Clinical Trials and Translational Research Advisory Committee *Ad hoc* Working Group on Cancer Screening Trials Working Group Report

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CTAC March 17, 2021

Today's Topics

- Introduction
- Working Group on Cancer Screening Trials Overview
- The Tomosynthesis Mammographic Imaging Screening Trial (TMIST)
  - Background and Current Status
  - Proposed Modification to TMIST by ECOG-ACRIN Study Investigators
- Working Group Recommendations and Respective Rationales
- Conclusion

Introduction

- After the onset of the COVID-19 pandemic, sharp declines in accrual to NCI NCTN and NCORP clinical trials began in April 2020
- While there has been some recovery of accrual, it has not been uniform
- Cancer screening trials have been disproportionately affected
- Decreased accrual rates in cancer screening trials will delay the completion of these trials, potentially increasing the cost
- In some cases, it may be unlikely that the trial will be able to answer the study questions as originally intended or that when complete, the findings would be relevant to contemporary practice

Tomosynthesis Mammographic Imaging Screening Trial (TMIST)

TMIST, a large, randomized breast cancer screening trial is an example of a trial affected by the COVID-19 pandemic

- Conducted by ECOG-ACRIN within NCI's NCTN and NCORP networks
- Launched in July 2017 to evaluate whether breast tomosynthesis reduces the incidence of advanced breast cancers, a surrogate for breast cancer mortality
- Scheduled to finish accrual in 2020, but accrual was only about 20% complete as of September 2020
- The pandemic significantly affected accrual, but the number of participants has been lower than expected throughout the trial

CTAC *Ad hoc* Working Group on Cancer Screening Trials

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Established in November 2020 to provide general guidance to the NCI regarding cancer screening trials and advise on:

- The real-world impact of the COVID-19 pandemic on screening trials
- Scientific questions that may be answered by existing screening trials
- Strategies and timelines for screening trial completion

Working Group Membership

Chair

Nancy E. Davidson, MD
Fred Hutchinson Cancer Research Center
and University of Washington

Members

Otis W. Brawley, MD, MACP, FASCO, FACE
Johns Hopkins University

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Ex Officio Members

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Division of Cancer Prevention, NCI

Executive Secretary

Sheila A. Prindiville, MD, MPH
Coordinating Center for
Clinical Trials, NCI

Working Group Focus

- Initial focus of the Working Group was TMIST, as charged by NCI
- Some of the issues related to accrual are more broadly applicable to other NCI cancer screening trials
- Working Group report contains two sets of recommendations: One specific to TMIST and the other applicable to NCI cancer screening trials in general

Working Group Activities & Timeline

- November 2020: Orientation meeting, charged by Dr. Sharpless
- December 2020 – February 2021: 3 virtual meetings
  - Invited presentations
    - TMIST study investigators from ECOG-ACRIN
    - Principal investigators of ongoing, related European tomosynthesis trials
    - Researchers from the Breast Cancer Surveillance Consortium (BSCS) mammography registry
  - Discussion topics included the TMIST study design, endpoints, accrual, value of biospecimens, diversity of study population, and implications for patient care
  - Developed draft working group recommendations
- February – March 2021: Finalized recommendations and drafted report

TMIST Background and Current Status

TMIST Background

- Two-dimensional digital mammography (DM) has been standard of care for breast cancer screening since 2005
- Three-dimensional tomosynthesis (TM) has been rapidly adopted in the United States since FDA approval of TM device in 2012
  - 74% of breast cancer screening clinics in the United States have at least one TM machine
  - 42% of all the mammography machines are TM units
- Results of prior studies on TM sensitivity and cancer detection rates are mixed
- TM may reduce screening recall
- Limited data on TM efficacy by race/ethnicity or subsets of breast cancer types
- Overall benefit of TM to patients is unclear

TMIST: Primary Aim

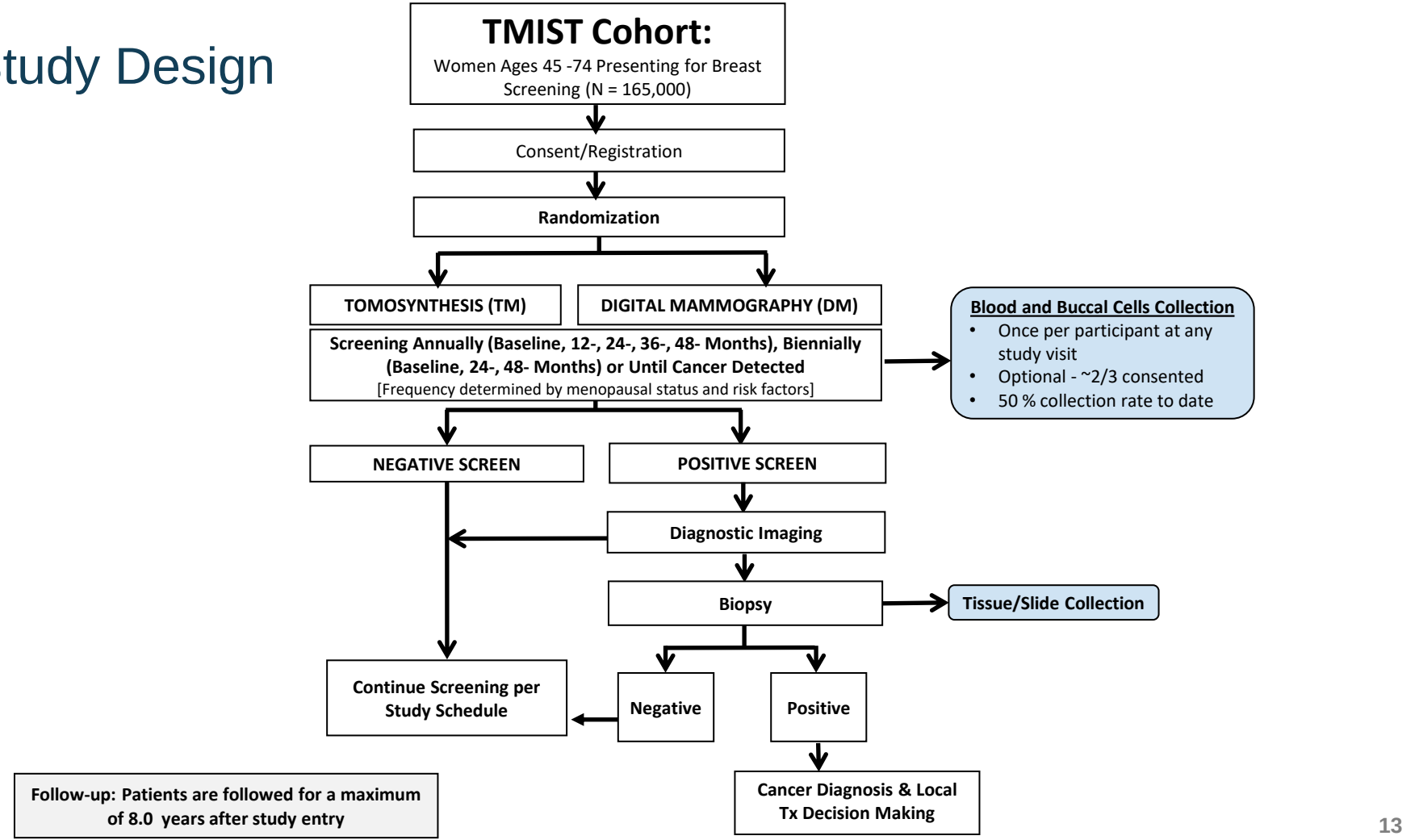
To determine whether the cumulative rate of advanced breast cancer in women undergoing screening with TM + DM is reduced compared to DM alone

Definition of Advanced Cancer

Any invasive cancer diagnosed in the 4.5 years after randomization that meets any of the following criteria:

- ✓ Distant metastases
- ✓ Positive lymph nodes
- ✓ Triple-negative or HER2+ and > 10 mm
- ✓ Tumor size > 20 mm

Study Design



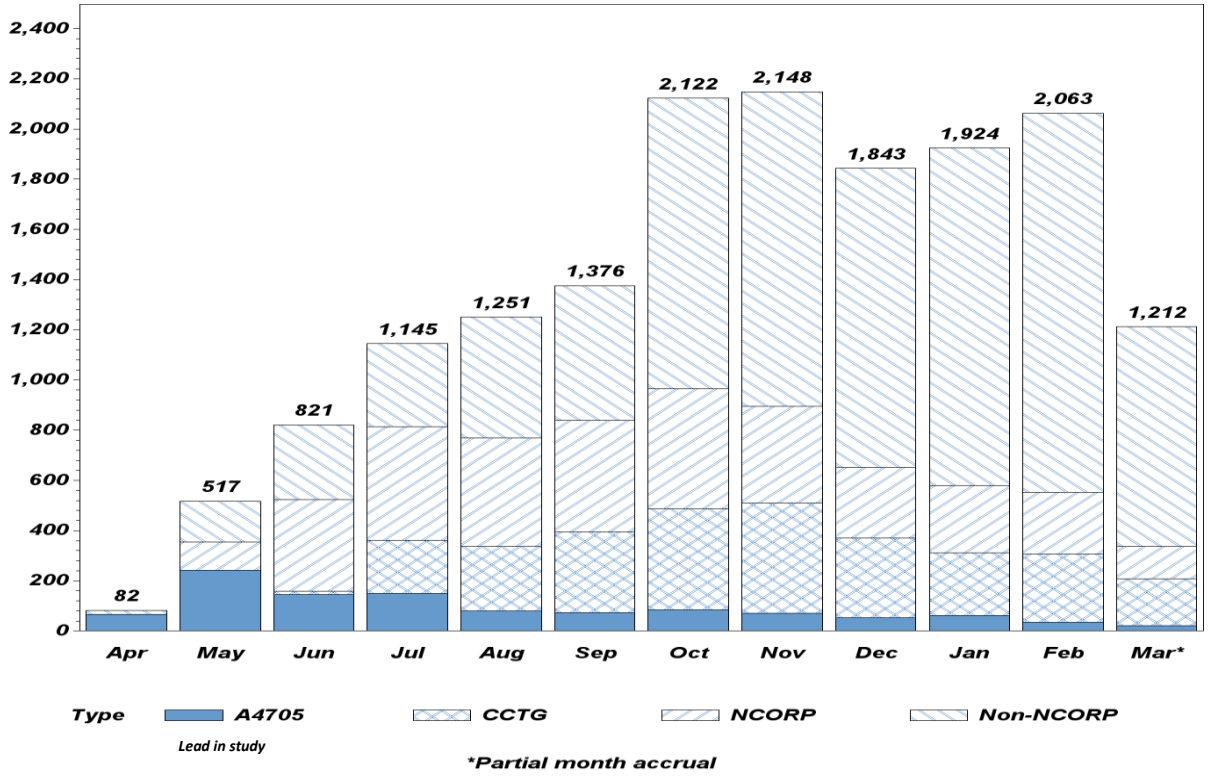
TMIST Secondary Aims

1. ***Health Care Utilization Aim***
   - To compare downstream health care utilization (including cancer care received) and cost of an episode of breast cancer screening by TM versus DM
2. ***Imaging Aims***
   - To compare the recall and biopsy rates due to abnormal screening examinations for TM versus DM
   - To compare diagnostic accuracy of TM versus DM
   - To compare interval cancer rates
3. ***Biological Aims***
   - To determine correlates of TM/DM findings, pathology and genetic analysis, and other patient characteristics with long-term patient outcomes, including interval cancer rate
   - To assess and compare the characteristics (e.g., stage, grade, cell subtype) of cancers detected from screening by TM and DM

TMIST Accrual as of 3/15/21

- Total accrual to date: 41,570 women (25% of planned)
- ~25 % accrual from minority and underrepresented groups; 19% Black
- 108 sites have enrolled at least one participant
- Rebound in accrual since April 2020

Monthly Accrual (April 2020 – March 2021)



Charts provided by ECOG-ACRIN

TMIST Proposed Modification

by ECOG-ACRIN Study Investigators

Summary of Proposed TMIST Modification as Presented by ECOG-ACRIN Investigators

- Reduce total sample size from 164,946 women to 102,544
- Primary endpoint (occurrence of advanced cancer) remains the same
- Utilize *time-to-advanced-cancer* assessment employing survival analysis methods instead of binary outcome assessment
- Effect size does not change – continue to assume 20% relative reduction in the proportion of participants with advanced cancer at 4.5 years
- Power will be decreased to 80% from the original 90%
- No change in screening schedule; participants to be followed from 4 to 9 years
- Accrual estimated to be completed in 2.5 years (2023)
- DSMC has approved; pending submission to NCI for scientific review

Recommendations

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Two overarching recommendations, each with a set of specific recommendations

I. TMIST specific recommendations

II. Recommendations applicable to NCI cancer screening trials more broadly

Overarching Recommendation I

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

Overarching Recommendation I – Rationale

- The randomized controlled trial (RCT) design of TMIST is a strength
- Identifying the best approach to performing mammography is important for patients and society
- Observational studies using population-based registries such as the Breast Cancer Surveillance Consortium will complement the TMIST data; they are less reliable in isolation because they are prone to biases
- Unique aspects of TMIST compared to European RCT's include:
  - Diverse, more representative population
  - Includes women under 50
  - Multiple screening rounds
  - Only study with a biorepository with tissue from biopsies as well as blood and buccal cells

Overarching Recommendation I – Rationale cont.

- There are many important secondary endpoints embedded in TMIST that will be of value regardless of the primary outcome of the study
- Despite these strengths, concerns remain which are addressed by the specific sub-recommendations

Specific Recommendation I-A

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

- *Ensure proportion of diversity among newly enrolled participants is, at a minimum, similar to the diversity of the current study population*
- *Establish a detailed plan for how overall and minority accrual goals will be achieved*

Rationale

- Despite the recent rebound in accrual, challenges may persist due to the increasing adoption of TM in the United States over time; thus, strict criteria for termination of the study are needed if accrual goals are not met
- The diversity of the study population is a unique attribute

Specific Recommendation I-B

Develop and implement a comprehensive communications and recruitment plan for TMIST that leverages the resources of the NCI Office of Communications and Public Liaison and augments the ECOG-ACRIN efforts to boost accrual

Rationale

- The monthly accrual goals are ambitious and will need a concerted and sustained effort to maximize the likelihood of success
- Approaches tailored to the recruitment of minority populations should be a high priority

Specific Recommendation I-C

Increase the rate of biospecimen collection, particularly from minority study participants, and incentivize sites to collect blood specimens at the time of the initial enrollment

Rationale

- The unique value of the TMIST biorepository will be diminished if biospecimen collection is limited, especially from diverse populations
- Biospecimens for studies evaluating biomarkers of risk as well as for early detection are most valuable when they are collected *prior* to the diagnosis of cancer
- The TMIST biorepository could be of great value in evaluating and validating biomarkers for early breast cancer detection

Specific Recommendation I-D

Ensure that data collection for the prespecified secondary outcomes is complete and that analytical and statistical plans are updated for these aims in the modified protocol

Rationale

- There are many important secondary endpoints centered around health care utilization, imaging, and biological studies

Specific Recommendation I-E

Consider incorporating predictive genomic information into the definition of advanced breast cancer

Rationale

- Clinical studies have shown that genomic information such as the 21-gene RT-PCR assay may predict a more aggressive subset of breast cancers
- Incorporating this information into the definition of advanced breast cancer may more accurately predict mortality
- The feasibility of modifying the definition of the primary endpoint can be assessed at the time of overall study is modified

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

Rationale

- Developing a plan for monitoring accrual, including that of diverse populations, and early termination criteria *prior* to the launch of large, resource intensive studies will help to identify and develop corrective actions plans for at-risk trials

Specific Recommendation II-A & II-B

II-A: Conduct a portfolio analysis of all ongoing and planned NCI-funded cancer screening trials

II-B: Assess overall and minority accrual rates for all ongoing screening trials

Rationale

- The Working Group's focus was on TMIST
- There is a need to determine if there are other ongoing and planned NCI-funded screening trials that could benefit from developing slow accrual guidelines and criteria for early termination, particularly large trials

Specific Recommendation II-C

Interim analyses that assess the evolving changes in screening technology and the therapeutic landscape should be built into large screening trials

- *Pre-planned interim analyses, independent of statistical interim analyses, should be conducted to assess whether the trial is still clinically relevant, taking into account therapeutic and diagnostic advances since the onset of the trial*
- *Criteria for early termination based on these considerations should be established*

Rationale

- Cancer therapeutics, imaging, and diagnostic tests evolve over time such that the scientific landscape present at the time of the design of a clinical trial may no longer be clinically relevant at the time the study is completed

Conclusion

Conclusion

- The randomized controlled trial design of TMIST as well as its unique aspects, including a clinically well-annotated biorepository and diverse study population, justify the continuation of the trial in a modified manner that allows accrual to be completed more quickly
- The Working Group's recommendations aim to:
  - Maximize the likelihood that TMIST will complete accrual in a timely fashion and that the results will be informative for patient care
  - Lay the groundwork for the design and operations of future large, NCI-supported cancer screening trials

With Appreciation…

- TMIST study participants
- Working Group members and Ex Officios
- ECOG-ACRIN Investigators and their Study Team

  Etta Pisano, Mitch Schnall, and Constantine Gatsonis
- European Tomosynthesis Trials Principal Investigators

  Solveig Hofvind (TOBE – Norway)

  Michael Michell (PROSPECTS – United Kingdom)

  Walter Heindel (TOSYMA – Germany)
- Breast Cancer Surveillance Consortium Researchers

  Karla Kerlikowske

  Diana Miglioretti

Questions?

Proposed motion:

Accept the CTAC Ad Hoc Working Group on Cancer Screening Trials Report