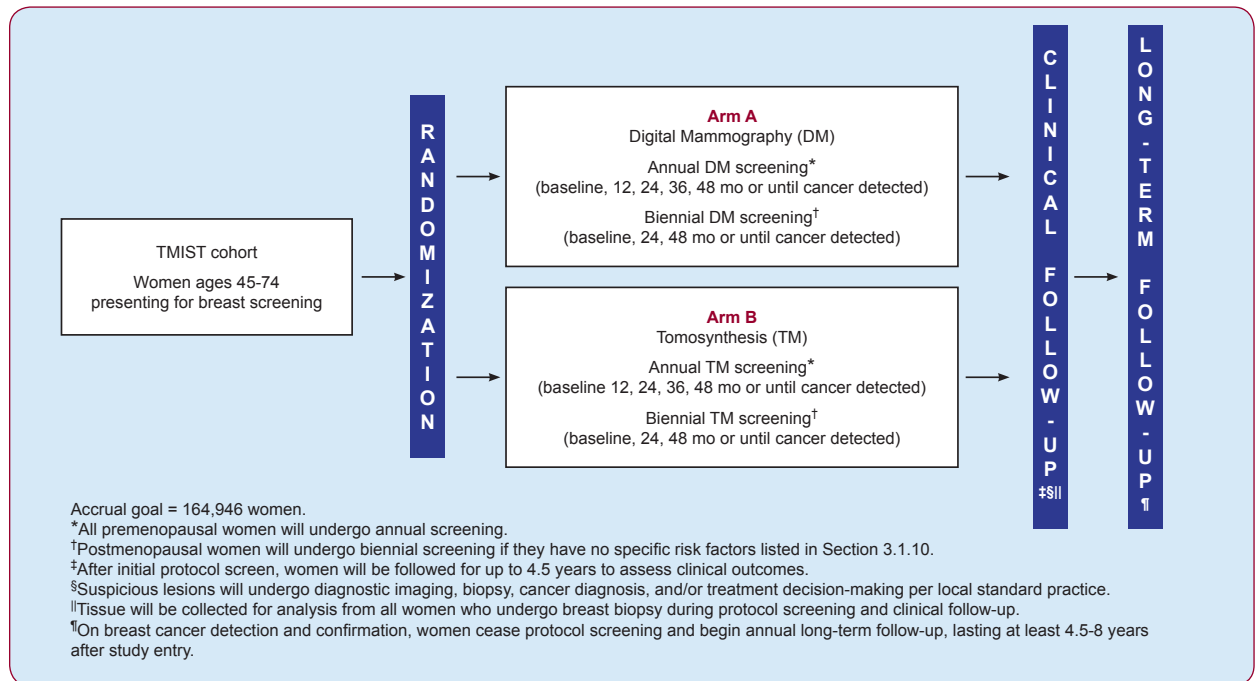


Tomosynthesis Mammographic Imaging Screening Trial

Overall Study Goal

To evaluate whether screening healthy women with breast tomosynthesis (TM) can produce a stage shift through earlier detection of the most aggressive tumors compared with digital mammography (DM)

Study Schema



Objectives

Primary Objectives

- Compare proportions of participants in the TM and DM study arms experiencing an “advanced” breast cancer at any time during 4.5 years from randomization, including during active screening and clinical follow-up after last screen (T4)
 - Advanced cancers meet any of the following criteria at time of diagnosis: distant metastases; positive lymph nodes (note that lymph nodes with micrometastases [none greater than 2 mm] and/or isolated tumor cells are not considered lymph node positive for definition of advanced cancer); invasive cancer ≥ 20 mm in size; or invasive cancer > 10 and < 20 mm in size and either estrogen receptor negative (ER-), progesterone receptor negative (PR-), or human epidermal growth factor receptor negative (HER2-) or HER2+
 - All cancers that meet these criteria and present within 4.5 years of randomization will be counted in the primary end point



Objectives (cont)

Secondary Objectives

- Assess potential effect of age, menopausal and hormonal status, breast density, and family cancer history on the primary end point difference between TM and DM
- Imaging—assess:
 - Diagnostic performance of TM and DM, measured by the area under the receiver operating characteristic curve (AUC), sensitivity, specificity, and positive and negative predictive value, including all invasive cancers and DCIS
 - Recall and biopsy rates for TM versus DM
 - Rate of interval cancers for TM and DM and their mechanism of diagnosis
 - Correlation of BIRADS imaging features with histologic and genetic features
- Long-term outcome—compare:
 - Breast cancer-specific mortality for TM and DM
- Breast biology and pathology assessment
 - Prevalence of breast cancer subtypes (luminal A, luminal B, HER2+, basal-like); low, medium, or high proliferation; and p53 mutant-like or wild-type-like for TM versus DM
 - Classification of histologically malignant and benign lesions
 - Agreement between local and expert study pathologists for all biopsied lesions
 - Creation of a blood and buccal cell biobank for future biomarker and genetic testing
- Health care utilization—compare:
 - Health care utilization and cost of screening by TM versus DM
- Medical physics
 - Implementation of a centralized quality control (QC) monitoring program for DM and TM
 - Assessment of temporal and site-to-site variations in image quality, breast radiation dose, and other QC parameters
 - Implementation of task-based measures of image quality to assess the effects of technical parameters on TM diagnostic accuracy
 - Evaluation of which QC tests are useful in determining image quality and those predictive of device failure

How Your Site Can Participate

Site Selection Process

- Interested sites should contact tmist@ecog-acrin.org so the TMIST study team can confirm the following:
 - Site must have a CTEP ID
 - Site must be a member/component of a participating NCTN/NCORP
 - Site must be a member or affiliate of a member institution with NCI CIRB
- Site Principal Investigators and/or Site Primary Contact will be notified of the requirements to activate the trial at their site

IRB Approval

- Investigators must obtain IRB approval and submit IRB approval and supporting documentation to the Cancer Trials Support Unit (CTSUS) Regulatory Office. Assignment of site registration status in the CTSUS Regulatory Support System (RSS) uses extensive data to determine whether a site has fulfilled all regulatory criteria, including but not limited to an active Federal Wide Assurance number, an active roster affiliation with the lead network or participating organization, a valid IRB approval, and compliance with all protocol-specific requirements. The site-protocol PI must meet the following: active registration status, IRB number of the site IRB of record listed on their Form FDA 1572, and active status on a participating roster at the registering site
 - Submit all required regulatory documents to:
 - CTSUS Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103
Fax: (215) 569-0206
E-mail: CTSUSRegulatory@ctsus.cocccg.org
Online: www.ctsu.org (members' section) a Regulatory Submission Portal
 - Required regulatory documentation:
 - Copy of IRB Informed Consent Document
 - CTSUS IRB Certification Form *or* signed HHS OMB No. 0990-0263 (replaced Form 310) *or* IRB Approval Letter*Note:* Submission must include all sites approved for the protocol under an assurance number; OHRP assurance number of reviewing IRB; full protocol title and number; version date; type of review (full board vs expedited); date of review; signature of IRB official.

- Sites participating on the NCI CIRB initiative and CIRB approved need not submit IRB approval documentation to CTSU. Their CIRB approval is applied to the CTSU RSS in an automated process. Signatory institutions must submit a Study Specific Worksheet for Local Context to the CIRB via IRBManager, indicating intent to open locally

CTEP Investigator and Personnel Registration

- All individuals contributing to NCI-sponsored trials must register and renew registration annually
- Registrants must obtain a CTEP Identity and Access Management (IAM) account (<https://ctepcore.nci.nih.gov/iam>)
- Sites must have a Lead Radiologist who is registered as a CTEP Investigator along with the Site Principal Investigator (if different people)
- Investigator (IVR), Non-physician Investigator (NPIVR), or Associate Plus (AP) must complete annual registration using CTEP's Web-based Registration and Credential Repository (RCR) (<https://ctepcore.nci.nih.gov/rcr>)
- Required documentation for IVR, NPIVR, and AP includes FDA Form 1572 (IVR and NPIVR only), Financial Disclosure Form, NCI Biosketch, HSP/GCP training, Agent Shipment Form (if applicable; IVR only), and CV (optional)
- IVRs and NPIVRs must list clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following: added to a site roster; assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN; act as site-protocol PI on IRB approval; assigned Clinical Investigator role on Delegation of Tasks Log (DTL)
- For questions, please contact RCR help desk via e-mail: RCRHelpDesk@nih.gov
- Check registration status at <https://www.ctsu.org>

Site Activation

- Sites will be activated over a 6-month period based on speed of completion of the following steps:
 - IRB approval
 - Submission of Physics/IT Survey
 - Submission of phantom and test images to TRIAD
 - Submission of sample de-identified radiology structured reports
 - Completion of study-specific training session
- Check activation clearance status at <https://www.ctsu.org>

Moving Through the Trial Process

Recruitment and Enrollment

- Recruit patients via patient-directed informational materials, the referral from primary care physician, or clinical trial volunteer portals
- We expect enrollment to last at least 3 years, with a total of 130 sites with an average of 3-5 subjects enrolled per site per day
- Enrollment is via CTSU OPEN, accessed at <http://open.ctsu.org>; address questions to the CTSU Help Desk at 1-888-823-5923 or contact ctsucontact@westat.com

Randomization and Imaging

- Randomization will occur electronically, via CTSU OPEN, at completion of registration
- Imaging will consist of
 - Standard bilateral screening mammogram
 - Breast tomosynthesis on FDA-approved systems using your site's standard-of-care protocol
- Screening imaging will be offered within 30 days of randomization
- In addition to screenings, participants can opt to have a blood draw and/or buccal rinse, ideally during the initial imaging visit
- Interpreting radiologists must be qualified, per the Mammography Quality Standards Act (MQSA) or equivalent for non-US sites, to interpret DM and TM images in an accredited clinical practice
- Radiologist reader interpretation of TMIST-enrolled subjects must be completed by a single radiologist

Submission of Clinical Data

- Enter case report forms electronically using Medidata Rave, which is used for all data collection; address questions to the CTSU Help Desk at 1-888-823-5923 or contact ctsucontact@westat.com
- Submit TM and DM images to ECOG-ACRIN through TRIAD, which will be the sole method of imaging data transfer to the ACR Clinical Research Center Core Laboratory. For questions, contact 703-390-9858 or TRIAD-Support@acr.org
- Submit pathologic materials for central diagnostic review and defined laboratory research studies (see Protocol Section 8)
- Submit biospecimens from breast biopsies to the TMIST biorepository



Moving Through the Trial Process (cont)

Follow-up

- To ensure follow-up screening rounds, schedule an appointment in the clinic at a recent screen or with reminder phone calls/ mailing
- After the 3 or 5 screening rounds, subjects return to their normal screening routines for long-term follow-up for at least 8 years

Contact Information

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For Further Study Information

- For more information about the TMIST/EA1151 study, please visit the following:
 - [Clinicaltrials.gov](https://clinicaltrials.gov); search **NCT03233191**
- Please direct general questions about the TMIST/EA1151 trial to tmist@ecog-acrin.org
- For more information about ECOG-ACRIN, visit ecog-acrin.org

