DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
49TH CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE MEETING

Summary of Meeting
November 9, 2022

Webinar

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
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The 49th meeting of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) was convened Wednesday, November 9, 2022, at 11:00 a.m. The CTAC chair, Dr. Neal J. Meropol, presided.[1] The meeting was adjourned at 2:52 p.m.

Chair
Neal J. Meropol

CTAC Members
Smita Bhatia
Charles D. Blanke
Edward Chu
Nancy E. Davidson
Adam P. Dicker
Gary C. Doolittle
Ernest T. Hawk
Michael V. Knopp
Seth P. Lerner
Mia Levy
Sumithra J. Mandrekar
Robert S. Mannel (absent)
Ruben A. Mesa
Carolyn Y. Muller
Raphael E. Pollock
Suresh S. Ramalingam
Victor M. Santana
Patricia A. Spears
Julie M. Vose
George Wilding

***Ex Officio* Members**
James H. Doroshow, NCI
Paulette S. Gray, NCI
James L. Gulley, 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

Monica Bertagnolli, MD, Director, NCI

James H. Doroshow, MD, Deputy Director for Clinical and Translational Research; Director, Division of Cancer Treatment and Diagnosis, NCI

Lisa Gallicchio, PhD, Program Director, Clinical and Translational Epidemiology Branch, Epidemiology and Genomics Research Program, Division of Cancer Control and Population Sciences, NCI

Karyn A. Goodman, MD, Professor, Radiation Oncology; Professor, Medicine, Hematology, and Medical Oncology, Mount Sinai Hospital

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.

Sumithra J. Mandrekar, PhD, Professor of Biostatistics and Oncology; Group Statistician, Alliance for Clinical Trials in Oncology, Quantitative Health Sciences, Mayo Clinic College of Medicine

Worta McCaskill-Stevens, MD, MS, Chief, Community Oncology and Prevention Trials Research Group, Division of Cancer Prevention, NCI

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

Linda Parreco, RN, MS, Nurse Consultant, Division of Cancer Prevention, NCI

Anil K. Rustgi, MD, Irving Professor of Medicine; Director, Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center

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I. Call to Order and Opening Remarks

Neal J. Meropol, MD

Dr. Meropol called the 49th meeting of CTAC to order at 11:00 a.m. He recognized Dr. James L. Gulley, who was attending his first CTAC meeting, and Dr. Julie Schneider, who was representing the U.S. Food and Drug Administration in place of Dr. Richard Pazdur 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 provided a videocast of the meeting. The videocast recording is available for viewing at https://videocast.nih.gov/watch=46500.

Motion. A motion to accept the minutes of the 47th CTAC meeting, held on March 16, 2022, was approved.

II. NCI Director's Update

Monica Bertagnolli, MD

Advancing Clinical Research. NCI aims to reinvent the design and conduct of clinical trials to make them nimbler, faster, and more accessible. Dr. Bertagnolli discussed important steps NCI is taking to reach that goal, which include launching a survey to evaluate the representation of underrepresented groups and women in leadership roles within NCI, the National Clinical Trials Network (NCTN), the National Community Oncology Research Program, and NCI Scientific Steering Committees; hosting a summit on increasing diversity, equity, and inclusion in early phase clinical trials; investing heavily in basic and translational research; considering the equitable delivery of cancer prevention and treatment; increasing the ethical and responsible collection and use of data, particularly from underrepresented populations; and increasing the diversity of the cancer research and care workforce to reflect the communities NCI serves.

Funding and Appropriations. In September, NCI shared its annual plan and budget proposal for Fiscal Year (FY) 2024, which totaled approximately $10 billion. The proposal is based on NCI professional judgment of the resources required to support the National Cancer Program to achieve President Biden's goals to reduce the cancer mortality rate by 50 percent over the next 25 years and end cancer as we know it. The FY 2024 budget has not yet been passed, nor have the appropriations for FY 2023. NCI is currently operating under a Continuing Resolution that will run through December 16, 2022. Until a new budget is passed for FY 2023, the NCI budget will mirror the $6.9 billion appropriations it received in FY 2022. NCI is doing all it can with the resources it has to continue realizing scientific opportunities and advancing progress in the meantime.

Advanced Research Projects Agency for Health (ARPA-H). This new agency will provide solutions to issues that impede progress in health care. It is not intended to reproduce or replace funding opportunities for research that is best achieved in established institutions like NCI. ARPA-H will fund high-risk activities that are focused and milestone driven. Dr. Bertagnolli has already begun partnering with ARPA-H Director Dr. Renee Wegrzyn.

Clinical Trials Partners. Clinical trials and translational science play an essential role in cancer research and in the NCI mission. NCI and its clinical trial network groups must work together more closely than ever before to develop solutions that advance progress in key areas. NCI, along with its partners, should work to adopt a policy of data sharing to the fullest extent allowed by adherence to ethical principles and patients' wishes. Making data sharing a routine feature of all cancer research can help establish strong collaborations to maintain a steady flow of knowledge from the bench to the bedside and back again.

Cancer Clinical Research Workforce. The needs of the cancer clinical research workforce must be addressed. NCI can accomplish this by achieving diversity, providing adequate support so that clinicians and researchers are not lost to burnout, and highly valuing the unique contribution of clinicians who conduct clinical research.

Questions and Discussion

Dr. Bertagnolli asked CTAC members to share what they see as the areas of greatest opportunity as well as greatest concern related to clinical trials and translational research. Ms. Spears noted that the COVID-19 pandemic has brought about more virtual access and a more patient-centered approach to care. She emphasized the importance of NCI ensuring continued access as well as equity in care. Dr. Bertagnolli noted that NCI has an increasing portfolio of implementation science directed toward improving the health care environment. She emphasized that access to participation in clinical research is a standard of care imperative. To address challenges related to recruitment and retention of the clinical workforce as well as patient access to trials, Dr. Mesa recommended that NCI work to reduce the complexity of clinical trials, support the use of telehealth for screening and consenting patients, and support the pipeline for qualified coordinators and other essential members of the clinical trials workforce. Dr. Bertagnolli stated that NCI will partner with the clinical trials community, including advocacy groups, to address these issues.

Dr. Levy suggested that NCI pay special attention to data sharing, as the ability to learn from patient experience can be hindered by a lack of clarity around consent and the secondary use of data. Dr. Bertagnolli agreed this is an important issue. Dr. Lerner recommended that NCI support innovation in surgery and include opportunities for surgical trials within NCTN. He also recommended NCI invest in complex trial designs that evaluate multiple disease states and treatments to help move the field forward more quickly. He went on to emphasize the importance of competitive compensation for retaining the workforce. Dr. Knopp suggested that NCI facilitate the connection of real-world data to clinical trials. This will require support from NCI leadership to navigate regulatory, legal, and privacy issues.

Dr. Dicker suggested incentivizing work across silos to reduce obstacles and achieve speed in clinical trials while retaining rigor and quality. Dr. Muller suggested that NCI strengthen the culture of clinical trials in order to build and support the workforce and other stakeholders. Dr. Ramalingam suggested that NCI explore ways to accelerate hypothesis-generating work by improving the delivery of biospecimens to researchers in translational work. Dr. Mandrekar suggested that NCI invest in strengthening systems and networks to make them nimbler and more site- and patient-friendly to facilitate the collection of quality data.

Recognition

Dr. Bertagnolli thanked Ms. Anjelica Davis, who will be rotating off CTAC, for her contributions not only to CTAC but to the broader cancer research community, including as a former Chair of the NCI National Council of Research Advocates.

III. Legislative Update

M.K. Holohan, JD

Presidential Appointments. NCI is the only National Institutes of Health (NIH) institute with a presidentially appointed director. President Biden recently appointed Dr. Bertagnolli as the 16th director of NCI. She is the first woman to hold that role. President Biden also nominated three accomplished cancer researchers to serve on the President's Cancer Panel as well as Dr. Renee Wegrzyn to serve as director of the Advanced Research Projects Agency for Health (ARPA-H).

Midterm Elections. The midterm elections, and thus control of the Senate, may not be decided until December 6, when the state of Georgia holds its runoff election. With most of the results in, Democrats outperformed expectations, especially as the party of a sitting President. Republicans likely will take control of the House and flip the majority, but their majority will be small, which may make it

challenging for the majority leader to get the necessary number of votes for contentious articles of legislation.

Fiscal Year (FY) 2023 and 2024 Budget and Appropriations. As Dr. Bertagnolli explained earlier, NCI has submitted its professional judgment budget proposal for FY 2024, but the appropriations for FY 2023 still have not been determined. Budget negotiations will reopen when Congress reconvenes on November 14. NIH and NCI have been fortunate as, even in years of intense partisanship, the members of the Appropriations subcommittee have made biomedical research a priority. Many of the champions of biomedical research on that subcommittee are retiring and are eager to complete the appropriations process and ensure funding before they leave office. Both the House and the Senate have seemed receptive to ARPA-H, while expressing a dedication to ensuring that funding for the new agency does not come at the expense of sustained increases for NIH and NCI.

ARPA-H. The Agency is moving quickly and has a $1 billion appropriation with 3-year budget authority, so they have until the end of FY 2024 to spend those funds. The placement of ARPA-H within the federal government could change; the Agency currently is nested within NIH, by recommendation of Secretary Xavier Becerra, Department of Health and Human Services, but this may change with continued negotiations and new legislation.

Legislation and the Lame Duck Congress. When Congress resumes, members have several urgent priorities, including the National Defense Authorization Act. Other important articles of legislation that have now been passed include the U.S. Food and Drug Administration authorization and the Small Business Innovation Research authorization. Congress may consider a health omnibus bill, and the White House may seek more funding for pandemic preparedness, COVID-19 mitigation, and additional aid for Ukraine. Priorities and legislation will depend significantly on the outcome of the midterm elections.

IV. Streamlining Clinical Trials Working Group: Interim Report

Neal J. Meropol, MD
Sumithra J. Mandrekar, PhD

NCI formed the *ad hoc* Streamlining Clinical Trials Working Group to address implementation of the CTAC Strategic Planning Working Group recommendations on limiting data collection in late-phase trials and more effectively integrating electronic health records into the clinical trials workflow. The working group reached consensus on a set of recommendations addressing reduced data collection in late-phase clinical trials, which they presented to CTAC as an interim report, allowing timely consideration of the recommendations by NCI in advance of the working group's final report.

Recommendation. The working group recommended establishing a set of standard practices for limiting data collection in NCI Cancer Therapy Evaluation Program Clinical Investigations Branch–managed phase III and phase II/III adult, Investigational New Drug (IND)-exempt, interventional treatment trials. The proposed practices are intended to define a "new normal" for data collection that is less burdensome, more efficient, and more sustainable. Investigators may depart from these standards, but for each proposed departure, there should be justification specific to the clinical details and objectives of the trial.

The working group proposed standard practices for the collection of seven categories of data: adverse events (AEs), medical history, concomitant medications, physical examinations, laboratory tests, imaging and other assessment procedures, and patient-reported outcomes.

Proposed Standard Practices. For AEs, the recommendation is to collect only data on adverse events of grade 3 or higher, unless the assessment of tolerability related to lower-grade AEs is a stated trial objective with a specified analysis plan. Only the Common Terminology Criteria for Adverse Events grade and term should be collected. Solicited AEs should be limited to those that would result in dose modification, treatment discontinuation, or nonadherence. AE attribution and AE start/stop times should not be collected.

For medical history, the recommendation is to collect only those medical history items that are relevant to the trial inclusion and exclusion criteria. At baseline, data on concomitant medications should be collected only if the medications' use requires modification of the study treatment. Changes in concomitant medications should be noted during the trial only if they cause modification or discontinuation of the study treatment. For physical examinations, the only findings that should be collected are those that are protocol-specified endpoints or are required to assess those endpoints, represent AEs, or result in dose modification or treatment discontinuation.

The working group recommended that only the following laboratory test results be collected: those that are protocol-specified endpoints or are required to assess those endpoints; those that represent AEs; or those that result in dose modification or treatment discontinuation. Imaging and other assessment procedures should be limited to those required to meet specified trial objectives. The cost of imaging and other assessment procedures not covered by insurance must be covered by the study. Finally, the working group recommended that patient medication diaries should not be required unless the protocol defines how the data will be analyzed to address specified trial objectives. Data collection plans for patient-reported outcomes must address how instruments will be chosen and data collection will be scheduled to achieve specified scientific objectives while minimizing patient burden.

Conclusion. The aim is to collect only those data that are necessary to achieve specified clinical and/or scientific objectives according to clearly defined analysis plans. Timely implementation of the recommended standard practices for limiting data collection in NCI phase III and phase II/III adult, IND-exempt interventional treatment trials will reduce operational burden and provide important insights that can inform the development of similar data collection standards for other types of trials. Broad stakeholder engagement will be necessary for successful implementation.

Questions and Discussion

Dr. Mesa commended the working group for its initial recommendations and said that they should continue to iterate and refine the ideas. Ms. Spears suggested that the group ensure that its stakeholder engagement process includes patients. She asked whether the key objectives discussed include exploratory objectives or just primary and secondary objectives. Dr. Mandrekar said that the group was largely focused on primary and secondary objectives, but that exploratory or other objectives could be included if the collection and analysis plan is clearly defined and consistent with the proposed standard practices.

Dr. Davidson suggested that the working group apply its recommended standard practices to existing National Clinical Trials Network trials to assess their utility and viability and to determine whether applying these guidelines would have led investigators to overlook important data. Drs. Meropol and Mandrekar will bring this topic back to the working group for further discussion.

Dr. Marc R. Theoret, Deputy Director of the U.S. Food and Drug Administration Oncology Center of Excellence, noted that there are different considerations for IND trials. He said that he would be happy to provide additional input regarding how to limit data collection in IND trials. Dr. Meropol responded that the comments from both Dr. Theoret and Ms. Spears emphasize the importance of broadening the circle of included stakeholders. If NCI decides to pursue a set of standard practices for IND trials, broad stakeholder buy-in will be needed to achieve robust implementation.

Motion. A motion to accept the interim report of the *ad hoc* working group on Streamlining Clinical Trials was approved.

V. Leveraging NCTN and NCORP Clinical Trial Populations for Observational Cancer Survivorship Research

Lisa Gallicchio, PhD

Dr. Gallicchio presented the findings from the NCI 2021 Request for Information (RFI) on leveraging National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program

(NCORP) clinical trial populations for observational cancer survivorship research. The RFI was in response to a 2019 National Cancer Advisory Board (NCAB) recommendation; it solicited information on specific research questions or evidence gaps in cancer survivorship that can be addressed using existing NCTN and NCORP study populations; general methodologies to conduct observational research studies utilizing clinical trial populations; strategies for using existing NCTN or NCORP infrastructure to support long-term cancer survivorship studies; and infrastructure needed to facilitate long-term cancer survivorship studies.

The RFI had 15 respondents, the majority of whom were affiliated with NCTN and/or NCORP. The most frequent response regarding research questions was that NCTN and NCORP populations can be leveraged to fill gaps with long-term survivorship outcomes associated with new or combination anti-cancer therapies. Survivorship outcomes of interest include aging, cardiotoxicity, cognitive function, sexual function, physical function, symptom and adverse outcome trajectories, and financial toxicity. Multiple responses suggested the establishment of a clinical trial survivorship registry that would include all patients affiliated with NCTN and NCORP. Regarding barriers to progress, nearly all respondents mentioned that clinical trial patients are not consented for ancillary or follow-up studies, and it can be difficult to locate trial participants for re-consent or follow-up. The routine collection of patient consent for survivorship studies at the time of clinical trial enrollment and the inclusion of a "contact for future research" section on the consent form could reduce this burden.

As previously mentioned, a common theme throughout the responses was the idea of a patient registry to facilitate long-term cancer survivorship studies. A conceptual model to describe how such a registry could work was created. Upon enrollment in an NCTN or NCORP study, a patient could consent to be re-contacted for future studies. If they consented, their name, contact information, and clinical trial information would flow into a registry. Demographics and other information could be collected under the purview of a clinical trial survivorship registry governing committee. After participation on the NCTN or NCORP study has concluded, follow-up in the registry can continue for a period of time during which the patient can be contacted regarding participation on long-term survivorship studies.

NCI contacted investigators at several of the NCORP research bases to solicit feedback on this idea. Investigators expressed a high level of enthusiasm for the concept and appreciated that NCI was following up on the NCAB working group recommendation. All research bases with whom meetings were held had discussed this concept previously in some form, and there is existing infrastructure at some research bases that could be utilized. Most investigators recognized the need to prioritize clinical trial populations for inclusion in the registry. Investigators felt that their patients would be very willing to consent. Key considerations include the protection of protected health information and preventing selection bias by self-selection into the registry. Investigators agreed that the primary barrier to developing such a registry is the funding needed to support re-contact of patients once they are included in the registry.

Gaps in knowledge exist surrounding the feasibility of creating such a registry. Unknowns include the number and types of NCTN and NCORP clinical trial patient populations available to participate; patient willingness to participate; NCORP community site willingness and capacity to take on additional work; which data beyond patient contact and clinical trial information should be collected and at what intervals; research base ability to conduct follow-up; and projected effort and costs for building and managing a registry.

Questions and Discussion

Dr. Gallicchio asked CTAC members whether they saw additional gaps in cancer survivorship knowledge not mentioned in the presentation, what they thought about the conceptual model for the registry, and what they considered the pros and cons of developing such a registry for observational cancer survivorship research.

Dr. Santana recommended that NCTN and NCORP consider bidirectionality in the flow of clinical trial data (e.g., feedback loop for data collected in long-term survivorship studies to inform endpoints in the primary NCTN or NCORP studies). He also suggested that any future registry should reflect the transition of care from pediatrics to non-pediatrics.

Dr. Bhatia commented that a similar registry concept is already underway in pediatrics. In that registry, a child is enrolled at a long-term follow-up center within 6 months of completing treatment and then followed for life with biannual communication to confirm contact information. When those patients reach the age of majority, they are reconsented as adults. She also suggested that NCI work to ensure that the adult population in the registry is representative of survivorship in the general population, not only those healthy enough to participate in clinical trials.

Dr. Meropol asked whether the question of including survivors who have not yet participated in a trial in the registry has arisen. Dr. Gallicchio said that it has not, but it is an important point. Regarding the potential expense associated with such a registry, Dr. Meropol suggested that NCI pursue public–private partnerships to support it. Dr. Bhatia indicated that she would be happy to discuss with Dr. Gallicchio how the long-term follow-up center is funded for their pediatric population.

Ms. Spears noted that patients living with metastatic and advanced disease are also survivors and recommended that the registry be inclusive of those populations. Dr. Gallicchio thanked her for her comment and said that the registry recognizes these patients as part of the survivor community.

Dr. Mandrekar suggested that the registry partner with existing clinical trial and data collection efforts rather than competing with them. Dr. Gallicchio thanked her for this comment and agreed that this would be a good idea.

Dr. Meropol asked what the next steps are for the registry. Dr. Gallicchio responded that the group is collecting information and having internal discussions about this topic.

VI. Cancer Screening Trials Working Group: Update on Implementation of Recommendations

Worta McCaskill-Stevens, MD, MS
Linda Parreco, RN, MS

Dr. McCaskill-Stevens began with a reminder that the CTAC Cancer Screening Trials Working Group was formed in November 2020 to advise the NCI Director and CTAC members on the real-world impact of COVID-19 on NCI-supported screening trials, the largest being the Tomosynthesis Mammographic Imaging Screening Trial (TMIST). This trial aimed to determine whether the cumulative rate of advanced breast cancer in women undergoing screening with a combination of tomosynthesis and digital mammography is reduced compared to digital mammography alone. The working group's report ultimately included recommendations that fell into two categories: TMIST-specific recommendations and recommendations regarding NCI screening trials in general. Dr. McCaskill-Stevens and Ms. Parreco updated CTAC members on progress toward the implementation of these recommendations.

TMIST. The working group's Overarching Recommendation-I stated that the TMIST trial should continue, but with modifications in a manner that allow accrual to be completed more quickly to answer the primary study questions and maximize the likelihood that results will inform patient care and advance research. In December 2021, the protocol was amended to reflect modifications to the study design, including changes to time-to-event endpoint (from occurrence of advanced breast cancer at any time up to 4.5 years from randomization to up to 7 years), power (from 90 percent to 85 percent), and sample size (from 164,946 to 128,905).

In addition to the overarching recommendation, the working group specified several sub-recommendations related to TMIST, including:

- Recommendation-IA: Establish a realistic timeline for overall and minority accrual goals as well as strict criteria for study termination if goals are not met.
- Recommendation-IC: Increase the rate of biospecimen collection, particularly from minority participants, and incentivize sites to collect blood specimens at initial enrollment.
- Recommendation-ID: Ensure that data collection for prespecified secondary outcomes is complete and analytical and statistical plans for these aims are included in the modified protocol.
- Recommendation-IE: Consider incorporating predictive genomic information into the definition of advanced breast cancer.

Dr. McCaskill-Stevens described the progress made related to these sub-recommendations:

Regarding Recommendation-IA, with the accrual-related modifications made to the study protocol, accrual is expected to be complete in 2024 or early 2025. There is close monitoring of both overall and minority recruitment and enrollment, and criteria for recommending the trial be terminated have been identified. Between March 2021 and November 2022, enrollment increased from approximately 41,000 participants to 78,186. Minority accrual increased from 20 percent to 21 percent in that timeframe. There are plans in place to sustain and hopefully increase minority accrual of participants identifying as Hispanic.

For Recommendation-ID, the protocol was amended to include full analysis plans of all study aims. Additionally, there are ongoing discussions with investigators from the randomized trials in the United Kingdom, Germany, and Norway—referenced in the working group's report—about ways to share data and collaborate further on the secondary endpoints.

Addressing Recommendation-IC, there was an amendment to the protocol requiring biospecimens to be collected at specified timepoints rather than any time during the study. There was also funding from Susan G. Komen to support increased biospecimen collection from African American women. Between March 2021 and November 2021, the collection of biospecimens from this group has significantly increased.

Regarding Recommendation-IE, the study team's statisticians, the Data and Safety Monitoring Committee, and other stakeholders considered the recommendation of including genomic information into the definition of advanced breast cancer but determined the scientific integrity of the study's primary endpoint could not be maintained at that point in the study.

Dr. McCaskill-Stevens concluded with a summary of additional modifications made to enhance and sustain enrollment in the trial and contribute to the science of screening, including reducing the frequency of quality control reporting for sites that have a history of good performance; streamlining the process of onboarding new sites; working to promote Hispanic participation in the trial; providing incentives to high-accrual sites to support collection of biospecimens; and collaborating with other scientific interests interested in utilizing TMIST data.

NCI Division of Cancer Prevention (DCP) Screening Trials. Ms. Parreco described the working group's Overarching Recommendation-II relating to screening trials in general, which is to develop a framework for the design and operation of NCI-supported cancer screening trials that incorporates slow accrual guidelines and early termination criteria. The working group also specified several sub-recommendations, including:

- Recommendation-IIA: Conduct a portfolio analysis of all ongoing and planned NCI-funded cancer screening trials.

- Recommendation-IIB: Assess overall and minority accrual rates for all ongoing screening trials.
- Recommendation-IIC: Build interim analyses to assess evolving changes in screening technology and the therapeutic landscape into large screening trials.

To address the recommendations, a subgroup of the Trans-DCP Clinical Trials Working Group, including DCP leadership, was formed into the Screening Trials Working Group. Membership of this DCP working group included representatives from the three programmatic areas within the division that have screening trials in their portfolio. After assessing the current and planned screening protocols against the CTAC working group's recommendations, the group described their findings, analysis, and recommendations in a report that was accepted by DCP leadership in April 2021. The DCP working group was next tasked with implementing their recommendations. These efforts include the creation of a set of new DCP screening trial requirements that must be included in the protocols for all future sponsored screening trials. Ms. Parreco noted a few examples of these requirements, including those related to study design (e.g., sample size, accrual duration, and eligibility are clearly defined and justified); recruitment planning (e.g., inclusion of plans for overall, minority, and non-English speaker recruitment); and accrual monitoring (e.g., clear definition of milestones, accrual monitoring plans, and stopping rules). The Trans-DCP Clinical Trials Working Group will oversee implementation of these new requirements, occurring in four phases, which began in September 2022. The final evaluation phase is planned to launch in early 2023. Preliminary slow accrual stopping rules, based on achieving a percentage of expected accrual by identified timepoints in the study, for new cancer screening trials as well as an implementation plan for these rules have been developed. Ongoing and future work will include a simplified NCI registration process for investigators participating in screening-only protocols; a Cancer Prevention and Control Planning Grant Program; funding for feasibility assessment; initiation of a new cancer screening research network; and implementation of the DCP screening requirements.

Questions and Discussion

Dr. Davidson said she is glad to see that the TMIST investigators were able to revise the trial and that it is now running smoothly.

Dr. Meropol asked whether the working group's recommendations were informed by experience with early stopping rules due to accrual in NCI National Clinical Trials Network (NCTN) cancer treatment studies. Lori Minasian, MD, Deputy Director of DCP, said that the group had considered the Cancer Therapy Evaluation Program (CTEP) stopping rules from earlier studies, but when applied to the cancer control trials, it was determined they did not fit. Therefore, a new set of stopping rules was developed, which are consistent with accrual data generated from previous screening trials. Over time, as more screening trials launch, the rules will be re-evaluated and potentially modified.

Dr. Knopp asked whether and how the proposed cancer screening research network will be integrated into other network structures to avoid competing infrastructures and processes. Dr. Minasian explained that the cancer screening research network will use the same back-end infrastructure that NCTN and National Community Oncology Research Program use. Because there have been challenges in engaging non-oncologists in the networks to date, the new network will provide an opportunity for oncologists and practitioners in other disciplines to collaborate to design, develop, and conduct cancer screening trials.

Ms. Spears noted that at a recent meeting of the Alliance for Clinical Trials in Oncology, presenters shared two maps of the United States. One map showed the incidence and mortality of lung cancer, and the other showed the locations of screening trials for lung cancer. The maps did not overlap. She asked whether DCP will take incidence and mortality into consideration when identifying sites for screening trials. Dr. Minasian responded that the new network will create opportunities to explore innovative ways of reaching and communicating with new audiences. In addition, NCI has now

implemented a new pilot and feasibility grant mechanism, which should encourage ideas from new contributors.

Dr. Muller commented that engaging stakeholders from non-oncology disciplines such as radiology for screening, obstetrics/gynecology, and gastrointestinal, requires a great deal of time and work. She suggested that in addition to evaluating feasibility and stopping rules, the Trans-DCP Clinical Trials Working Group also evaluate the effort and resources required to engage these stakeholders without whose buy-in the trials will not succeed.

Dr. McCaskill-Stevens noted that there are many parts of the United States that are not engaged in clinical research. Changing the culture to encourage medical professionals to engage in clinical research will be a slow process but is extremely important and will help ensure that patients everywhere in the country have equal access.

VII. Gastric and Esophageal Cancers Working Group Report

Anil K. Rustgi, MD
Karyn A. Goodman, MD

Dr. Rustgi provided a brief overview of the epidemiology of gastric cancer (gastric adenocarcinoma) and the two major types of esophageal cancers (squamous cell carcinoma and adenocarcinoma), which all have low 5-year survival rates. In December 2021, the NCI convened the *ad hoc* Working Group on Gastric and Esophageal Cancers, which was charged with identifying the most impactful translational research questions to advance the prevention, diagnosis, and treatment of gastric and esophageal cancers. The working group had four subgroups; multiomic technologies, experimental model systems, prevention/screening/surveillance/early detection, and treatment/correlative studies/additional enabling technologies.

Overarching Research Strategy. The working group concluded that the research strategy should focus on building a more robust pipeline of translational opportunities. It should address strengthening key enabling resources and tools and applying these resources and tools to identify new markers, targets, interventions, and population strategies with sufficient promise to justify focused translational efforts. The strategy should include development of precision approaches for the prevention, screening, detection, surveillance, and treatment of gastric and esophageal cancers by building repositories of well-characterized biospecimens and model systems; further developing analytic tools and computational methods; identifying actionable markers and targets; and developing novel clinical assessment tools and interventions.

Specific Recommendations. The group's specific recommendations have two themes: 1) enabling resources via biospecimen repositories and research tools and 2) future research directions for fundamental research, treatment, and prevention.

Enabling Resources via Biospecimen Repositories and Research Tools

Recommendations regarding biospecimen repository resources include:

- Launching a concerted effort to overcome logistical obstacles and assembling repositories of clinically annotated biospecimens that embody key stages in gastric and esophageal carcinogenesis and progression across diverse populations.
- Identifying an initial set of high-priority biospecimens to be made available through a national repository that is accessible to all qualified researchers with meritorious proposals.

Sub-recommendations regarding biospecimen repositories include collecting specimens from both observational and interventional study cohorts that illuminate key events in carcinogenesis and progression as well as variations in these processes across populations; creating observational and interventional study cohorts that enable efficient collection of specimens with desired characteristics; and

promulgating standards for collection, processing, and characterization of tissue specimens needed for different analyses.

The recommendation regarding research tools is to develop and refine research tools to further enhance the ability to derive insight into the biology of gastric and esophageal cancers from patients, biospecimens, and model systems. Specific sub-recommendations for research tools related to model systems as well as laboratory analytic and computational methods were further delineated.

Sub-recommendations regarding model systems include developing preclinical and animal models that more faithfully recapitulate gastric and esophageal carcinogenesis and progression in humans and that represent diverse populations and prioritized questions; collaborating with bioengineers, medical physicists, and other specialists to develop model systems with greater complexity and biological realism for gastric and esophageal cancers; collaborating with bioengineers, chemical engineers, and others to develop more economical synthetic reagents and culture systems and more efficient ways to replicate and distribute model systems; and promulgating standardized methods for generating and replicating uniform, well-characterized model systems.

A sub-recommendation on laboratory analytic methods includes developing and refining biological, chemical, and physical analytic methods, including incorporation of the spatial domain to complement the growing variety of -omics tools and further enhance our ability to derive insight into the biology of gastric and esophageal cancer from patients, biospecimens, and model systems. A sub-recommendation on computational methods includes collaborating with bioengineers, medical physicists, bioinformatics specialists, and other disciplines to develop and validate machine learning approaches for assessing patterns within and across diverse -omics and other data types to infer interventional targets for prevention or treatment of gastric and esophageal cancer.

Future Research Directions

The group's specific recommendations regarding future directions concerned three areas: fundamental research, treatment, and prevention.

Fundamental Research. The high-level recommendation related to fundamental research and biological insights is to apply -omics and other emerging analytical tools and computational methods to characterize gastric and esophageal cancer pathophysiologic processes with greater clarity and insight and identify translationally actionable markers and targets within the processes of gastroesophageal carcinogenesis and progression. Sub-recommendations for fundamental research include:

- Improving molecular characterization of gastric and esophageal precancer and disease progression from emergence of precancer through early-stage cancer to disease recurrence and advanced disease across diverse racial/ethnic populations, hereditary risk groups, and cancer subtypes.
- Elucidating the functional significance for gastric and esophageal cancer of genomics, proteomics, metabolomics, microbiomics, and tumor microenvironment and characterizing associated targets that may be susceptible to intervention.
- Investigating the biology of exceptional responders in gastric and esophageal cancer and of acquired and de novo resistance to immunotherapies and targeted therapies.

Treatment. The high-level treatment recommendation is to translate emerging biological insights on gastric and esophageal cancer into improved clinical assessment tools and therapeutic regimens tailored more effectively to the distinctive characteristics of each patient's disease process. Sub-recommendations for future treatment research directions include:

- Developing improved methods for predicting and monitoring response and resistance of gastric and esophageal cancer to therapy, particularly for guiding treatment of patients receiving front-line therapy and immunotherapy combinations.
- Developing surrogate markers of therapeutic effect in gastric and esophageal cancer to enable rapid assessment of new agents and accelerate clinical trials.
- Developing improved treatments for gastric and esophageal cancer, particularly for patients with refractory disease, including optimized and novel: immunotherapy and immune-oncology combination regimens, targeted therapies, and cell-based therapies.
- Identifying targets and developing methods for image-guided treatment in gastric and esophageal cancer.
- Developing new approaches to preventing or mitigating adverse effects associated with gastric and esophageal cancer and/or its treatment.

Prevention. The high-level recommendation is to translate emerging biological insights into improved practical tools and strategies for risk stratification, screening, early detection, and surveillance of both precancerous lesions and gastric and esophageal cancers, as well as practical and effective preventive interventions tailored to the characteristics of specific populations. Sub-recommendations for future prevention research include:

- Developing more sensitive and accurate assessment tools for screening and early detection of gastric and esophageal cancer.
- Developing more sensitive and accurate assessment tools to characterize gastric and esophageal cancer risk.
- Developing more sensitive and accurate assessment tools for gastric and esophageal cancer disease surveillance.
- Developing novel preventive interventions for gastric and esophageal cancer.
- Applying state-of-the-art vaccine development technologies to advance the development of *H. pylori* vaccines.
- Defining optimal antibiotic stewardship practices for *H. pylori* eradication, including surveillance systems for antibiotic resistance.

Conclusions. The epidemiologic and clinical realities of gastric and esophageal cancers define a compelling need for substantial advances in prevention, detection, surveillance, and treatment. The group concluded that no one intervention or priority will serve as a panacea; instead, a broad-based, interdisciplinary approach is needed, but dedicated biospecimen and model system resources are critical to this effort. This approach requires a focus on collaborations between federal agencies, public and private institutions, industry, patient advocates, and philanthropy.

Questions and Discussion

Dr. Goodman said that the working group was given a challenging topic and realized that a great deal of additional data and information would be needed before they could tackle questions around prevention and treatment. This highlighted the need for preclinical data and biospecimen repositories to help understand the transition from normal tissue to dysplasia to cancer as well as the effects of treatment at all stages of the process. Dr. Rustgi added that while the continuum from normal to precancer to cancer is not unique to gastric and esophageal cancers, what is different is the access to tissue at different stages. Critical to the centralized biospecimen repository recommendation is the inclusion of precancerous tissue.

Dr. Davidson remarked that members of the Translational Research Strategy Subcommittee (TRSS) were impressed with the working group's report, especially the comprehensiveness of its analysis and the group's focused prioritization of biospecimen acquisition. Dr. Rustgi responded that the working group wanted to avoid being too broad or too specific in its recommendations, so as to allow investigators to take novel approaches in addressing these issues. Dr. Hawk said that the working group had hoped to be able to prioritize further, but prioritizing across multiple diseases proved challenging. He acknowledged that the recommendations are numerous and pointed out that genetically based cancers and adenocarcinoma probably deserve prioritization.

Dr. Mesa commented that the deep-dive approach the working group undertook was successful, but that it raised the question of whether there are other areas that would benefit from similar attention.

Motion. A motion to accept the report of the *ad hoc* Working Group on Gastric and Esophageal Cancers was approved.

VIII. Ongoing and New Business

Neal J. Meropol, MD

Dr. Prindiville made two announcements related to NCI opportunities. NCI has created a new program, the R50 award for clinician scientists (PAR-21-306). The next receipt date is February 7, 2023. NCI will also be hosting a virtual summit, "Increasing Diversity, Equity and Inclusion in Early Phase Clinical Trials," which will take place on November 16, 2022.

Dr. Prindiville shared a list of future CTAC meetings, which will be held on March 15, July 19, and November 8, 2023; and March 13, July 17, and November 6, 2024.

IX. Adjourn

Neal J. Meropol, MD

There being no further business, the 49th meeting of CTAC was adjourned at 2:52 p.m. on Wednesday, November 9, 2022.

Date Neal J. Meropol, MD, Chair

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

Appendix

November 2022

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

CHAIR

Neal J. Meropol, MD 2023
Vice President of Research Oncology
Scientific and Clinical Lead, Clinical Research
Flatiron Health
New York, New York

MEMBERS

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Department of Pediatrics
University of Alabama at Birmingham
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Professor
Knight Cancer Institute
Oregon Health and Sciences University
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Edward Chu, MD 2025
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Albert Einstein Cancer Center
Carol and Roger Einiger Professor of Cancer Medicine
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Seattle Cancer Care Alliance Head, Division of Medical Oncology, Department of Medicine
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Professor
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