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CANCER SCREENING TRIALS WORKING GROUP

WORKING GROUP REPORT

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INTRODUCTION

The COVID-19 pandemic has introduced substantial challenges for several segments of the United States health care system. As the responsibilities of many cancer clinical and research staff were shifted from investigational programs to assist in COVID-19-associated medical interventions, accrual to many cancer clinical trials plummeted. Beginning in April 2020, sharp declines were experienced in clinical trial accrual to National Cancer Institute (NCI) funded clinical trials networks such as the NCI National Clinical Trials Network (NCTN) and the NCI Community Oncology Research Program (NCORP). While there has been some recovery of the accrual, it has not been uniform, and some types of trials, such as large cancer screening trials, have been disproportionately affected. Compounding the problem, poor accrual during the pandemic has been superimposed on preexisting accrual difficulties of some cancer screening trials. Decreased accrual rates in cancer screening trials will delay the completion of these trials and potentially increase the overall cost of their conduct. Additionally, in some cases, it may be unlikely that the trial will be able to answer the study questions as originally intended or that when completed, the findings would be relevant to contemporary practice.

In November 2020, the Clinical Trials and Translational Research Advisory Committee (CTAC) *ad hoc* Working Group on Cancer Screening Trials was established to advise the NCI Director and CTAC on the real-world impact of the COVID-19 pandemic on NCI-supported screening trials. Tasks included assessing the scientific questions that may be answered by existing screening trials and advising on strategies and timelines for their completion.

The Working Group, chaired by Dr. Nancy Davidson, Senior Vice President and Director, Clinical Research Division, Fred Hutchinson Cancer Research Center, and its membership represent a broad range of stakeholders in the cancer screening enterprise, including select members of current NCI advisory boards as well as other individuals with expertise in oncology, cancer screening, imaging, epidemiology, statistics, and advocacy. See Appendix 1 for the membership of the Working Group.

The Working Group recommendations presented in this report were developed through a sequential process, beginning with a virtual orientation meeting on November 18, 2020. The NCI Director, Dr. Norman "Ned" Sharpless, reviewed the charge to the Working Group and noted that the initial focus of the Working Group should be the Tomosynthesis Mammographic Imaging Screening Trial (TMIST) funded by the NCI NCORP program. TMIST is a large, randomized screening trial, launched in July 2017 to evaluate whether breast tomosynthesis reduces the incidence of advanced breast cancers, a surrogate for breast cancer mortality.[1] TMIST was scheduled to complete enrollment in 2020, but accrual was only 20 percent complete as of September 2020. While the pandemic significantly affected accrual, the number of participants enrolled has been consistently lower than expected throughout the trial.

Subsequently, three virtual Working Group meetings were held between December 2020 and February 2021 to gather information and develop recommendations through consensus building. The Working Group invited presentations from the Eastern Cooperative Oncology Group (ECOG)-American College of

Radiology Imaging Network (ACRIN) TMIST study team, the principal investigators of ongoing related European tomosynthesis trials, and researchers from the Breast Cancer Surveillance Consortium. Background information provided to the Working Group members included a literature review of relevant publications and the TMIST protocol (version date August 11, 2020). Discussion topics included the TMIST study design, endpoints, accrual, biospecimens, and implications of the study for patient care. During their deliberations, members considered the original TMIST trial design as well as modifications proposed by the TMIST study team.

This report summarizes the background information reviewed by the Working Group and their recommendations. Although the deliberations focused on TMIST, some of the issues related to accrual are more broadly applicable to other NCI cancer screening trials. Thus, there are two sets of recommendations, one specific to TMIST and the other applicable to NCI cancer screening trials in general.

BACKGROUND

Two-dimensional digital mammography (DM) has been the standard of care for breast cancer screening since 2005.[2] The FDA approved the first three-dimensional breast tomosynthesis (TM) device for breast cancer screening in 2012. TM has been rapidly adopted by breast cancer screening facilities in the United States and Canada, with the majority of facilities that have adopted TM typically offering both TM and DM for screening.[3] As of December 2020, approximately 74 percent (6,407 out of 8,670) of breast cancer screening clinics in the United States have at least one TM system, and 42 percent (9,429 out of 22,386) of the mammography machines are TM units.[4]

There is evidence that screening utilizing TM may reduce recall rates and improve cancer detection, but the results are mixed among the American and European studies evaluating TM versus DM, and there are no or limited data available on efficacy by race/ethnicity or subsets of breast cancer types. Questions still remain regarding the overall benefit to patients. TM may carry higher out of pocket costs for women and is more labor intensive and costly for health care systems in that it requires about twice as much reader time for interpretation.[5] As currently performed, DM plus TM requires twice as much radiation exposure as DM alone; although newer systems providing synthetic two-dimensional digital mammography with TM deliver about the same radiation dose as DM alone.

The information reviewed by the Working Group is summarized in this section and includes the current status of TMIST and the proposed modification to the trial. Updates on related European randomized controlled trials and results of observational research conducted by the Breast Cancer Surveillance Consortium were also considered.

1) TOMOSYNTHESIS MAMMOGRAPHIC IMAGING SCREENING TRIAL (TMIST)

Current Status

TMIST is a randomized controlled breast cancer screening trial that was designed to address whether three-dimensional tomosynthesis (TM) should replace two-dimensional digital mammography (DM) for breast cancer screening.[1] The trial is led by the Eastern Cooperative Oncology Group (ECOG)-American College of Radiology Imaging Network (ACRIN) and is conducted within NCI's National Clinical Trials Network (NCTN) and NCI's Community Oncology Research Program (NCORP). The trial was activated in July 2017 with the first enrollment in September 2017. A lead-in trial to TMIST was conducted in Canada, supported by the Canadian Breast Cancer Foundation, and enrolled 3,078 women who reconsented to transition into TMIST if eligible by age.[6]

The main hypothesis of TMIST is that TM will decrease the cumulative incidence of advanced breast cancers, a surrogate for mortality, compared to standard DM. The primary endpoint is a comparison of the proportions of participants in the TM and DM study arms diagnosed with an advanced breast cancer at any time during a period of 4.5 years from randomization. Advanced breast cancer is defined in TMIST as an invasive cancer meeting any of the following criteria: (1) distant metastases; (2) at least one lymph node macrometastasis; (3) tumor size larger than 1 cm, and triple-negative or human epidermal growth factor receptor (HER2) positive; or (4) tumor size of 20 mm or larger unless of pure mucinous or other favorable histologies. The total study sample size of 164,946 participants (84,273 per arm) was estimated to be sufficient to provide 90 percent power to detect a 20 percent relative reduction in the proportion of advanced cancers in the intervention arm compared to the control arm.

Women eligible for the trial include those aged 45 to 74 without a history of breast cancer, presenting for breast screening within accredited screening facilities, who have not had a mammogram within the last 11 months prior to enrollment. Study participants are randomized to TM or DM, screened annually or biennially based on menopausal status and breast cancer risk factors, and followed for the duration of the study, estimated to be at least 4.5 to 8 years after study entry.

TMIST focuses on patient outcomes rather than the diagnostic performance of DM versus TM and is expected to provide the best estimate of the effect of TM on breast cancer mortality. Secondary analyses of the effect of age, menopausal and hormonal status, breast density, and family cancer history on the primary endpoint are planned. Numerous other secondary endpoints focus on three areas: health care utilization, imaging, and biological surrogates.

ECOG-ACRIN has a long history of successfully conducting cancer screening clinical trials, including the ACRIN 6652 Digital Mammographic Imaging Screening Trial (DMIST). These trials require the engagement of a full network of stakeholders, such as cancer centers, primary care providers, radiologists, and other relevant specialties. The recent merger of ECOG with ACRIN and expansion of the infrastructure to the NCTN and NCORP for TMIST have enabled active outreach to these stakeholders and the addition of multiple new 'screening only' clinics in the NCTN. While the time

necessary to establish this infrastructure may have contributed to the lag in accrual early in the trial, there are now more than 115 sites open to accrual, of which 104 have enrolled at least one participant.

As of February 2021, more than 38,000 participants have been enrolled. The TMIST monthly enrollment was significantly affected by the COVID-19 pandemic, with the greatest decrease in April 2020 coinciding with the recommendation of temporary suspension of U.S.-based cancer screening mammography by the Centers for Disease Control and Prevention (CDC). The accrual rates have since improved with approximately 2,000 patients accrued monthly since October 2020. The number of active sites has doubled since the study began in September 2017, and an additional 26 U.S. sites are currently working to open TMIST.

Twenty-five percent of enrolled participants are women from racial and ethnic minority groups, and 19 percent are Black/African American women. Efforts continue to focus on improving enrollments for Hispanic women, with sites planned to open in California, Florida, New Jersey, and Texas.

TMIST has established a biorepository to comprehensively collect clinically well-annotated tumor tissue and benign lesions from this large cohort of women undergoing screening in the modern era. Given the rates of participation of Black/African American women in TMIST, it is expected that the biorepository will have the largest sample collection ever accumulated in this subset of women. Optional blood plasma and buccal specimens are also being collected, with approximately two-thirds of study participants consenting to collection of these specimens. Plasma and buccal cells are to be collected at the time of any of the study imaging visits, but collection at the enrollment visit is encouraged. There is an approximate 50 percent rate of specimen collection to date.

TMIST Proposed Study Modification

In response to input from the TMIST Data Safety Monitoring Committee and in preparation for this CTAC Working Group, TMIST investigators presented a proposed modification to the study that would reduce the total sample size from 164,946 participants to 102,544 (51,272 per arm). The primary endpoint (occurrence of advanced cancer) would remain the same in the proposed modification; the change is a revised approach for assessing the primary endpoint. In the original design, the primary endpoint was assessed as a binary outcome (i.e., the occurrence of an advanced cancer within 4.5 years from randomization). In the modified design, the primary endpoint will be assessed using *time-to-advanced cancer* methods employing survival analysis methods. With this revised analytic approach, an advanced cancer is counted if it occurs at any time while the participant is on study. The sample size computations for comparison of arms will continue to assume a 20 percent relative reduction in the proportion of participants with advanced cancer at 4.5 years from randomization. The desired statistical power will be decreased to 80 percent from the original 90 percent. Participants will be followed from 4 to 9 years, and the accrual will be extended from 3 to 5.5 years, with no change in the screening schedule of participants. With this modification, and assuming that all screening sites remain open, the total target sample size of 102,544 can be achieved with accrual of 26,000 women per year in each of the next 2.5 years, with completion of trial accrual in 2023 and follow-up for the primary outcome in 2027. The trial will be monitored for efficacy and futility.

2) RELATED EUROPEAN RANDOMIZED CONTROLLED TOMOSYNTHESIS SCREENING TRIALS

There are several related ongoing European randomized controlled trials evaluating tomosynthesis (summarized in Appendix 2).[7-15] The Working Group heard presentations or received written updates on three of these trials, as summarized below.

The Digital Breast Tomosynthesis Trials in Bergen (TOBE-1 and TOBE-2)

The Digital Breast Tomosynthesis Trial in Bergen (TOBE-1) is a large-scale, parallel group, randomized, controlled trial.[7,8] TOBE-1 was performed in an everyday screening setting in Bergen, Norway, in conjunction with BreastScreen Norway, a program that provides biennial two-view mammography screening to women ages 50 to 69. The primary aim of TOBE-1 was to determine whether the proportion of screen-detected breast cancer was favorable for TM plus synthetic two-dimensional (2D) images compared with standard DM. The study enrolled more than 29,000 participants from January 2016 to December 2017, randomized equally to one round of TM or DM. No differences in cancer detection rate between TM plus synthetic 2D and DM was seen with two years of follow-up. The recall rate was lower in the TM group.

A follow-up study, TOBE-2 was conducted in the subsequent screening round from January 2018 to January 2020.[9] The study design is similar to the TOBE-1 study, with the exception that the entire cohort of 31,082 women enrolled were screened with TM plus synthetic 2D and with different equipment. Of the 31,082 women enrolled, 28,810 participated in both TOBE-1 and TOBE-2 and 8,272 in TOBE-2 only. There is little racial or ethnic diversity of the study population. The two objectives were to investigate rates and histopathologic tumor characteristics of: (1) interval cancer among women screened in TOBE-1 and (2) subsequent round screen-detected cancer for women screened. The study was completed in January 2020 with results expected to be reported soon.

Prospective Trial of Digital Breast Tomosynthesis (DBT) in Breast Cancer Screening (PROSPECTS)

The PROSPECTS trial will compare TM plus DM versus DM every 3 years in 100,000 women aged 50 to 69 participating in the National Health Service (NHS) Breast Screening Programme in the United Kingdom.[10] The trial's primary objectives are to (1) measure the effectiveness of breast cancer screening using the two approaches and (2) perform a health economic analysis. Secondary objectives are to assess specificity, subgroup analysis, and reader performance (e.g., eye-tracking study, artificial intelligence).

Eight trial sites have been established in the United Kingdom; site locations were selected to maximize the demographic diversity of study participants. Randomization of the clinics, rather than the participants, has been planned. The goal is for all sites to begin recruiting by January 2021 with an estimated completion of Round 1 screening by June 2022 so that a preliminary report would be available by March 2023.

The trial design includes two rounds of screening, although the investigators are currently assessing whether the second round should be canceled because of COVID-19-related delays. The logistical capabilities for trial implementation during the COVID-19 pandemic are currently under discussion.

Digital Breast Tomosynthesis Plus Synthesised Images Versus Standard Full-Field Digital Mammography in Population-Based Screening (TOSYMA)

The TOSYMA study has been ongoing since June 2018 and has a target enrollment of 80,000 women aged 50 to 69 already participating in a routine mammography screening program in Germany.[11,12] The trial is a randomized controlled trial comparing TM plus synthesized 2D mammograms with standard DM. The primary endpoints are the detection of invasive screened breast cancers and interval cancers in the 2-year follow-up period. The initial analysis for screen detected cancers is scheduled for fall 2021 and the data on interval cancers expected in 2023.

3) BREAST CANCER SURVEILLANCE CONSORTIUM (BCSC) RELATED RESEARCH

The BCSC is an NCI-funded collaborative network of breast imaging registries across the United States conducting research to assess and improve the delivery of breast cancer screening and related patient outcomes. As the nation's largest longitudinal collection of mammography data from breast cancer screening in community practice, it serves as a national resource for population-based comparative effectiveness research.[16]

The observational data collected by the BCSC are extensive and cover many variables. Data sources for the BCSC include self-reports from women, radiology data, information on radiology facilities and practices, pathology information, cancer registry information, and information from state death tapes. Breast imaging data collected by the BCSC from 2005 to 2019 included information from 1.8 million women, 7.9 million mammograms, and 84,000 incident invasive breast cancers. These data are geospatial and linked to Medicare claims data. Data are collected from 203 facilities, of which only 5 percent are academic facilities; the remainder are community based. The race and ethnicity data associated with the mammograms recorded from 1996 to 2016 indicate that 73.2 percent of the mammograms were from White women; 10.8 percent Black; 9.2 percent Asian or Pacific Islander; 0.3 percent American Indian or Alaska Native; 1.6 percent Other or Mixed; and 4.8 percent Hispanic.

Recent studies include an analysis of the differences in recall and cancer detection rates (CDRs) for women who used TM versus DM by screening round, age, and breast density.[17] The investigators observed lower recall rates and greater CDRs for TM compared to DM, with the lowest recall rates and the greatest increase in CDRs seen in the baseline exam compared to subsequent exams. A modest recall reduction in women with scattered fibroglandular density was found with TM as well as an increase in CDRs in women with heterogeneously dense breasts on subsequent examinations. CDRs and recall rates were unchanged for women with extremely dense breasts. Work in progress includes a study assessing differences in cancer detection rates for early-stage and advanced cancer for women undergoing TM relative to DM.

In another recent study, BCSC investigators evaluated various definitions of advanced cancer and staging systems to determine which system and definitions most accurately predicted breast cancer mortality in a screening population.[18] Findings showed that the American Joint Committee on Cancer (AJCC) prognostic pathologic staging system (8th edition)[19] more accurately predicted 5-year breast cancer mortality than the AJCC anatomic staging system. The investigators also assessed the performance of the TMIST definition of advanced cancer and found it was more likely to categorize women as having advanced cancer than the AJCC anatomic or pathologic definitions of advanced cancer and was not as accurate as the AJCC prognostic pathologic staging for predicting breast cancer mortality. The investigators concluded that defining advanced cancer using the AJCC prognostic pathologic stage IIA or higher most accurately predicts breast cancer mortality.

RECOMMENDATIONS

The Working Group recommendations presented in this report were developed through consensus building. The first overarching recommendation focuses on the Tomosynthesis Mammographic Imaging Screening Trial (TMIST), and the second one is more broadly applicable to all NCI cancer screening trials. In developing the recommendations related to TMIST, the Working Group addressed whether TMIST could answer the questions it was designed to answer given the untoward effect of the pandemic on accrual and the lower than expected accrual rate throughout the trial. Additionally, strategies and the timeline for completion of the study were discussed, as well as whether TMIST should continue as is, be modified, or discontinued.

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

In reaching this overarching recommendation, the Working Group weighed the strengths and weaknesses of the TMIST study in the context of current clinical practice patterns in the United States, ongoing European tomosynthesis trials, and research questions that could be answered by observational studies utilizing registries such as the Breast Cancer Surveillance Consortium (BCSC). Specific areas discussed in relation to TMIST include the primary and secondary endpoints, feasibility and likelihood of achieving accrual in a timely fashion, value of biospecimens, diversity of the participants, and implications for patient care.

Additionally, the Working Group considered the proposed Eastern Cooperative Oncology Group (ECOG)-American College of Radiology Imaging Network (ACRIN) modification to TMIST which includes reducing the sample size needed by utilizing time-to-advanced cancer analysis methods to assess the primary endpoint and decreasing the statistical power to 80 percent. With an annual accrual of approximately 26,000 participants, the study team estimates that they could achieve the revised

accrual target of 102,544 in 2.5 years, thus completing accrual in 2023 and follow-up for primary outcome in 2027.

The randomized controlled trial design of TMIST is a strength if the trial can be completed in a timely and cost-efficient manner. Identifying the best approach to performing mammography in the United States is important for patients and society. Optimizing the identification of cancers most likely to be potentially lethal while minimizing harm from unnecessary procedures and costs is a meaningful goal. Observational studies using population-based data from registries such as the BCSC will complement the TMIST data; they are less reliable in isolation because they can be prone to biases and are limited in the geographic areas covered.

TMIST has several unique aspects when compared to the related European randomized controlled trials. It is the only study to include women under 50 and has a much more diverse population of women, representative of the United States. The study design of TMIST differs from the other studies in that it includes multiple rounds of screening rather than just one round. Thus, if there is a benefit to three-dimensional tomosynthesis (TM) over two-dimensional digital mammography (DM), TMIST will be able to determine if it persists beyond the first screen. Additionally, TMIST is the only study with a biorepository of paraffin blocks from cancers and biopsies, including benign and preneoplastic lesions, along with blood plasma and buccal cells for DNA. This clinically well-annotated biorepository provides the potential to gain a more detailed understanding of breast cancer subtypes, understand the progression of benign disease to invasive cancer, and identify genetic and circulating markers of risk.

Despite these strengths, the Working Group remains concerned about the relevancy of the findings and clinical impact given the high uptake of TM over time in the United States. In weighing these concerns, the Working Group noted there is substantial disparity in availability, insurance payment, and out-of-pocket patient costs for TM.[20] If TMIST finds that TM reduces advanced cancers in the screening population compared to DM, then TM should become the standard of care for breast cancer screening, thus reducing these disparities. Additionally, there are many important secondary endpoints embedded in the TMIST study that will be of value regardless of the primary outcome of the study.

Other concerns identified by the Working Group are discussed further in context of the specific recommendations that follow.

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

The TMIST monthly enrollment was significantly affected by the COVID-19 pandemic, with the greatest decrease in April 2020 coinciding with the temporary suspension of U.S.-based cancer screening mammography by the Centers for Disease Control and Prevention (CDC). It is encouraging that accrual rates have since rebounded, with approximately 2,000 patients accrued per month since October 2020,

for a total accrual of more than 38,000 women as of February 2021. Notably, 25 percent of enrolled participants are women from racial and ethnic minority groups, and 19 percent are Black/African American women.

Working Group members emphasized that one of the strengths of the current study is the diversity of the study population. It is strongly recommended that specific accrual goals for underrepresented populations be developed to ensure that the proportion of diverse participants among new enrollees is similar to the diversity of the current study population, at a minimum. A detailed plan for how the overall and minority accrual goals will be achieved should be included in the proposed study modification.

Despite the recent rebound in accrual, challenges may persist due to the increasing adoption of TM in the United States over time. Because of this, the Working Group recommends that strict criteria for termination of the study be prospectively defined in the event that accrual goals are not met.

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

The monthly accrual goals for the modified TMIST study are ambitious and will need a concerted and sustained effort to maximize the likelihood of success. In addition to ECOG-ACRIN's outreach and recruitment efforts, the Division of Cancer Prevention should partner with the NCI Office of Communications and Public Liaison (OCPL) to develop and implement a comprehensive recruitment plan that leverages OCPL's outreach and communications expertise and resources. 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

Approximately two-thirds of the current TMIST participants have consented to the optional blood and buccal specimen collection. Of those, only 50 percent of specimens have been collected to date. The unique value of the TMIST biorepository will be diminished if the biospecimen collection is limited, particularly in diverse populations. Of note, the rate of blood collection from African Americans/Black women is lower than for White women. A plan with goals for increasing the rate of biospecimen collection, particularly from minority participants, should be developed and implemented.

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. Concerted efforts are ongoing to identify novel biomarkers for early breast cancer detection. The TMIST biospecimen repository could ultimately be of great potential value in evaluating and validating such biomarkers. Thus, sites should be strongly encouraged to collect the blood specimens at the time of initial enrollment rather than at any point in time during the study.

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

There are many important secondary endpoints embedded in TMIST that will be of value regardless of the primary outcome of the study. These secondary endpoints focus on three areas: health care utilization, imaging, and biological surrogates. The analyses of the molecular characteristics of breast cancer subtypes and benign lesions have the potential to provide new insights into the biology of radiographically detected cancers. Updated analytical and statistical plans should be developed to ensure these aims can still be achieved with the proposed study modification.

TM is already installed in nearly 75 percent of mammography facilities in the United States; 40 to 45 percent of screening mammograms currently use TM. Both these percentages continue to increase as radiologists replace old DM equipment with TM equipment. The investment in equipment and the increased information available from TM images make it likely that radiologists will continue to use TM even in the setting of a negative TMIST primary outcome. The TMIST secondary analyses of the primary outcome will still be clinically relevant in this setting in that they will better inform health care providers on how and for whom TM should be used. Expanding the scope of some of these secondary analyses may maximize the likelihood that the trial results will inform patient care and advance research. Suggestions for additional secondary analyses were proposed by some Working Group members (see Appendix 3).

Specific Recommendation I-E

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

Given that the TMIST study will be modified and the definition of 'advanced breast cancer' is an evolving concept, the Working Group encourages the TMIST investigators to consider incorporating predictive genomic information into the definition of advanced cancer. Consultation with the Data Safety Monitoring Committee and biostatisticians is recommended to assess whether the scientific integrity of the study can be maintained if the primary endpoint is modified at this point in the trial.

Clinical studies have shown that genomic information such as the 21-gene RT-PCR assay (Oncotype DX) predicts a more aggressive subset of ER-positive, HER-2 negative tumors.[21] Incorporating genomic information into the definition of advanced cancer may increase the numbers of advanced cancers identified in TMIST. The 2016 (8th edition) American Joint Committee on Cancer (AJCC) prognostic pathologic breast cancer staging system includes anatomic staging elements plus tumor grade, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and genomic information, when available. A recent analysis using registry data from the Breast Cancer Surveillance Consortium, designed to assess the accuracy of various definitions of advanced breast cancer, found that the 8th edition AJCC prognostic pathologic stage IIA or higher predicted breast cancer mortality more accurately than the advanced cancer definition used by TMIST or the AJCC anatomic stage alone.[18]

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

Guidelines for slow accruing NCI National Clinical Trials Network (NCTN) late phase and NCI Experimental Therapeutics Clinical Trials Network (ETCTN) early phase treatment trials are well established and have been instrumental in identifying trials at risk for early termination due to failure to accrue.[22,23] Similar guidelines have been developed for NCI Community Oncology Research Program (NCORP) Research Base trials, although greater individualization is needed for each trial, given the variability among the types of cancer control trials (symptom science, prevention, screening, etc.).[24] No standard guidelines exist for the very large NCORP screening and prevention trials. Developing a plan for monitoring accrual, including that of diverse populations, and early termination criteria *prior* to the launch of cancer screening studies, particularly very large and resource-intensive studies, is strongly recommended to identify and develop corrective action plans for at-risk trials.

Specific Recommendation II-A

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

There is a need to identify all ongoing and planned NCI-funded screening trials that could benefit from developing accrual guidelines and criteria for early termination, particularly large trials. Additionally, inconsistent application of ClinicalTrials.gov primary purpose classification terms for cancer control studies hampers the identification of screening trials. Cancer screening trials that are assessing the efficacy of an intervention often cannot be easily distinguished from trials assessing screening uptake. NCI should work with its investigators to standardize the application of existing nomenclature for classification of cancer screening efficacy trials to make them easier to identify. Conducting a portfolio analysis would identify the trials needing review as well as characterize the inconsistencies in the application of coding terms.

Specific Recommendation II-B

Assess overall and minority accrual rates for all ongoing screening trials

The focus of the deliberations of the Working Group was on the accrual to the TMIST study, yet there may be other screening trials that have underlying accrual issues and/or were impacted by the COVID-19 pandemic. Identifying these trials and putting accrual corrective action plans in place will facilitate the timely completion of these 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

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. This is especially pertinent to large screening trials which often take many years to complete. 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. Communicating upfront to study investigators and participants the value of periodically assessing the continued relevancy of the trial will set clear expectations for all.

CONCLUSION

Determination of the best approach to performing breast cancer screening in the United States is important for patients and society. The randomized controlled trial design of the Tomosynthesis Mammographic Imaging Screening Trial (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. Additionally, there are many important secondary endpoints embedded in TMIST that will be of value regardless of the primary outcome of the trial.

The recent rebound in accrual to TMIST is encouraging, although challenges may persist due to the increasing adoption of tomosynthesis in the United States over time. Thus, it is critically important that strict criteria for termination of the study be defined and adhered to in the modified study.

This report outlines a series of recommendations that aim to maximize the likelihood that TMIST will complete accrual in a timely fashion and that the results will be informative for patient care. Although not exhaustive, this series of recommendations also lays the groundwork for the design and operations of future large NCI-supported cancer screening trials, including the incorporation of guidelines for addressing slow accrual, early termination criteria, and interim relevancy analyses.

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APPENDIX 1: WORKING GROUP ROSTER

October 2020
NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
Clinical Trials and Translational Research Advisory Committee

***Ad hoc* Working Group on Cancer Screening Trials**

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APPENDIX 2: RANDOMIZED CONTROLLED TOMOSYNTHESIS TRIALS*

	***TOSYMA*[1] (DEU)**	***PROSPECT* (UK)**	***To-Be*[2] (NOR)**	***RETomo*[3,4] (ITA)**	***TMIST* (International – USA, CAN, ARG, KOR)**
NCT ID	NCT03377036	NCT03733106	NCT02835625	NCT02698202	NCT03233191
Intervention	1. DM 2. TM+Synthetic 2D One screening round with 2 years of registry follow-up	1. DM 2. TM+DM Two screening rounds 3-year screening interval, with one-year follow-up	1. DM 2. TM+Synthetic 2D One screening round with 2 years of follow-up GE TM only	1. DM 2. TM+DM Two screening rounds: 1st with randomization assignment and 2nd with SOC DM 2-year screening interval with one year of follow-up GE TM only	1. DM 2. Tomo as clinically performed • TM+DM, TM+synthetic 2D, etc.
Primary Endpoint	Compare detection rate of invasive breast cancer based on pathologic tumor size	Compare cost effectiveness of breast cancer screening using TM versus DM	Compare rates of screening detected breast cancer in TM versus DM **Result: No difference in cancer detection rate TM-0.66% (0.53-0.79) Dm-0.61% (0.48-0.73)**	Compare rates of interval cancer and cumulative incidence of cancer after 2 screening rounds **Prelim Results presented at RSNA 2020: more interval cancers found with TM+DM compared to DM(NS); More cumulative cancers detected with TM+DM compared to DM over 3 years (NS).**	Compare the cumulative proportions of participants experience advanced breast cancer in TM versus DM
Sample Size	80,000	100,000	28,749 (actual)	16,717 (actual)	164,949
Age Range	50-69	50-70	50-69	50-69	45-74
Eligibility Criteria	Participating in national screening program	Participating in routine breast screening using x-ray mammography	Participating in national screening program	Invited to breast cancer screening program with no prior history of breast cancer, no prior DBT performed, no breast implants	No prior personal history of breast cancer including DCIS No breast implants
Length of Trial	3 years Expected end 2023	7 years Expected end 2024	3 years Actual end 2019	5 years Actual end 2019	8 years Expected end 2025

*Adapted from table provided by TMIST study team

[1] Weigel S, Gerss J, Hense H-W, et al. Digital breast tomosynthesis plus synthesised images versus standard full-field digital mammography in population-based screening (TOSYMA): protocol of a randomised controlled trial. *BMJ Open* 2018;8(5):e020475.

[2] Hofvind S, Holen ÅS, Aase HS, et al. Two-view digital breast tomosynthesis versus digital mammography in a population-based breast cancer screening programme (To-Be): a randomised, controlled trial [Internet]. *The Lancet Oncology* 2019;20(6):795–805.

[3] Pattacini P, Nitrosi A, Rossi PG, et al. Digital Mammography versus Digital Mammography Plus Tomosynthesis for Breast Cancer Screening: The Reggio Emilia Tomosynthesis Randomized Trial [Internet]. *Radiology* 2018;288(2):375–85.

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APPENDIX 3: ADDITIONAL SECONDARY ANALYSES

This appendix describes suggestions for additional secondary analyses proposed by some Working Group members.

1. Perform an Analysis of the Primary and Secondary Outcomes Excluding Baseline Examinations

The only way that any imaging examination can reduce the frequency of "advanced cancers" in a screening study is by enabling detection of these cancers so that these lesions are removed from the population, which then is observed and re-screened subsequently during the rest of the study. Therefore, a baseline imaging examination must occur prior to any positive outcome. At randomization, almost all TMIST study subjects have had previous DM exams, but only about 28% of study subjects have had previous TM exams. In TMIST data analysis, including the "advanced cancers" detected at baseline DM versus the "advanced cancers" detected at baseline TM examinations likely will affect outcomes differently because of the above difference in frequency of baseline examination for DM and TM, but the extent to which this occurs is unknown. Specifically, because the "advanced cancers" detected at baseline examination are not relevant to primary or secondary outcomes, this analytic approach would dilute any positive outcomes. By analyzing all TMIST data (primary and secondary outcomes) by comparing inclusion of all TMIST examinations (current approach) versus inclusion of all TMIST examinations *except* for baseline TMIST examinations (suggested additional approach), one can determine the magnitude of disparate outcomes expected from the known different frequencies of baseline examination for DM and TM, something that currently is unknown, and something that is better determined in a RCT (such as TMIST) than in observational studies. Specifically, consider an additional analysis which excludes [a] baseline DM exams in the cohort not invited to receive TM, [b] baseline DM+TM exams in the cohort invited to receive TM, and [c] baseline TM exams in the cohort invited to receive TM. In addition, as a supplementary validation of effective randomization, there should be no meaningful difference in outcomes between [a] and [b], but there should be a difference in outcomes between [a] and [c]. This additional analysis is expected to inform on whether inclusion/exclusion of baseline examinations is the preferred methodology not only for TMIST, but also in the design of future screening RCTs using "advanced cancers" as the primary outcome.

2. Conduct Sensitivity Analyses of TM versus DM Using Expanded Definitions of Advanced Cancer

Although the TMIST definition of "advanced cancer" was determined after extensive consultation with experts, the TMIST definition is not the only reasonable definition by which data may be analyzed. Indeed, the BCSC study on TM versus DM presented to the CTAC Working Group models outcomes using several definitions of "advanced cancer". TMIST should consider conducting and reporting sensitivity analyses that compare the TMIST definition of "advanced cancer" with expanded definitions that include more cancers as "advanced", specifically by including invasive cancers smaller in size (consider both a 15 mm and a 10 mm limit), by including some aggressive types of > 2 cm DCIS (high nuclear grade, presence of comedonecrosis), etc. Although "advanced cancer" is an accepted surrogate for breast cancer mortality, there are numerous cancers detected at screening that ultimately prove fatal yet are not included in the current TMIST definition of "advanced cancer"; many of these fatal cancers would be

counted as “advanced cancer” using the expanded definitions described above. Also, “advanced cancer” as a clinically meaningful endpoint should include lesions that substantially affect the well-being of breast cancer survivors, which includes not only reduction in breast cancer death but also extending disease-free survival and total survival from breast cancer, as well as reducing the frequency, extent, and intensiveness of cancer treatment, all of which also are pertinent to the expanded definitions described above. By adding the suggested (and perhaps other) definitions of “advanced cancer” to secondary analyses, important new data from the large, randomized TMIST trial (given its diverse patient population) will inform on outcomes that to date have been assessed only by observational studies. Adding these definitions of “advanced cancer” to secondary analyses also will increase the number of advanced cancers for data so analyzed, thereby increasing statistical power, so that otherwise non-significant positive trends may become statistically significant outcomes. If even a subset of expanded definitions of “advanced cancer” in this augmented analytical approach results in clinically relevant and statistically significant positive outcomes, that subset could better inform health care providers on how and for whom TM should be used; also, that subset could be incorporated into the definition of “advanced cancers” in future screening trials.