Clinical Trials & Translational Research Advisory Committee: Cancer Screening Trials Working Group Report

NCI's Implementation of Recommendations

Part I: TMIST

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Chief, Community Oncology and Prevention Trials Research Group
Director, NCI Community Oncology Program (NCORP)
Division of Cancer Prevention

November 9, 2022

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Background: CTAC Working Group on Cancer Screening Trial

- **Established in November 2020**
  - Purpose: Advise NCI Director and CTAC on real-world impact of COVID-19 on NCI-supported screening trials with initial focus on Tomosynthesis Mammographic Imaging Trial (TMIST)
  - 3 virtual WG Meetings between December 2020 and February 2021
  - Chair: Nancy Davidson, MD., Report accepted March 2021

- **Two Sets of Recommendations:**
  - Set-I: TMIST-specific
    Worta McCaskill-Stevens, MS, Chief, Community Oncology & Prevention Trials Research Group
  - Set-II: NCI/DCP cancer screening trials in general
    Linda Parreco, RN, MS on behalf of the trans-DCP Clinical Trials Working Group

ECOG/ACRIN 1151: Tomosynthesis Mammographic Imaging Screening Trial (TMIST)

- **Primary Objective:**
  - To determine whether the cumulative rate of advanced breast cancer* in women undergoing screening with tomosynthesis + digital mammography (TM) is reduced compared to digital mammography (DM) alone.
- **Trial Design: Occurrence of advanced breast cancer at any time during a period of 4.5 years from randomization, including active screening, and follow-up after the last screen (T4). A sample size of 64,881 participants with complete data per arm provides 90% power to detect a relative reduction of 20%. After adjustment for loss to follow-up, dropout, and crossover, the required sample size is 164,946.**
- **Biorepository: Biopsy, tissue, blood, and buccal cell biospecimens**

*Definition of Advanced Cancer

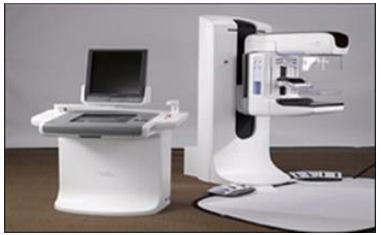
- ✓ Distant metastases
- ✓ A least one lymph node macrometastasis
- ✓ Invasive and is greater than 10 mm in size and is either ER- and PR- and HER2- or is HER2+
- ✓ Invasive and greater than or equal to 20 mm in size, unless of pure mucinous, papillary, tubular, adenoid cystic, or invasive cribriform histology

Overarching Recommendation-I for TMIST

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 the results will inform patient care and advance research.

ECOG/ACRIN 1151: TMIST Design Modifications*

- **Primary Objective:**
  - **To determine whether the cumulative rate of advanced breast cancer in women undergoing screening with tomosynthesis + digital mammography (TM) is reduced compared to digital mammography (DM) alone.**
- **Trial Design: Occurrence of advanced breast cancer at any time up to 7 years from randomization (time-to-event endpoint and powered at 85% for a 20% reduction in advanced cancer at 4.5 years from randomization. After adjustment for loss to follow-up, and crossover, the required sample size is 128,905. Follow-up will last for a least 3 and up to 8 years after study entry.**
- **Biorepository: Biopsy, tissue, blood, and buccal cell biospecimens**



*Protocol Amendment: Approved December 2021

Recommendation-IA: Establish a realistic timeline for overall and minority accrual goals as well as strict criteria for termination of the study if these goals are not met.

- With the protocol trial design modifications, accrual is expected to end in 2024/early 2025.
- Monitoring is related to the primary endpoint. Further recommendations will be based on the boundaries for futility and efficacy.
  - Futility analysis by the DSMC: when 50% of person-year follow-up data is in-hand.
  - Conditional power for futility analysis is 25%. If the conditional power in the futility analysis is below 25%, the recommendation would be to stop the trial.
- Overall recruitment and enrollment are monitored monthly within NCORP, the TMIST Steering Committees and the Study team/site meetings; and biannually by the DSMC.
- Minority accrual is monitored by NCORP of all participating sites to incentivize successful sites, share best practices and support new sites and initiatives, e.g., Xavier (HBC), MS.

Recommendation-IE: Consider incorporating predictive genomic information into the definition of advanced breast cancer

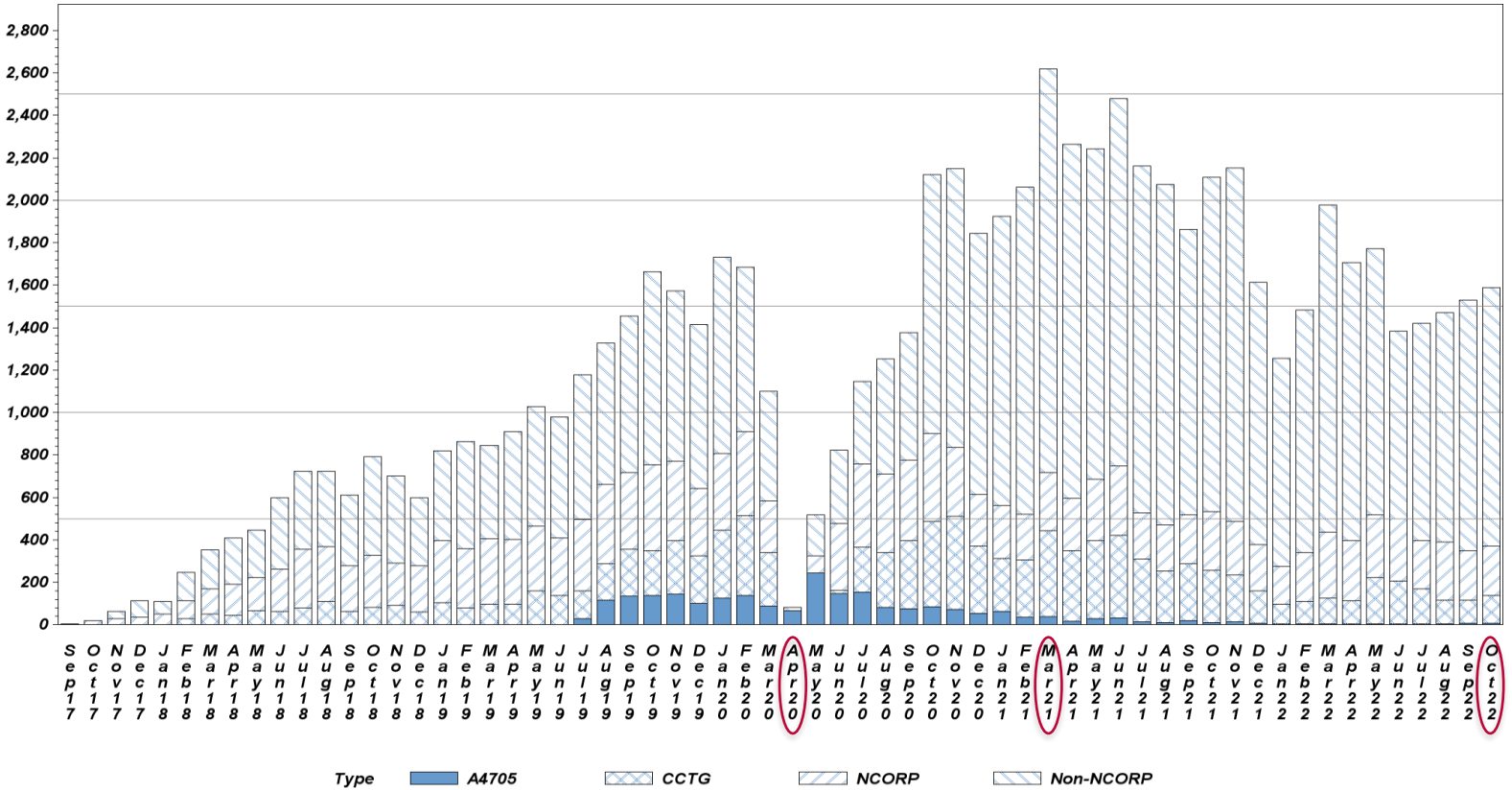
- **The NCI, study team's statisticians, and the DSMC considered the recommendation of including genomic information into the definition of advanced breast cancer and determined that the scientific integrity of the study's primary endpoint could not be maintained.**

Recommendation-ID: Ensure that data collection for the prespecified secondary outcomes is complete and include analytical and statistical plans for aims in the modified protocol

- **The protocol has been amended with full analysis plans of all study aims**
  - ✓ Imaging Assessment, recall rates and biopsy rates for interval cancers
  - ✓ correlation between BIRADS imaging features and histologic and genetic features
  - ✓ To assess different combinations of TM and synthesized 2D or DM
  - ✓ Assessment of long-term outcome
  - ✓ Breast Biology and Pathology Assessment
  - ✓ To assess the agreement between local and expert study pathologists for all breast lesions
  - ✓ Medical physics To implement a centralized QC monitoring program for

- **On going discussions with international RCTs for collaborations of mutual interest**
  - ➢ PROSPECTS (UK)
  - ➢ TOSYMA (Germany)
  - ➢ TO-BE (Norway)

TMIST Accrual: 124 Sites
41,576 (March 2021) - 78,054 (November 2022)



TMIST Participants Demographics (November 2022)

		US		CCTG		International		All	
		N	%	N	%	N	%	N	%
Race	American Indian or Alaska Native	99	0.3	12	<0.1	35	0.1	146	0.2
	Asian	627	1.9	473	3.7	61	0.2	1,161	1.5
	Black or African American	6,688	20.7	192	1.5	19	<0.1	6,899	8.9
	Multiple Races Endorsed	186	0.6	39	0.3	11	<0.1	236	0.3
	Native Hawaiian or Other Pacific Islander	76	0.2	9	<0.1	7	<0.1	92	0.1
	White	23,558	73.1	11,014	87.0	32,468	99.4	67,040	86.4
	Unknown/Not Reported	1,008	3.1	917	7.2	50	0.2	1,975	2.5
Total		32,242	100.0	12,656	100.0	32,651	100.0	77,549	100.0
Ethnicity	Hispanic or Latino	1,933	6.0	169	1.3	32,549	99.7	34,651	44.7
	Not Hispanic or Latino	29,841	92.6	10,956	86.6	87	0.3	40,884	52.7
	Unknown/Not Reported	468	1.5	1,531	12.1	15	<0.1	2,014	2.6
Total		32,242	100.0	12,656	100.0	32,651	100.0	77,549	100.0

Percentages may not total to 100 due to rounding

Recommendation-IC: Increase the rate of biospecimen collection particularly from minority participants and incentivize sites to collect blood specimens at initial enrollment.

March 1, 2021 (N=41,576				
Black or African Am.	Type of Sample	Enrolled	Consented	Collected
	Buccal	4,677	2,331 (49.8)	1,019 (43.7%)
	Blood	4,677	2,166 (46.3%)	870 (40.2%)
White	Buccal	34,872	25,133 (72.1%)	10,435 (41.5%)
	Blood	34,872	24,687 (70.8%)	10,398 (42.1%)
November 1, 2022 (N=77,958)				
Black or African Am.	Type of Sample	Enrolled	Consented	Collected
	Buccal	6,899	3,087 (44.7%)	1,660 (53.%)
	Blood	6,899	2,748 (39.8%)	1,415 (51.5%)
White	Buccal	67,040	50,838 (75.8%)	19,850 (39%)
	Blood	67.040	50,041 (74.6%)	19,807(39.6%)

- **Protocol Amendment: Requires biospecimen collection prior to T2 for blood and T3 for buccal specimens.**
- **Komen Foundation funding to increase biospecimen collection among AA women**

Modifications to enhance enrollment and contributions to the science of screening

- Minimizing frequent QC reporting in sites with "Gold Status sites". Those sites who have demonstrated well-conducted QC and stable results.
- New sites on-boarding and implementation of new rostering categories
- Collaborating with Communications to promote Hispanic participation
- Incentives provided for lower resources institutions and high accruing sites having reached a cap to further enrollment to support the collection of biospecimens
- Potential Concepts utilizing TMIST data:
  - Precision screening to personalize by prediction to avoid advanced cancers, image failures and false positives --TMIST/"All OF US" collaboration
  - Abbreviated breast MRI versus conventional diagnostic imaging in TMIST participants presenting for diagnostic breast imaging.
  - The development of a prognostic/individualized therapy tool using Therapeutic Tumor Infiltrating Lymphocytes (TILS)

Cancer Screening Trials Working Group

Update on Implementation of Recommendations

Linda Parreco, RN, MS
Nurse Consultant
Office of the Deputy Director
NCI, Division of Cancer Prevention

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CTAC Recommendations

- Overarching Recommendation II: Develop a framework for the design and operations of NCI-supported cancer screening trials that incorporates slow accrual guidelines and early termination criteria
  - Specific Recommendation II-A: Conduct a portfolio analysis of all ongoing and planned NCI-funded cancer screening trials
  - Specific Recommendation II-B: Assess overall and minority accrual rates for all ongoing screening trials
  - Specific Recommendation II-C: Interim analyses to assess the evolving changes in screening technology and the therapeutic landscape should be built into large screening trials

Organization, Charge & Methods

Trans-DCP Clinical Trials Working Group

- Linda Parreco, Co-Chair
- Val Dyer, Co-Chair
- Phil Castle
- Lori Minasian
- Leslie Ford
- Troy Budd
- Brandy Heckman-Stoddard
- Victor Kipnis
- Worta McCaskill-Stevens
- Paul Pinsky
- Vikrant Sahasrabuddhe
- Eva Szabo

Screening Trials Working Group

- Linda Parreco, Co-Chair
- Val Dyer, Co-Chair
- Wanda Bryant-Davis
- Cecilia Lee
- Phil Prorok
- Worta McCaskill-Stevens
- Vikrant Sahasrabuddhe
- Claire Zhu

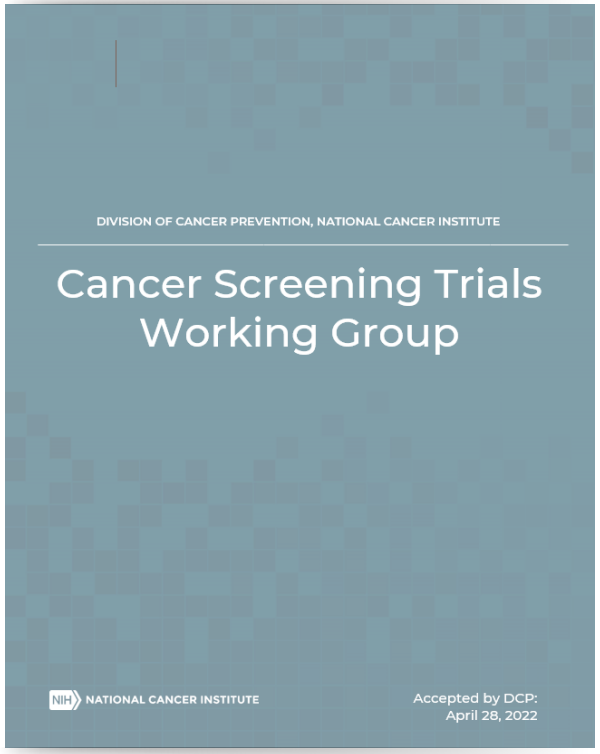
Working Group Charge

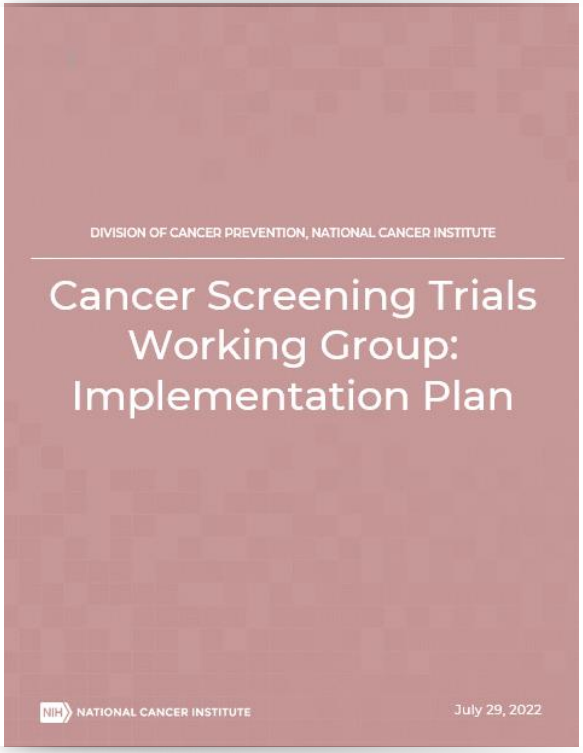
1. Assess ongoing and planned DCP screening protocols against the CTAC recommendations
2. Recommend changes to ensure future success

Methods

- Review program materials
- Portfolio analysis
- IT systems analysis
- Identify challenges
- Make recommendations

Screening Trials Working Group Deliverables





New DCP Screening Trial Requirements

Study Design/ Study Plan

- Sample size appropriately justified
- Accrual duration explicitly stated
- Eligibility criteria clearly defined

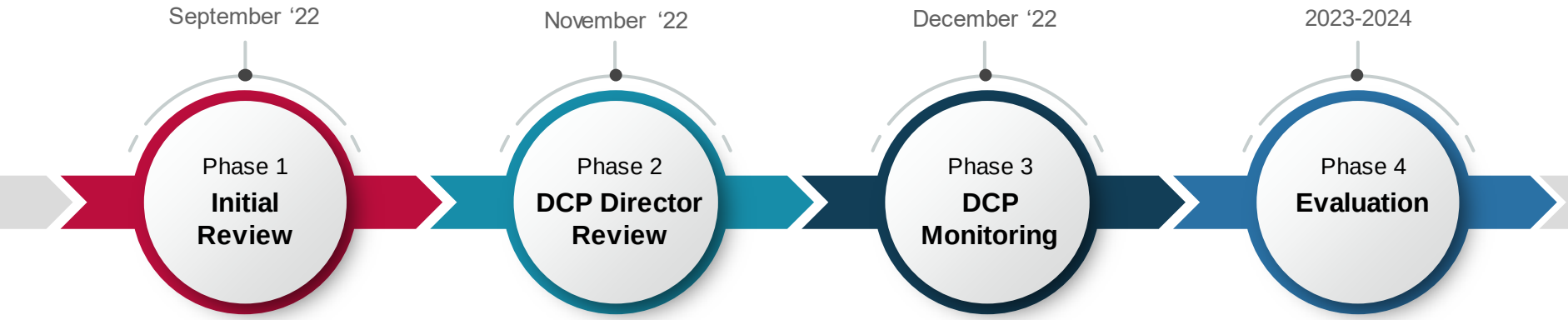
Recruitment Planning

- Overall and minority recruitment plans detailed
- Non-English speakers included
- Participant Advisory Boards required for trials >10,000

Accrual: Milestones & Monitoring

- Expected overall and minority accrual milestone dates stated
- Overall and minority accrual monitoring described
- Stopping rules are addressed

Implementation Plan



- One time assessment
- Revise documents and processes to comply with new requirements
- Timeline & communication plan

- Before DCP approval, DCP Director reviews:
- New screening trial protocol documents
- Significant amendments to ongoing trials

- DCP CTWG meets quarterly
- Reviews accrual on ongoing screening trials
- Ensure warning letters are issued as needed and stopping rules are implemented

- Process evaluation
- Outcome evaluation

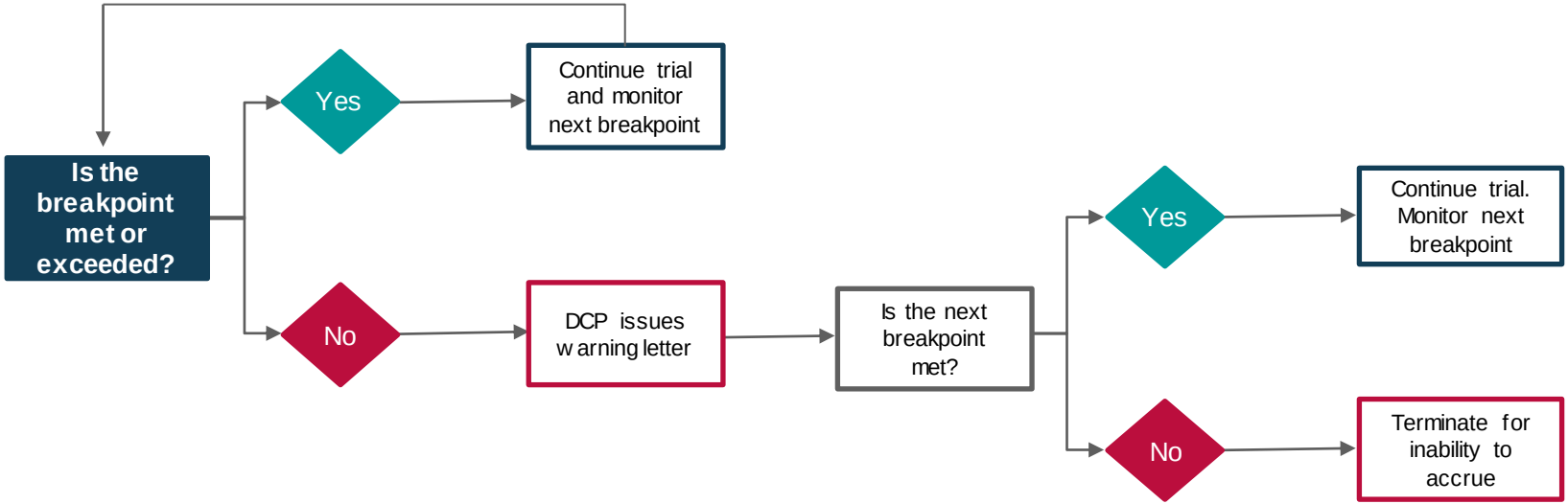
Development of Slow Accrual Stopping Rules for New Cancer Screening Trials

- Collected and analyzed data from ongoing and past screening protocols and large prevention trials (n=12).
- Small number of trials
  - Not sufficient to establish definitive set of stopping rules
  - However, data can be used to develop preliminary rules that will be refined over time
- Proposed rules based on % of expected accrual achieved at specific time points in the time frame for accrual.
- Implemented on 10/1/22 for all future screening trials

Proposed Slow Accrual Stopping Rules

Accrual evaluation breakpoints are expressed as a % of expected accrual at a specific time point in the projected accrual period

Implementing the stopping rules



Going forward

- Early ‘23: simplified NCI-registration process for investigators participating in only screening protocols
- Mid ‘23:Cancer Prevention and Control Planning Grant Program (R34, U34)
  - Funding for feasibility assessment
  - Enhance rigor while saving time and cost to ensure future trial success
- Late ‘23/Early ‘24:Cancer Screening Research Network
  - Initiating new network to conduct cancer screening clinical trials
  - Will implement the new DCP Screening Trial Requirements and stopping rules
- Continue full implementation of the DCP Screening Requirements

QUESTIONS?