DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
53RD CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE MEETING

Summary of Meeting
March 13, 2024

Webinar

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The 53rd meeting of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) was convened Wednesday, March 13, 2024, at 11:00 a.m. The CTAC chair, Dr. Julie M. Vose, presided.[1] The meeting was adjourned at 2:48 p.m.

Chair
Julie M. Vose

CTAC Members
Nilofer S. Azad
Smita Bhatia
Charles D. Blanke
Edward Chu (absent)
Adam P. Dicker
Gary C. Doolittle (absent)
Ernest T. Hawk
Ken Kobayashi
Seth P. Lerner
Sumithra J. Mandrekar
Robert S. Mannel
Ruben A. Mesa
Carolyn Y. Muller
Raymond U. Osarogiagbon
Raphael E. Pollock
Suresh S. Ramalingam
Victor M. Santana
Patricia A. Spears
George Wilding

Ex Officio Members
James H. Doroshow, NCI
Paulette S. Gray, NCI
James L. Gulley, NCI (absent)
Michael J. Kelley, US Department of Veteran Affairs
Anthony Kerlavage, NCI
Richard Pazdur, US Food and Drug Administration (absent)

Designated Federal Official
Sheila A. Prindiville, NCI

Presenters

Helen Chen, MD, Associate Chief, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, NCI

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

Lyndsay Harris, MD, FRCP, Association Director, Cancer Diagnosis Program, Division of Cancer Treatment and Diagnosis, NCI

M.K. Holohan, JD, Director, Office of Government and Congressional Relations, Office of the Director, NCI

Christopher Karlovich, PhD, Association Director, Molecular Characterization Laboratory, Frederick National Laboratory for Cancer Research

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

Elyse LeeVan, MD, MPH, Program Officer, Division of Cancer Prevention, Early Detection Research Group, NCI

Richard F. Little, MD, Head, Hematologic, HIV, and Stem Therapeutics, Clinical Investigations Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, NCI

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

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

Sheila A. Prindiville, MD, MPH, Director, Coordinating Center for Clinical Trials, Office of the Director, NCI

W. Kimryn Rathmell, MD, PhD, Director, NCI

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

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I. Call to Order and Opening Remarks

Julie M. Vose, MD

Dr. Vose called the 53rd meeting of CTAC to order at 10:00 a.m. She welcomed three new members: Drs. Azad, Kobayashi, and Osarogiagbon. She also recognized Dr. Schneider, who was representing the U.S. Food and Drug Administration (FDA) as well as Mia Levy, MD, PhD, Chief Medical Officer, Foundation Medicine, who recently rotated off the Committee.

Dr. Vose reviewed the confidentiality and conflict-of-interest practices required of CTAC members during their deliberations. She invited members of the public to send written comments on issues discussed during the meeting to Dr. Prindiville within 10 days of the meeting. 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=54127.

Motion. A motion to accept the minutes of the 51st CTAC meeting, held on July 19, 2023, was approved.

II. NCI Director's Update

W. Kimryn Rathmell, MD, PhD

Brief Introduction. Dr. Rathmell described her background as a biophysicist and clinician focused on kidney cancer. Before joining NCI, she led the Vanderbilt School of Medicine's Division of Hematology and Oncology and then became chair of the Department of Medicine. In that position, she learned about organizational structure, health care in communities, and working with advocates. Dr. Rathmell also obtained a master's degree in management and health care administration. She values listening, transparency, collaboration within diverse teams, and solving complex problems.

Dr. Rathmell shared a personal experience about a young Black patient with renal medullar carcinoma, a rare form of kidney cancer. Her time as his provider taught her to listen to patients in a different way and has subsequently led to strong connections with advocates.

Budget. While operating under a Continuing Resolution (CR), NCI has set interim grant policies based on fiscal year (FY) 2023 budget numbers. Final adjustments will be made when NCI receives a full-year appropriation. NCI has proactively contacted appropriators to ensure they are informed about the importance of funding cancer research. Members of appropriations committees have responded with enthusiasm.

The total appropriated in FY23 to NCI was $7.3 billion. Dr. Rathmell reviewed how NCI spends its appropriations, noting that about 75% of the NCI budget supports extramural activities, and the remainder funds intramural research as well as research management and support. Research project grants account for about 44% of the NCI budget with the largest portion awarded to treatment-based studies.

NCI has received an increase in appropriations every year for the past 5 years. Since FY19, NCI's number of grants awarded has increased. Collaborative research that links extramural and intramural investigators with the NIH Clinical Center offers another way to do more with NCI funds.

The Opportunities for Collaborative Research at the NIH Clinical Center U01 program enables extramural researchers to take advantage of unique Clinical Center resources and patient populations, such as unique biospecimen resources, state-of-the-art imaging and testing facilities, and patients with rare diseases. Dr. Rathmell noted she would appreciate input from CTAC members on how best to use the U01 mechanism.

The NCI Professional Judgment Budget Proposal requested $9.988 billion for FY24 and $11.466 billion for FY25. President Biden's FY25 budget proposal calls for increases in NCI's base funding and Cancer Moonshot funding totaling $9.287 billion, which would result in a total that is close to NCI's proposal. With this funding, NCI plans to lead progress against cancer, which includes revolutionizing clinical trials, clarifying the impact of the environment on cancer risk, and harnessing the power of cancer data.

The final FY24 budget may provide a level of funding similar to the $7.3 billion in the FY23 budget. Because of cost-of-living increases, increases in the cost to fully fund grants, and other increases in non-negotiable expenses, a flat budget would effectively be a funding reduction.

National Cancer Plan and the Cancer Moonshot. Former NCI Director Dr. Bertagnolli rolled out the National Cancer Plan in spring 2023. The Plan identifies eight goals: prevent cancer, detect cancers early, develop effective treatments, deliver optimal care, maximize data utility, eliminate inequities, optimize the workforce, and engage every person. NCI is using the Plan as a roadmap to reach the Cancer Moonshot's goals of reducing cancer mortality by 50% by 2047 and improving the experience of people and their families living with and surviving cancer.

Recent Cancer Research Accomplishments. The FDA approved tumor-infiltrating lymphocytes for advanced melanoma, which is the first-ever FDA approval of cellular therapy for solid tumors. This advance stems from decades of collaborative work and will contribute to solid tumor treatment. This accomplishment directly contributes to three National Cancer Plan goals: develop effective treatments, engage every person, and maximize data utility.

In January, NCI announced the Self-Collection for HPV Testing to Improve Cervical Cancer Prevention (SHIP) Trial Network as part of an effort to increase uptake of HPV screening. Enabling patients to test themselves would help change the mindset around screening and bring screening to a new group of patients. The network stems from a partnership among NCI, academic centers, FDA, and a variety of companies.

NCI also recently launched the first large-scale cancer screening research network (CSRN). The network's first trial will focus on multicancer detection (MCD) tests, which could change how patients view their health and manage their risk for cancer.

The NCI Virtual Clinical Trials Office is a pilot program that will provide centralized, remote staff support for NCI-supported clinical trials with the goal of improving accrual and retention rates to trials by addressing staffing challenges and burdens of clinical research.

The Childhood Cancer Data Initiative (CCDI) has matured quickly and is now moving into molecular characterization of pediatric, adolescent, and young adult tumors.

The Cancer Grand Challenges initiative is a partnership with Cancer Research United Kingdom. Cancer Grand Challenges teams were selected to work on four major challenges: reducing cancer inequities, understanding mechanisms of early-onset cancers, developing drugs for solid tumors in children, and broadening knowledge about how T cells recognize cancer cells.

Dr. Rathmell asked CTAC members for guidance on NCI's clinical research portfolio and setting clinical research priorities. She requested input on gaps, NCI activities in spaces that are better served by foundations or industry, and whether programs have the resources they need to be successful.

Questions and Discussion

Dr. Mesa shared his enthusiasm for the CSRN, which engages stakeholders that are not typically involved in cancer clinical trials. NCI's portfolio seems balanced with survivorship and other key pieces well represented in the NCI Community Oncology Research Program (NCORP). Preserving support for survivorship trials will be critical.

Ms. Spears applauded Dr. Rathmell's comments on patient experience and community engagement to conduct research. She noted the need for increased survivorship research as the number of cancer survivors will increase as Cancer Moonshot goals are met. Dr. Rathmell agreed and expressed her strong support for obtaining the perspective of advocates.

Dr. Mannel commented on the value of the NCI brand, which makes it possible to rely on industry and the academic and philanthropic communities to fill in funding gaps as needed. The cancer community relies on NCI to start new initiatives, maintain a vision for cancer research, and think big even in times of a flat budget.

III. Legislative Update

M.K. Holohan, JD

The federal government, including the NCI, is operating under a fourth CR for FY24 that provides funding for federal agencies at FY23 levels through March 2024. President Biden signed half of the FY24 appropriations bills into law on March 9. However, NIH funding is among the bills that are still waiting to be finalized. CR

funding for agencies including the Departments of Defense, Labor, Health and Human Services, and Education, ends after March 22; the draft set of bills is anticipated soon. The delay in appropriations bills this year is due in part to House majority resistance to the spending caps passed in the Fiscal Responsibility Act in June 2023.

The House version of the appropriations bill for FY24 provides flat funding for NIH and NCI, which would effectively represent a funding decrease, as this bill does not replace 21st Century Cures Act funding that ended in FY23. The Senate version of the bill does replace the 21st Century Cures Act funding and increases NCI's base budget by $60 million.

CR funding is still in place 165 days into FY24. A CR of long duration creates uncertainty and difficulty for program and grants staff as new initiatives cannot begin. Understanding this, NCI has tried to be transparent and clear with the messaging about the current funding status and will work as quickly as possible once FY24 funding is resolved.

President Biden's budget proposal for FY25, released on March 11, forecasts the administration's priorities and provides updates on the status of various federal programs, although Congress determines the final budget. Cancer research is incredibly important to President Biden and his family, and efforts to improve conditions for cancer patients and their families are reflected in the proposal.

Several members of Congress have recently announced their retirement. The number of retirements is not unusual, but it is surprising that several representatives in senior, influential positions have decided to leave. Examples include Cathy McMorris Rodgers (R-WA), chair of the House Energy & Commerce (E&C) committee; Anna Eshoo (D-CA), ranking member on the E&C Health subcommittee and a longtime proponent of NIH and NCI; and Derek Kilmer (D-WA) and Brian Higgins (D-NY), co-chairs of the House Cancer Caucus. With these departures, the Republican majority in the House has further narrowed and presents challenges for leadership.

Because appropriations committees must cooperate on spending bills every year, those committees are often less partisan than others. In general, appropriators want to understand the value of their investments in federal programs. NCI incorporates examples demonstrating the value of investment in biomedical research into communications with congressional staff and other audiences. Cancer patients, oncologists, and cancer researchers are valuable messengers. Sharing stories about cancer research advances and patient experiences with members of Congress is important. Understanding the return on investment helps members justify their advocacy and support of cancer research. Ms. Holohan encouraged CTAC members to share their perspectives about the importance of cancer research.

IV. Streamlining Clinical Trials Working Group Report

Sumithra Mandrekar, PhD
Neal Meropol, MD

The November 2020 Strategic Planning Working Group (SPWG) report included 15 recommendations and three operational initiatives designed to support development of flexible, faster, simpler, less expensive, high-impact clinical trials that seamlessly integrate with clinical practice. In June 2022, NCI formed the CTAC Streamlining Clinical Trials Working Group (SCTWG)—co-chaired by Drs. Sumithra Mandrekar and Neal Meropol—to address recommendations on limiting data elements collected in clinical trials and utilizing electronic health records (EHRs) to support clinical trials.

The SCTWG specifically focused on (1) limiting data elements in late-phase trials to only those that are essential for primary and secondary objectives, (2) resolving logistical and data quality challenges of extracting clinical trial data from EHRs, and (3) engaging EHR and Clinical Trial Management Systems vendors to create mechanisms for automated integration of study-specific documents into local implementations of their products.

Standard Practices for Trial Data Collection. In November 2022, CTAC accepted an interim report from the SCTWG, which included proposed standard practices for collection of data for investigational new drug (IND)-exempt trials, aiming to limit the data submitted to clinical trial databases. The recommended standard practices were finalized in November 2023 and were informed by feedback from the National Clinical Trials Network (NCTN) Streamlining Clinical Trials Implementation Committee (SCTIC), which included representatives from each of the NCTN Groups as well as the Imaging and Radiation Oncology Core (IROC). The standard practices apply to NCI Cancer Therapy Evaluation Program (CTEP)/Clinical Investigators Branch-

managed, IND-exempt trials that are Phase III or Phase II/III, interventional, and focused on treatment both in the adult and pediatric setting. Data categories specified in the standard practices include adverse events (AE), medical history, concomitant medications, physical exams, lab tests, imaging and other assessment procedures, and patient reported outcome (PRO) data. The standard practices address data submission to the clinical trial database but not data collected in local medical records. Departure from the standard practices requires approval from both CTEP and the NCTN Group and must be justified—based on clinical/regulatory requirements and/or scientific objectives—by investigators on a trial-specific basis.

For the following data categories: medical history, concomitant medications, physical exam, laboratory testing, imaging and other assessment procedures, the standard practices include submitting data only needed for:

- Analyses prespecified in the statistical plan (endpoint data, stratification factors, etc.)
- Documentation of patient characteristics for publication or other reporting purposes
- Determination of eligibility or treatment assignment and dosing (at group discretion)

For AEs, only Grade 3 AEs or higher should be submitted to the clinical trial database unless there is a stated objective for use of lower grade AEs in analyses prespecified in the statistical plan. Solicited AEs may be submitted to the database if needed for analyses that are prespecified in the statistical plan. Only Common Terminology Criteria for Adverse Events (CTCAE) term and grade for each AE should be submitted. AE attribution and start/stop time data should not be submitted. For PRO data, submission is limited to data needed for analyses prespecified in the statistical plan (e.g., endpoint data or stratification factors).

Opportunities to further streamline data collection include full utilization of IROC infrastructure and capabilities for managing submission of imaging and radiation therapy (RT) data; reduction in the number of data elements submitted to document administration of pharmacologic therapies; and, in certain clinical and regulatory contexts, extension of standard practice principles to studies conducted under an IND.

Utilizing EHRS to Support Clinical Trials. The SCTWG discussed the current landscape of academic and commercial initiatives targeting automated or semi-automated extraction of oncology clinical trial data from EHRs. Potential pilot testing of such tools in NCI clinical trial networks will be informed by a recent CCDI Request for Information (RFI) seeking input on current capability in automated data entry and extraction from EHRs, including tools to auomatically populate clinical trial case report forms with data from EHRs.

The SCTWG was briefed on two NCI initiatives aimed at efficient implementation of clinical trial order sets and investigational drug medication data in trial site EHRs: The Clinical Trials Support Unit (CTSU) Site Study Setup Initiative (SSSI) and the NCI-funded Clinical Trials Rapid Activation (CTRAC) consortium.

The CTSU SSSI extracts key protocol information needed for EHR study builds into structured Excel templates, sparing duplicative efforts at clinical trial sites. Completed templates are available for all CTEP-sponsored NCTN studies as well as for Experimental Therapeutics Clinical Trials Network (ETCTN) studies for which protocols have been centrally drafted.

The CTRAC consortium is developing tools to automate tasks associated with site EHR study builds. Initial goals include standard, structured representations of protocol-specified investigational drug data, treatment plans, and assessment procedures as well as software tools to facilitate import of these structured electronic documents to EHRs.

Recommendations. The final SCTWG report includes the following recommendations for limiting data elements in late-phase trials and utilizing EHRs to support clinical trials:

- **Recommendation 1.** The working group recommends implementation of the Standard Practices for Data Submission to the Clinical Trial Database for the following categories of data: AEs, Medical History, Concomitant Medications, Physical Exam, Laboratory Tests, Imaging and Other Assessment Procedures, and Patient-Reported Data.

- **Recommendation 2.** The working group recommends that NCI, IROC, and the NCTN Groups work together to address the institutional privacy/confidentiality and data flow issues hampering submission of imaging and RT data.

- **Recommendation 3.** The working group recommends that NCI and NCTN work together in a timely manner to develop guidance for submission of treatment data that aligns with the Standard Practice principles.
- **Recommendation 4.** The working group recommends that NCI work with FDA to identify the clinical and regulatory contexts in which the Standard Practices for Data Submission could be extended to studies conducted under an IND/Investigational Device Exemption (IDE).
- **Recommendation 5.** The working group recommends that NCI support the timely further testing and implementation within NCI clinical trial networks of tools for extracting clinical trial data from electronic health records and report periodically to CTAC on progress.
- **Recommendation 6.** The working group recommends that NCI maintain the CTSU SSSI, continue to support the CTRAC consortium, and report periodically to CTAC on CTRAC progress.

Questions and Discussion

Dr. Kobayashi asked whether the recommendations related to limiting data submission apply to approved, marketed agents and late phase trials. Dr. Mandrekar confirmed this was accurate.

Ms. Spears asked how success of the recommended actions would be assessed. Dr. Mandrekar said that this is being discussed by the SCTIC. She suggested one approach would be to compare the number of data elements included in analyses before and after implementation to see if there is a reduction. The more challenging measure would be determining whether that reduction leads to improved efficiency while ensuring there is no negative impact.

Dr. Hawk suggested that updates on implementation of these standard practices be made at CTAC to determine if re-evaluation or modification of these practices are needed.

Dr. Muller pointed out that the recommendations will support the need to do more with less. She expressed concerns about the number of different EHR products being used and being careful to avoid inadvertently creating more inequities, especially for those in community settings. Dr. Meropol noted that the RFI was intended to improve understanding of what products are available. Interoperability of the tools is being developed across different EHR systems. Dr. Doroshow added that plans are under way to host a workshop for those who respond to the RFI. It may be a long time before these goals are attainable, but intermediate tools that facilitate the process could be available much sooner.

Dr. Kelley suggested standardizing patient selection criteria terms for automation across health information systems as an aid to identify patients for potential enrollment into studies. Dr. Meropol acknowledged that several entities are exploring this area; however, it is out of scope for the current CTAC effort.

Dr. Montello encouraged making the study builds as agnostic as possible to currently available EHR products.

Motion. A motion to accept the Streamlining Clinical Trials Working Group report was unanimously approved.

V. NCI's New Precision Medicine Initiatives

Chris Karlovich, PhD
Lyndsay Harris, MD
Helen Chen, MD
Richard Little, MD

Dr. Doroshow introduced NCI's new precision medicine initiatives: ComboMATCH, Immunotherapy Match (iMATCH), and MyeloMATCH. He highlighted the immense amount of time and effort committed over the past 5 years, state-of-the-art facilities at the Frederick National Laboratory for Cancer Research (FNLCR), and flexible contract mechanisms that made these initiatives possible.

Molecular Diagnostic Network (MDNet). Dr. Karlovich provided an overview of MDNet at the FNLCR, which was built upon the NCI-MATCH/PedsMATCH experience to establish a genomic assay network to support

the NCI Precision Medicine Trials Initiative. The network focuses on providing accurate, "fit for intended use," and well-documented assays to support data reproducibility and availability in the public domain. MDNet uses a designated laboratory (DL) network for standard-of-care assays (ComboMATCH) and subcontracts with external or FNLCR labs for new and novel assays. FNLCR staff work with NCI and trial investigators to develop a biomarker plan that defines the assay's intended use, specific biomarkers and their thresholds, specimen preanalytics, and the required turnaround time.

Dr. Karlovich outlined assay support for each initiative by type (i.e., exploratory, integral, integrated), laboratory, and biomarker. iMATCH assays are under development for biomarkers that measure tumor mutational burden (TMB), calculate inflammation scores, identify gene expression signatures from tumor and immune pathways, and produce somatic mutation profiles. ComboMATCH assays include next generation sequencing (NGS), whole exome sequencing (WES), RNA sequencing, and NGS of circulating tumor DNA. ComboMATCH DL applications were solicited via an RFI and were evaluated for assay performance, validation reports, and cross-lab comparability studies. Ongoing monitoring of DLs will continue during the ComboMATCH trial. MyeloMATCH assays include cytogenetics/fluorescence *in situ* hybridization, MyeloMATCH NGS, flow cytometry, and NGS Myeloid Duplex Sequencing for minimal residual disease detection.

MDNet works closely with NCI on FDA submissions, providing assay expertise and risk determination. For example, FDA deemed MyeloMATCH assays a significant risk and required a full IDE; therefore annual audits of MyeloMATCH labs will be conducted.

ComboMATCH. Dr. Harris explained that, as the successor trial to NCI-MATCH, ComboMATCH focuses on therapeutic combinations that are more likely to provide clinical benefit than single agents in most situations. The hypothesis is that data from *in vivo* models of combinations demonstrating synergy and prolonged tumor regressions can predict clinical benefit in defined patient groups. ComboMATCH will use single-arm studies and phase II randomized trials in histology-agnostic and histology-specific patient cohorts. ComboMATCHbox algorithms interpret commercial NGS testing for eligibility via a DL report. For research purposes, there is a collection of a fresh tumor biopsy at baseline and progression and ctDNA assessments before, during, and after treatment that are analyzed by MDNet.

Dr. Harris outlined the organization of the ComboMATCHsystem. Each NCTN group has a cassette of treatment trials. She described the pathway for patients moving through the ComboMATCH registration trial and the subsequent treatment trial. The physician identifies the patient as being potentially eligbile for ComboMATCH based on a mutation that is relevant to one of the treatment trials. MATCHBox then uses the genomic data from the DL and clinical data collected at the time of the screening study as part of the algorithm to assign the patient to a ComboMATCH treatment trial. The patient is then assessed for treatment trial eligibility, consented if eligible, and enrolled within a goal of less than three weeks to assignment. If the patient progresses, they can then be assessed for a different treatment trial.

Dr. Harris described the ComboMATCH committee structure, including roles and responsibilities of its working groups, and the ComboMATCH Protocol Review process for concepts, protocols, and amendments. Eight arms are open in ComboMATCH, each with a different drug combination. Dr. Harris noted that some arms have exclusionary variants that, if present in the NGS report, represent ineligibility for that patient as the protein product from that gene may lead to drug resistance. Physicians can directly refer patients if inclusionary variants are listed on the Clinical Laboratory Improvement Amendments (CLIA) report from the DL.

iMATCH. Dr. Chen presented iMATCH, a cross-NCTN effort aimed toward precision immunotherapy (IO). iMATCH trials will use currently available clinical grade markers to perform prospective molecular characterizations designed to stratify or enrich immune-based subgroups with relevant biology for regimens under study. The goal of iMATCH is to enhance clinical evaluation of novel IO agents and combinations by providing a central assay platform for prospective patient enrichment and stratification as well as retrospective exploratory analysis. Integral markers such as TMB and tumor inflammation signature will be used to define immune-based subgroups. Comprehensive retrospective analysis using the same and additional assays will be conducted to optimize classifiers, enhance bological understanding, and explore predictive markers. Independent therapeutic protocols can be developed under the central assay protocol with a focus on signal-seeking trials.

The iMATCH platform will require new biopsies unless recent specimens are available. WES and IO 360 will be performed upfront to generate integral markers for prospective use and support deeper retrospective

analyses. This will enable design of trials with predefined sample sizes for a given subgroup. Cutoffs will be prespecifed with the understanding that markers may not accurately reflect the biology and may be adjusted after interim data analysis. A pilot trial of this upfront use of complex assays is going to assess platform feasibility (e.g., turnround time), inform potential need for cutoff adjustment, and optimize selection of assays.

Each potential therapeutic trial will make use of the iMATCH central screening protocol plus stand-alone therapeutic protocols focused on a specific clinical setting (single or limited histology, IO-naïve or exposed setting). Each protocol may use some or all of the integral markers to define subgroups for enrichment and/or for stratification as appropriate for the disease setting and agents in question. A variety of regimens may be tested to address resistance mechanisms in different immune statuses.

MyeloMATCH. Dr. Little introduced the MyeloMATCH initiative, which aims to create a portfolio of rationally designed treatment substudies onto which patients sequentially enroll over their entire treatment journey until cure, progession, or death. As tumor burden is reduced, residual disease will be targeted more effectively. An efficient operational model will be designed to attract industry partners and NCTN sites to foster acceleration of therapeutic advances for myeloid malignancies. Furthermore, the initiative aims to develop junior investigators by promoting leadership. Administrative components of MyeloMATCH enhance collaboration across NCTN groups and the Bone Marrow Transplant Clinical Trials Network. The Senior Scientific Council and Agents and Genes Committees evaluate novel agents and recommend the development of Cooperative Research and Development Agreements between drug companies and NCI to allow drugs to enter the program more efficiently. There are also five working groups with representation from all NCTN groups comprising junior and mid-career investigators who develop the clinical trials.

Patients with newly diagnosed acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) will be enrolled into the master screening and reassessment protocol with rapid laboratory analysis completed within 72 hours. Patients will be enrolled in tier 1 treatment trials and can advance into higher tier treatment trials (tiers 2–4) with the idea that as disease burden is lowered, new assays can interrogate the lower disease burden. Tier 4 is envisioned for patients with complete response where trials are designed to validate the clinical utility of NGS and other assays to assign therapy.

MyeloMATCH will be conducted under one IND and one IDE. MDNet integral assays will be performed under the NCI IDE. The MyeloMATCH team is working on analytical data and planning additional experiments in preparation for going to FDA to discuss bringing duplex sequencing into the IDE. Currently, 16 MyeloMATCH treatment substudies are in development by NCTN groups. Three substudies, including the master screening and reassessment protocol, have full FDA approval.

Dr. Little noted that MyeloMATCH assay data will promote rapid treatment assignment, inform clonal evoluation, and provide insights into treatment sensitivity and resistance. The trial platform may provide insights toward changing AML and MDS treatment paradigms.

Questions and Discussion

CTAC members were asked to consider and provide feedback on the following questions:

- What challenges do you foresee for these trials and what are strategies to maximize success?
- How do we encourage sites to open master protocol treatment substudies when only a small number of patients will have the targeted alteration?
- How do we best engage clinical sites for biospecimen collection?

Dr. Dicker commented on the importance of considering how data structure across these initiatives will impact future data mining efforts. Dr. Little responded that MyeloMATCH genomic data, regardless of investigator group affiliation, will be held in one place to provide equal access and to support collaboration. Ad hoc investigations will be encouraged. Dr. Karlovich explained that all of the data will ultimately be in the public domain and will be accessible. Users will be able to access raw data files to run through their own pipelines or use the pipelines available on data commons platforms.

Dr. Ramalingam suggested maximizing participation by using archival tissue samples as much as possible. Dr. Harris noted that ComboMATCH has been successful at collecting fresh biopsy samples and archival tissuefor NGS testing; all of the specimens go to the ECOG-ACRIN bank located at MD Anderson Cancer Center with the understanding that these specimens will be available to the NCTN groups depending on what assays have been preplanned for a given protocol.

Dr. Ramalingam also noted that some trials require multiple cassettes in place. Additionally, he indicated that at times there are gaps in trial availability. Dr. Vose commented on potential challenges in meeting turnaround times. For MyeloMATCH, Dr. Little noted the one of the primary endpoints is to study time from lab receipt to patient assignment. Ms. Spears commented on the possibility that many patients who are screened will not have a mutation that matches a substudy. She suggested including a no-mutation or no-target path and coordination of screening across substudies to expand trial opportunities. Dr. Little explained that patients who do not match an open substudy will receive standard care and be re-evaluated for potential assignment to a higher tier. This will help with loss of patients from the initiative.

Dr. Karlovich noted the challenge of blood collection, especially during the time of progression, and asked for advice on encouraging patients to comply. Dr. Mesa suggested developing patient materials explaining why subsequent blood tests are needed. Dr. Kobayashi emphasized the importance of retention plans designed to engage the patient community throughout treatment. Ms. Spears suggested that compliance also will improve if trialists find ways to make compliance less burdensome for patients.

Dr. Mesa commented on the opportunity to study the spectrum of myeloid malignancies beyond AML and MDS. Dr. Little responded that the initiative could add other malignancies later.

CTAC members discussed ways to encourage sites to open master protocol treatment substudies given that only a small number of patients will have the targeted alteration. Dr. Vose asked about opening the master protocol without having the small separate studies open. Dr. Little responded that sites are not required to open all the studies. Dr. Kobayashi suggested implementing a just-in-time approach in which sites are prequalified and quickly complete the last few steps when a patient is identified. Dr. Harris responded that ComboMATCH had tried this approach, which did not work well for larger academic institutions with many-layered internal review processes; however, community and private sites might be more likely to be able to participate in this way.

Dr. Kobayashi suggested that investigators could be motivated to participate in biospecimen collection by showing real-time examples of how biopsy material has had an impact on understanding and interpreting trials.

Dr. Blanke suggested that NCI consider providing credit to sites for opening studies that have low biomarker prevalence regardless of accrual. Otherwise, cancer center directors may not want to open studies where accrual will be slow. Dr. Azad agreed; some major centers have placed a moratorium on opening studies that will not accrue.

VI. Cancer Screening Research Network

Elyse LeeVan, MD, MPH

Launched in February 2024, the Cancer Screening Research Network (CSRN) aims to conduct multicenter cancer screening trials and studies, improve early cancer detection, and evaluate emerging cancer screening technologies with the ultimate goal of reducing cancer-related morbidity and mortality. Network components include Accrual, Enrollment, and Screening Sites (ACCESS hubs) that participate in the scientific development of CSRN trials and studies, recruit participants, and conduct study protocols; a Statistics and Data Management Center (SDMC) that provides statistical expertise and centralized data management, quality control, and reporting; and a Coordinating and Communication Center (CCC) that coordinates study operations and develops and implements communication activities.

CCC and SDMC grants were awarded to Fred Hutchinson Cancer Center. ACCESS hub grants were awarded to seven institutions. The Department of Veterans Affairs (VA) and Department of Defense will also serve as ACCESS hubs using funds from their own institutions. The broad diversity of expertise and disciplines in the leadership teams will enable the network to access patients where they seek care and receive cancer screening. The network also includes federally qualified health centers, tribal populations, rural populations, and individuals

historically underrepresented in clinical trials. The network will utilize the same clinical trials infrastructure used by NCTN and NCORP.

A variety of technologies are rapidly developing to improve early detection of cancer. MCD assays offer the potential to revolutionize cancer screening, but insufficient data are available to understand how best to use them. CSRN is uniquely positioned to conduct studies for evaluating new screening modalities in representative populations across the United States.

MCD assays detect multiple cancer types simultaneously, representing a significant shift from traditional cancer screening tools. MCD assays measure different analytes in blood and detect different sets of cancer types. They include biologic measurement and software algorithms, usually machine learning or artificial intelligence, to determine a cut point for positive versus negative results. Algorithms can be updated frequently to improve test performance.

A systematic review of predictive performance of MCD tests reported wide variation in accuracy and sensitivity, which overall ranged from 27% to 95%. Most studies published to date reported the performance of the test on storage samples of individuals with and without cancer, which is likely to overestimate how well tests function compared with when they are used in a population that requires cancer screening.

It is unclear whether screening an asymptomatic population for cancer with MCD assays will result in mortality reduction from cancer. Potential harms from using MCD assays to screen for cancer are also unknown. For example, it is unknown whether a blood test will make screening more accessible or exacerbate disparities. Additionally, false positives may subject people to unnecessary invasive procedures with potential complications, and false negatives may delay diagnosis and treatment. Given these many unknowns, NCI hosted a study design workshop in October 2021, which made the following recommendations: evaluate MCD assays for clinical benefit with strong support for a large MCD randomized control trial (RCT); evaluate harms and benefits of MCD tests; and conduct a pilot study to optimize study design.

In 2024, the network will launch the Vanguard study, a pilot to assess feasibility of a large MCD assay platform RCT. The Vanguard study will assess participant willingness for randomization; determine adherence to testing and diagnostic follow-up; evaluate feasibility of protocol-defined diagnostic workflows; determine reliability and timeliness of blood specimen testing and return by MCD companies; and identify facilitators and barriers to recruitment, retention, and adherence of diverse participant groups. The study will include three arms, each containing approximately 8,000 people, for a total sample size of 24,000. The control arm will receive standard of care screening, and each MCD arm will receive a different MCD test likely focusing on different cancer types in addition to standard of care screening. The diagnostic workup component of the study will be particularly complicated because MCD tests lack a direct pathway from a positive test to cancer diagnosis. Additionally, it is not clear how costs of these tests will be covered for uninsured and underinsured individuals.

To aid in assay selection, NCI hosted a virtual workshop in May 2023 to engage MCD assay developers, which was followed by an application period, suitability ranking, and specimen testing. Assay application review criteria included types of cancer detected, sensitivity, specificity, tissue of origin accuracy, sample type and volume, prior studies conducted, and scalability to meet the Vanguard study requirements. An independent verification of assay performance characteristics was conducted in partnership with Alliance.

Next steps for CSRN in early 2024 include establishing and populating workgroups, presenting workgroup findings to investigators, and writing protocols. In mid- to late-2024, the aim will be to submit the protocol to the institutional review board and finalize contracts with assay developers. The goal is to launch the Vanguard study in late 2024.

Questions and Discussion

CTAC members were asked to consider and provide feedback on the following questions:

- Do you have any thoughts about ways to improve the Vanguard trial design?
- Do you have any recommendations regarding data elements to capture in this pilot trial that would guide the design for a large platform randomized control trial?

- What do you foresee as the biggest challenges to the success of this study, and do you have recommendations to mitigate them?

Dr. Dicker asked how messaging to potential participants—patients and clinicians—will be tested. Communication of complex concepts will be key to Vanguard's success. Dr. LeeVan agreed and noted that NCI has initiated physician and lay population focus groups to assess the current understanding about MCD tests. Some grantees are using pilot funds to test messaging. The CCC will also provide expertise and serve as a repository of best practices for communications, informed consent, etc.

Dr. Ramalingam asked who will fund additional testing for study participants who receive a positive MCD test. Dr. LeeVan reported that funds have been allocated to ACCESS hubs to conduct diagnostic workups for under- and uninsured individuals. Dr. Hawk recommended collecting data on insurance status and household income as a way to understand the implications of patients' ability to pay for downstream diagnosis and treament. In addition, long-term follow-up data will be valuable.

Dr. Hawk also noted that the pace of technologic improvements—including algorithmic updates—will be another challenge because the tests that the Vanguard study evaluate this year may not be the same tests in three years. Because the MCD tests were intended to serve average-risk populations, the baseline risk assessment will be incredibly important. The samples used to verify assay performance may not reflect the molecular diversity of tumors.

Ms. Spears commented that false positives pose a significant challenge. Participants who receive a false positive will need to be convinced that the result is a false positive. There may also be additional costs to patients to follow up after a false positive test. When measuring costs associated with false positives, the study should collect data on the costs of increased visits, anxiety, etc. Dr. Muller added that dissecting patient understanding of these tests will be critical, especially when only a small percentage of these tests will be true positives.

Dr. Osarogiagbon noted that there are MCD assay development efforts to convince Congress to fast-track support for these tests without data. Anecdotes can resonate with Congress, so he recommended providing Congress with accurate data to avert emotionally driven decision-making. Dr. LeeVan agreed and reported that NCI is working with government entities, including FDA, Centers for Medicare & Medicaid Services, and White House representatives to create a unified message about this exciting technology. Clinicians are also concerned about widescale use of MCDs without guidelines for their use.

VII. Ongoing and New Business

Dr. Vose
Dr. Prindiville

Dr. Prindiville called attention to recent FDA and Office for Human Research Protections (OHRP) Draft Guidance on Informed Consent. The guidance addresses the revised Common Rule requirement that the informed consent form begin with key information that is most likely to help prospective participants understand reasons why one might or might not want to participate in research. Comments from the public can be submitted until April 30, 2024.

Dr. Prindiville referenced the NCI and VA Interagency Group to Accelerate Trials Enrollment (NAVIGATE), which is a partnership between VA and NCI to enhance veteran participation in NCTN and NCORP studies. Initially, the NAVIGATE consortium consisted of 12 VA sites and a coordinating center and has since expanded to now include 16 sites. The VA is also participating in the CSRN.

Dr. Prindiville noted the dates of future CTAC meetings and encouraged members to submit topics for the July 17, 2024 CTAC agenda.

VIII. Adjourn

Julie M. Vose, MD

There being no further business, the 53rd meeting of CTAC was adjourned at 2:48 p.m. on Wednesday, March 13, 2024.

Date	Julie M. Vose, MD, Chair
Date	Sheila A. Prindiville, MD, MPH, Executive Secretary

Appendix

March 2024

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
Clinical Trials and Translational Research Advisory Committee

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