead in 44 trials, and the remaining nine were led by other consortia. The study concluded that guidelines without attention to specific template language are not enough to remove clinical trial barriers. Criteria not addressed in protocols may allow, but does not actively promote, inclusion (e.g., brain metastases). The next step is to conduct a pilot in which the CTEP Protocol Review Committee at the time of initial protocol review conducts focused reviews of eligibility criteria and compares them to ASCO/Friends eligibility criteria as well as NCI protocol template language in NCTN and ETCTN protocols. Eligibility criteria not adhering to the guidance will be noted and flagged for the study investigators to address. Scientific or clinical rationale must be provided to support any restrictive criteria, and this will be tracked. The pilot will begin in early 2022 and will include reviewing new NCTN and ETCTN protocols. The pilot will run for approximately 6 months depending on the volume of protocols reviewed during this time period.

Ms. Denicoff posed the following questions to CTAC members for advice:

- ASCO/Friends May 2021 papers recommend using minimal exclusion criteria. At the same time, there is an argument for adding expanded "inclusion criteria" to encourage enrolling investigators to consider patients who may have previously been excluded. Should protocols generally include fewer, minimal criteria or more criteria emphasizing patients who can be included?
- NCI-supported trials take different approaches to criteria excluding participants with psychiatric or social conditions that may make it difficult to comply with the study requirements. NCI wants to ensure that these exclusion criteria do not contribute to implicit biases that inappropriately exclude certain groups. How does CTAC recommend this issue be approached?
- Are there additional actions that NCI should take at this time?
- Should a pilot study be considered to expand select criteria further?

**Questions and Discussion**

Dr. Hawk commented that staff attrition is a critical problem in response to Dr. Doroshow's remarks about emerging issues in the oncology workforce. He noted staff are all susceptible to greater national recruitment pressures from a variety of industries. Dr. Muller pointed out that staff who remain are experiencing burnout from heavier workloads.

Dr. Muller commented on the approach to criteria excluding study participants with psychiatric conditions and recommended that psychiatric exclusions should be removed if patients are able to consent. Dr. Meropol suggested that the psycho-social criteria be modified to allow clinician best judgment; Dr. Levy and Dr. Dicker concurred. Dr. Hawk commented that the psycho-social criteria be minimized so long as patients' autonomy and safety can be reasonably supported.

Dr. Levy encouraged NCI to keep trial documents as simple as possible and to develop standardized eligibility criteria that are accepted by a disease area to give investigators a set of templates from which to work. Dr. Vose suggested that basic templates be developed by disease committees, followed by a review of the eligibility criteria by a small central committee familiar with the ASCO/Friends criteria early in the protocol development process. Dr. Mandrekar noted that templates require regular review and maintenance lest they become outdated. Dr. Levy agreed that maintenance and updating of protocols will be needed as best practices evolve. Dr. Mandrekar also commented that frequent changes in eligibility criteria place a burden on data centers to update databases and integration, thereby slowing the trial process. Ms. Davis agreed that it is necessary to identify best practice procedures. Dr. Muller suggested that the task force/steering committee should provide feedback on eligibility during concept development.

Dr. Meropol transitioned to the need for pilot studies and how they should be handled. Dr. Ramalingam commented that it's important to make it easier for patients to participate in trials by looking at study procedures, in addition to expanding the inclusion criteria. Dr. Meropol suggested that there is an opportunity for real world data to inform patient decisions about participating in a trial. Dr. Levy commented that there have been studies (e.g., immunotherapy with patients with autoimmune disease) that have incorporated real world data that have been very successful. Dr. Knopp said that the common theme in all discussions about speeding up the clinical trial process is the importance of minimizing the burden of data collection. He suggested that there are opportunities to aggregate information on clinical trials with real world data in innovative ways.

Dr. Meropol asked Dr. Blanke to comment on whether the NCTN would likely be open to including scientific questions about broadening eligibility into their trials. Dr. Blanke responded that they would welcome proof on the issue, echoing an earlier comment from Dr. Levy that investigators tend to pull eligibility criteria from old protocols. There is a need to educate young investigators to be more rigorous. Dr. Dicker concurred, noting that this is part of a culture change that NCI leadership should encourage.

## VI. FDA Draft Guidance on the Inclusion of Patient Reported Outcomes (PROs) in Cancer Clinical Trials

**FDA Draft Guidance on PROs**
*Vishal Bhatnagar, MD*
*Paul G. Kluetz, MD*

Dr. Bhatnagar introduced FDA's Oncology Center of Excellence (OCE) and its mission to achieve patient-centered regulatory decision making through innovation and collaboration. The 21st Century Cures Act encourages FDA to review and communicate patient experience data submitted in product reviews. This can be challenging as there is heterogeneity in the analysis and presentation of patient reported outcome (PRO) data submitted in product applications as well as limited space on in the product label to adequately communicate the patient experience information from cancer trials.

Nearly all cancer clinical trials collect outcome data, including tumor size, clinician-reported safety, and outcomes, such as hospitalization. Patient-generated data should also be collected in cancer trials, and FDA recommends a core set of outcomes focused on patient-reported disease symptoms, symptomatic adverse effects, overall side effect impact, physical functioning, and role functioning (ability to work and perform leisure activities). This core set can form a minimum expectation and result in a standard set of high-quality, patient-generated symptom and functional data. Assessments should be conducted at regular intervals throughout the treatment period, with higher frequency of collection at the beginning of the trial, when patients are most likely to experience side effects from treatment and/or potential disease symptom improvement for effective treatments. There are efficient methods to obtain this data, with a goal to minimize patient burden using assessments taking 5 minutes or less. Guidelines for collecting these PROs are included in the draft Core Patient-Reported Outcomes in Cancer Clinical Trials Draft Guidance for Industry (June 2021).

Dr. Kluetz explained that drug tolerability is impacted by symptomatic side effects such as diarrhea, rash, neuropathy, and nausea. Data about symptomatic toxicity can be obtained from two sources: 1) Clinicians—using Common Terminology Criteria for Adverse Events (CTCAE) developed by NCI, and 2) Patients—using validated patient-reported outcome measures such as PRO-CTCAE. Dr. Kluetz noted that CTCAE and PRO-CTCAE are not equivalent. The first addresses treatment safety as assessed by the clinician, while the second represents data generated by patients without interpretation by clinicians or other health care providers. Differences between patient-reported and clinician-reported symptomatic adverse events are expected. PROs are not used to inform errors in clinician reporting and there is no expectation that PROs will be monitored in real time, although this should be made clear to patients in all study materials. It is important for patients to be informed about how their data will be used.

OCE created a publicly available website called Project Patient Voice to pilot the sharing of patient-reported symptom data collected from registrational cancer clinical trials. Dr. Kluetz highlighted what patients can learn about specific symptoms, (e.g., diarrhea), using the data on the website. OCE is looking at other concepts, (e.g., physical function) to include on Project Patient Voice in the future.

**Inclusion of PROs in NCI Clinical Trials**
*Lori Minasian, MD*

Dr. Minasian distinguished between Health-Related Quality of Life (HRQOL) and PROs. HRQOL is a multi-dimensional concept with domains for physical, mental, and emotional and social functioning. It is designed to assess the overall impact of disease and treatment together, but not designed to determine a treatment effect. PROs include any set of survey questions completed by patients, such as a symptom inventory or patient diary. Item libraries of PRO survey questions (e.g., Patient-Reported Outcomes Measurement Information System [PROMIS]) are available, and some have been developed to assess specific constructs, such as PRO-CTCAE for symptomatic adverse events.

NCI has funded the inclusion of HRQOL endpoints in phase III trials for more than 30 years. In 2010, 50 percent of NCI National Clinical Trials Network (NCTN) phase III trials had HRQOL endpoints. These endpoints are typically published independently of treatment results, and thus are not disseminated together with the treatment results.

NCI reviews the inclusion of PRO endpoints in NCTN and NCI National Community Oncology Research Program (NCORP) trials to assure that the PROs are hypothesis-driven and a rationale is provided for the use of any PRO measure included in the study. Funding for PROs is limited to NCTN and NCORP trials, primarily phase III, but also some phase II trials. In these trials, all measures are assessed at baseline, with different assessment frequency for each core measure used. It is not typical to have frequent (weekly) assessments for PROs (as recommended by FDA for most PRO measures) in NCTN/NCORP trials.

NCI's approach aligns with the FDA's draft guidance to include trial design considerations, such as accounting for missing data, reducing patient burden via electronic data collection, and capturing other relevant data. FDA guidance also addresses effective ways to communicate the analysis. NCI's approach to these elements includes having a process for handling missing data in the statistical sections for PRO analysis and primarily utilizing paper-based collection of PRO data but also developing electronic means. Publication of PROs is currently the only means to communicate the results.

NCI is piloting the Electronic Collection Medidata Patient Cloud (ePRO) tool with five NCTN Groups. Historically, NCI trials have relied on PRO data collection by paper and pencil. Today, however, the industry standard is electronic data capture. The implementation of the Medidata ePRO tool has been mixed. Testers generally like the app and better-quality data has been obtained. There have been several challenges in terms of syncing ePRO with the cycle-based calendar and getting access to the electronic versions of licensed tools. Additionally, some patients do not have smart phones or, even if they have a smart phone, prefer to fill out paper forms.

One of the Cancer Moonshot's research initiatives is the routine monitoring and management of patient-reported symptoms to minimize debilitating side effects of cancer and its treatment. To address the initiative, Moonshot RFA-CA-17-052, Analyzing and Interpreting Clinician and Patient Adverse Event Data to Better Understand Tolerability, funded investigators to use PRO-CTCAE with CTCAE data together with other clinically relevant data to determine tolerability. A consortium was created to share analytic approaches and develop graphic displays to facilitate the understanding and interpretation of patient and clinician generated data. Dr. Minasian displayed examples of visualizations created by the consortium.

Translated PROs of non-English-speaking patients are needed to support diversity in NCI clinical trials. Accessing existing translated PRO measures can be challenging as permissions for use may be required and consistent alignment of the questions across languages must be assured.

NCORP investigators identified the challenges of PROs and the lessons learned to date. Challenges identified included data accessibility; protocol development timelines and data issues for opening trials; ensuring that investigators work with PRO experts to design endpoints; certified translations for PROs; lack of proactive emails to remind patients/sites for PRO completion; and a concern that reliance on standard monitoring through Medidata Rave is insufficient. Lessons learned included the importance of early adoption of PROs into study design; understanding that patients are willing to participate but want to know that it matters; and acknowledgment that technology can be leveraged to enhance data collection.

**The Value of and Challenges in Implementing PROs in Cancer Clinical Trials**
*Amylou C. Dueck, PhD*

PROs provide value in cancer clinical trials through 1) assistance in selecting the best treatment by measuring benefits and harms from the patient perspective; 2) provision of unique information that for certain domains is not well measured by other biomedical outcomes; and 3) advancement of clinical trial methods.

Dr. Dueck reviewed several clinical trials to illustrate the "value added" by PROs. For example, in a phase III randomized trial of stereotactic radiosurgery (SRS) with or without whole brain radiation therapy (WBRT) in patients with cerebral metastases, no difference was found in overall survival between the two arms. However, there were significant patient-reported benefits, such as physical and functional well-being and quality of life (QOL), associated with the less invasive treatment. This led to a change in practice, and the results are now explicitly mentioned in the National Comprehensive Cancer Network (NCCN) guidelines. A phase III trial from NRG looking at hypofractionated versus conventional radiotherapy for patients with low-risk prostate cancer showed that hypofractionation was non-inferior in terms of overall disease-free survival; however, the PROs showed that hypofractionation did not negatively impact bowel, bladder, and

sexual functioning, nor QOL, anxiety, and depression. These findings led to changes in multiple practice guidelines, making hypofractionation the new standard of care.

In a trial comparing manuka liquid honey versus manuka lozenge versus supportive care for chemoradiation-induced esophagitis in lung cancer, PRO-CTCAE data provided in-depth profiles of the severity of side effects, such as radiation dermatitis (increase over time through the week 12 follow-up) and dysphagia (increase over the 4 weeks of treatment, but decrease by week 12), yielding far more useful data than CTCAE and/or a simple overall score of each side effect.

In a phase III, placebo-controlled, double-blind randomized study of Sorafenib in patients with desmoid tumors or aggressive fibromatosis (DT/DF), PRO-CTCAE and QOL data were collected via paper booklets during clinic visits at baseline and every 4 weeks during blinded treatment. This was an optional sub-study in the trial, and 63 of 85 patients who received treatment participated. Sorafenib contributed to disease progression-free survival, but side-effects of such a powerful and toxic drug were a concern. The PRO-CTCAE data, adjusted for baseline reports of symptoms, were included in the primary publication about the study. Additional plotting of the data in a subsequent publication showed that symptoms were mild and tolerable. This study led to methodological advancements, such as development of a grading algorithm to define data across dissimilar items for the same symptom within PRO-CTCAE and a macro to generate standardized tables of PRO-CTCAE data.

Key issues in the further use of PROs include limited resources despite high demand; the need for training and knowledge sharing about their use; and the need for multiple modes of administration and enhanced monitoring to minimize missing data.

**Questions and Discussion**

At the conclusion of the presentations, CTAC members were asked to provide input on the issues NCI should think about when considering implementation of FDA's draft guidance on PROs, particularly around early phase trials.

The discussion began with comments from several CTAC members with PRO experience. Dr. Dicker identified four issues for consideration: 1) The oncology field is inexperienced in thinking probabilistically, identifying and managing risks, and communicating them effectively; 2) There is an excellent research opportunity to combine datasets to determine minimum data requirements; 3) There needs to be more PRO data collection in early phase trials to determine what should be studied in phases II and III; and 4) The FDA and NCI working together on this issue will stimulate others to work on PRO issues. Dr. Mandrekar agreed with Dr. Dicker on each issue. She pointed out that Medidata Rave does not provide the same level of support for PROs as it does for other areas; there is a need for technology and implementation infrastructure and support.

Dr. Meropol proposed that it would be valuable if the PRO data patients provided were sent to their providers because this would enhance their care. Dr. Dueck said that using PROs as a monitoring tool positively impacted patient care. In a recent rectal cancer study known as the PROSPECT trial, she and her colleagues conducted a clustered randomized comparison in which clinical staff at some sites received PRO-CTCAE data while other sites did not. The interim analysis revealed a dramatic increase in terms of what clinicians receiving the data reported as adverse events at a time when clinical results were still immature. Dr. Minasian said that patients are happy to complete PRO questionnaires if they know the information is analyzed and they receive results. Studies rarely provide PRO data to providers and patients; Project Patient Voice can fulfill that function.

Dr. Meropol inquired about the collection of PRO data in early phase trials. Dr. Kluetz responded that PRO data can play an important role in informing early phase trials, given safety and tolerability are key objectives. Patients are willing to complete questionnaires, and the goal should be to have a clear objective

and make the data collection as least burdensome as possible. Symptomatic side effects often occur early, and assessment of tolerability and symptom data are most important during the first 3 to 6 months of a trial, which is the rationale for data collection to be more frequent up front. Longer term outcomes can also be assessed at a few later timepoints, depending on the context of the disease and trial objectives.

Dr. Ramalingam commented about making sure PRO questions are comprehensible to patient with low health literacy. Dr. Dueck responded by noting that the validation study for PRO-CTCAE targeted enrollment of underrepresented minorities. Dr. Minasian noted that development of PRO-CTCAE was grounded in interviews for cognitive validity to assure that patients understood the questions; the interview sample was enriched with low socio-economic status (SES) patients. With respect to early phase trials, Princess Margaret has implemented the entire PRO-CTCAE library in its phase I clinic with a positive response from patients. In thinking about PROs, there should be an opportunity for write-in data, particularly in the early phase, because researchers need to capture what they don't yet know.

## VII. Ongoing and New Business

*Neal. J. Meropol, MD*
*James H. Doroshow, MD*

After recognizing the contributions of retiring CTAC member, Debra L. Barton, Dr. Doroshow provided CTAC members with updates on the activities of the working groups formed under CTAC's Translational Research Strategy Subcommittee (TRSS). Some recommendations included in the report from the *ad hoc* Working Group on Radiation Oncology were translated into a Request for Application (RFA). The *ad hoc* Working Group on Gastric and Esophageal Cancers, chaired by Karyn Goodman, MD, Mount Sinai, and Anil Rustgi, MD, Columbia University Herbert Irving Comprehensive Cancer Center, formed to address translational research gaps and opportunities in the field, will hold its initial meeting on December 13, 2021. Additionally, the Glioblastoma Therapeutics Network (GTN), a concept that was approved by the Board of Scientific Advisors in May 2020, has been formed. The purpose of the GTN is to improve the treatment of adult glioblastoma by developing novel effective agents and testing them in human pilot pharmacodynamics (PD) studies.

Dr. Prindiville reminded CTAC members of the next meeting on March 16, 2022, which is currently planned to be virtual. Potential topics on the agenda include updates on Electronic Health Records (EHR) integration and telehealth projects, the implementation of the recommendations from CTAC's Cancer Screening Trials Working Group, and the NCI and the Department of Veterans Affairs Interagency Group to Accelerate Trials Enrollment (NAVIGATE) program. She invited CTAC members to submit additional topics for the meeting.

## VIII. Adjourn

*Neal. J. Meropol, MD*

There being no further business, the 46th meeting of CTAC was adjourned at 3:00 p.m. on Wednesday, November 10, 2021.

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Date Neal J. Meropol, MD, Chair

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

## Appendix

*October 2021*

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

### ACTING CHAIR

**Neal J. Meropol, M.D. 2021**
Vice President of Research Oncology
Scientific and Clinical Lead, Clinical Research
Flatiron Health
New York, New York

### MEMBERS

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Mary Lou Willard French Endowed Chair
Department of Systems, Populations and Leadership
Professor of Nursing Professor of Psychiatry
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President & Executive Director
Seattle Cancer Care Alliance Head, Division of Medical Oncology Department of Medicine
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