ECOG-ACRIN cancer research group
Reshaping the future of patient care

EAQ201

COVID-19 Related Financial Hardship and Distress in Women Who Decline TMIST (EA1151) Participation

STUDY CHAIR:	Ruth C. Carlos, MD
STUDY STATISTICIANS:	Fenghai Duan, PhD Constantine Gatsonis, PhD
STUDY CO-CHAIR:	Gelareh Sadigh, MD
STUDY EPIDEMIOLOGIST:	Ilana F. Gareen, PhD
IMAGING STATISTICIAN:	Na An, MS
CANCER CARE DELIVERY RESEARCH (CCDR) COMMITTEE CHAIR:	Ruth C. Carlos, MD
CANCER CONTROL AND SURVIVORSHIP COMMITTEE CHAIR:	Lynne Wagner, PhD

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STUDY PARTICIPANTS

ECOG-ACRIN / NCORP SITES ONLY
ALLIANCE / Alliance for Clinical Trials in Oncology – NCORP SITES ONLY
NRG / NRG Oncology - NCORP SITES ONLY
SWOG / SWOG - NCORP SITES ONLY

Limited to following selected non-NCORP sites:
Rev. Add2
Cleveland Clinic (OH027)
University of Iowa/Holden CCC (IA018)
University of Virginia Health System (VA009)

ACTIVATION DATE

December 2, 2021
Amendment #1 - incorporated prior to activation
Amendment #2

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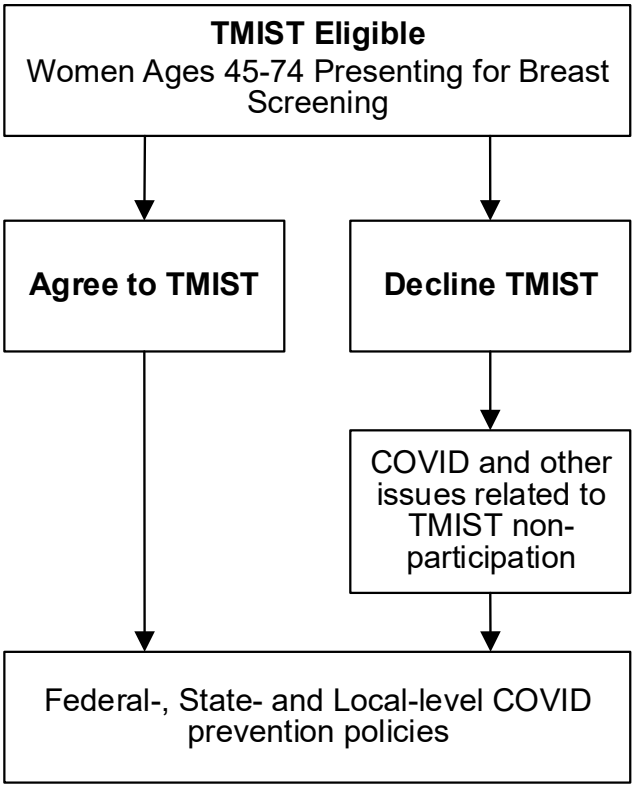
STUDY CHAIR

Ruth C. Carlos, MD
University of Michigan
Department of Radiology
1500 E Medical Center Dr.
Ann Arbor, MI 48109
rcarlos@med.umich.edu

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation can be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with subjects waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Refer to the participant enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email : 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done through Medidata Rave and the ECOG-ACRIN Systems for Easy entry of PRO data (EASEE-PRO). Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e., subject eligibility or treatment-related) Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to subject eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org.		

Schema


TMIST Eligible
Women Ages 45-74 Presenting for Breast Screening
Agree to TMIST
Decline TMIST
COVID and other issues related to TMIST non-participation
Federal-, State- and Local-level COVID prevention policies

1. Introduction

1.1 Study Foundation

Breast cancer claims 40-250% more African-American lives compared to White and Asian-Americans[1] and is the most frequent cause of cancer deaths in Hispanics/Latinas. Breast cancer is diagnosed at later stages in African-Americans and Latinas suggesting persistent disparities in care delivery by race/ethnicity[3]. Participation in clinical trials by women of color (WOC, which is defined as non-white women for the purposes of this study) is needed to improve outcomes, reduce health inequity and increase trial generalizability. Disappointingly, within ECOG-ACRIN, WOC participation remains less than 10% regardless of trial type (therapeutic, diagnostic/ surveillance or screening). Improving clinical trial participation among WOC is therefore a high priority to ensure that trial results are truly generalizable to women of all racial/ethnic groups.

1.2 Background

In EA1151 Tomosynthesis Mammographic Imaging Screening Trial (TMIST), a randomized controlled trial of digital mammography (DM) vs tomosynthesis (TM) to evaluate stage shift in screen-detected cancers, participation by Asians and Hispanics in particular have lagged. Cost concerns are a known barrier to trial participation[2] disproportionately affecting WOC. The COVID-19 pandemic will likely worsen trial participation among WOC. Unfortunately for many women, participation in TMIST can result in out-of-pocket costs since commercial insurance coverage of TM is widely variable[4]. Concerns about study-related costs are a known barrier to trial participation[2] and the COVID-19 pandemic has resulted in record unemployment[5,6] and insurance loss that has disproportionately affected minorities[7].

The economic toll can be broadly considered as financial hardship which has two main components, 1) material condition referring to actual financial resources available, and 2) psychological response to their material condition (see model). This financial hardship will further constrain many participants' financial resources (material condition) and ability to afford out-of-pocket expenses associated with trial participation and may lead to financial distress (representing the psychological response), preferentially affecting WOC who decline participation compared to non-WOC who decline. Additional federal-, state- and local-level factors (e.g., shelter-in-place policies, local unemployment during COVID-19) may also contribute to trial nonparticipation (Fig 1). COVID-19 is a natural experiment to compare the role of financial hardship on willingness to participate in clinical trials between WOC and non-WOC and any widening of disparities in WOC trial participation in TMIST. This observational ancillary study results will be used to inform future trials of interventions to improve trial participation among WOC, e.g., financial assistance and financial navigation services for trial-related expenses.

In a population of women who decline participation in TMIST (EAQ201 participants), we plan to compare the proportion of WOC who experience COVID-related change in their material condition (income/employment/insurance loss) vs non-WOC. Secondary and exploratory analyses will compare the proportions of WOC vs non-WOC with other person-level COVID-related factors

(including distress and fear of exposure during medical care) and assess federal-, state- or local-level COVID-related factors (e.g., state infection rates and shelter-in-place policies and local-level unemployment during shelter-in-place) as moderators. We hypothesize that COVID-19 related financial hardship and distress are more prevalent in WOC who decline TMIST participation compared to non-WOC who decline participation.

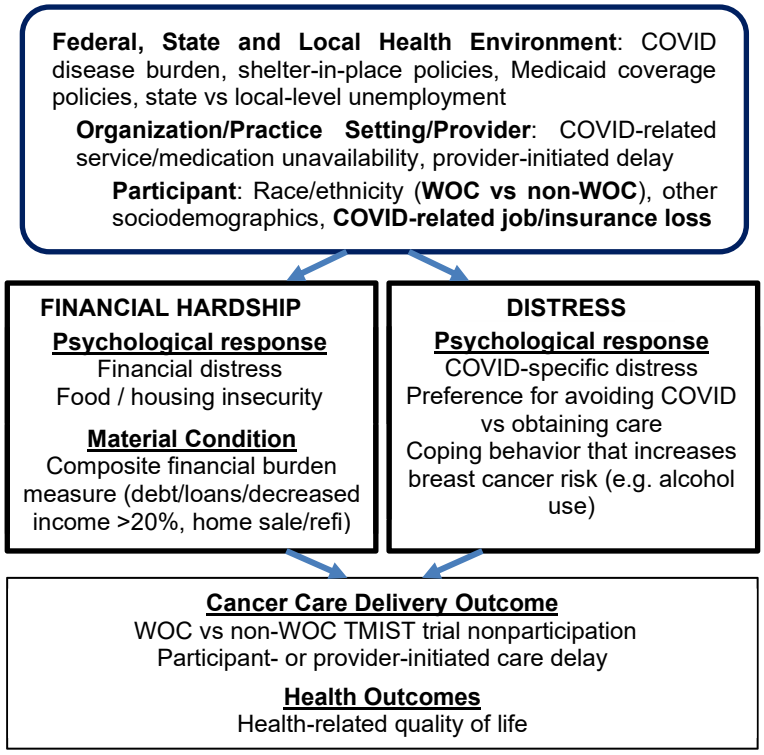
We will compare the effects of sociodemographics, and federal-, state- or local-level COVID-19 factors on TMIST participation, in WOC vs non-WOC. We hypothesize that federal-, state- or local-level COVID-19 factors more severely affect participation among WOC after controlling for other sociodemographic factors at the person-level (e.g., insurance type, socioeconomic status (SES)).

Our conceptual model integrates components of a traditional health services/care delivery model, an emerging model of financial hardship effect on health, and a model of psychological distress and coping to provide an innovative multi-level perspective on the effects of COVID-19 on a unique outcome, screening trial nonparticipation. While other studies have evaluated person-level factors[9-11] or region-level[12] factors, few can integrate factors at the individual, provider/organization, federal and state level to comprehensively evaluate barriers to trial participation. Incorporating COVID-specific distress and financial distress in trial nonparticipation is also novel, and to date the impact of these factors, particularly among WOC, is completely unknown.

We previously demonstrated that imaging out-of-pocket (OOP) costs cause worry among 36% of outpatients undergoing CT/MRI at UMichigan out-patient imaging clinics[13]. Those with ACA marketplace insurance were twice as likely to report worry over OOP costs of the test (OR 2.0, 95%CI 1.1, 3.5) compared to those with employer-sponsored insurance. 10% reported nonadherence to recommended care over the last 3 months such as declining a test or skipping or taking less medication than prescribed because of cost. Participants who worry about OOP costs were more likely to report nonadherence by 5-fold (OR 5.7, 95%CI 3.3, 9.8) than that those who did not. We hypothesize that when approached to participate for an imaging trial such as TMIST, women with existing OOP concerns or less generous insurance plans are more likely to decline participation than those who do not have existing OOP concerns or more generous insurance plans.

We have successfully used a combination of paper and online survey administration and data collection in EAQ162CD, a longitudinal observational study of financial hardship in early stage colorectal cancer and two imaging trials that collected patient reported outcomes, E4112 Prospective Study of MRI and Multiparametric Expression Assay in Ductal Carcinoma in Situ and EA1141 Comparison of Abbreviated Breast MRI and Digital Breast Tomosynthesis in Breast Cancer Screening in Women with Dense Breasts[14]. Depending on the study, 47-78% of women opted for online surveys. We have developed email and telephone reminders (see Section 4.3.5) for timely survey completion and processes for collecting any missing information.

Fig 1: Model of COVID effects on health



2. Objectives

2.1 Primary Objectives

2.1.1 In a population of women who decline participation in TMIST (EAQ201 participants), we will compare the proportion of WOC vs non-WOC with respect to who experience COVID-related financial hardship, a composite endpoint defined as any psychological response (financial distress, food/housing insecurity) or change in their material condition.

2.2 Secondary Objectives

2.2.1 Compare the proportions of WOC vs non-WOC EAQ201 participants with COVID-related change in their material condition, a composite measure.

2.2.2 Compare the proportions of WOC vs non-WOC EAQ201 participants with COVID-specific perceived financial distress.

2.2.3 Compare the proportion of WOC in TMIST participants vs EAQ201 participants. A key hypothesis (now 2.2.3) is that financial hardship preferentially affects WOC and therefore their participation in TMIST. In order, to test this hypothesis, we need to compare the proportion of WOC who participated in TMIST compared to those who declined to participate in TMIST (estimated by EAQ201 participants).

2.3 Exploratory Objectives

2.3.1 Compare the proportion of WOC vs non-WOC EAQ201 participants with COVID-related employment change, a composite measure.

2.3.2 Compare the proportions of WOC vs non-WOC EAQ201 participants with COVID-specific perceived distress and perceived susceptibility to COVID and breast cancer.

2.3.3 Compare the proportions of WOC vs non-WOC EAQ201 participants with relative increase in smoking and alcohol use, risk factors for breast cancer.

2.3.4 Compare participant-reported quality of life, anxiety and depression between WOC and non-WOC EAQ201 participants.

2.3.5 Assess the effects of sociodemographic characteristics, and federal-, state- or local-level COVID-19 factors on TMIST participation, in WOC vs non-WOC.

Rev. Add2 **3. Selection of Sites**

All interested NCORP and the three selected non-NCORP TMIST sites located in the United States will be invited to participate. There will be no specific exclusion criteria (i.e., minimum number of cases) because we would like to include a wide variety of different systems to better understand the variability in available financial resources and participant experiences.

Selection of Participant

Each of the criteria in the checklist that follows must be met in order for a person to be considered eligible for this study. Use the checklist to confirm a person's eligibility. For each person, this checklist must be photocopied, completed and maintained in the person's chart.

ECOG-ACRIN Participant No. _____

Person's Initials (L, F, M) _____

Treating Physician (Radiologist) or Designated Study Personnel Signature and Date

_____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit, and require reporting to the IRB of record as non-compliance.

All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Eligibility Criteria for Participants

Rev. Add2 _____ 3.1.1 Participant must have been eligible for and declined EA1151/TMIST in the preceding 6 months.

_____ 3.1.2 Participant must be able to complete questionnaires in English.

_____ 3.1.3 Participant must have a U.S. zip code.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

4. Site Investigators and Personnel CTEP Registration Procedures

Cancer Therapy Evaluation Program Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all 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 the site-protocol PI on the IRB approval

In addition, all investigators act as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization. Additional

information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm.

For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

Cancer Trials Support Unit Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

Downloading Site Registration Documents:

- Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.
- Log in to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the *Protocols* tab in the upper left of the screen
  - Enter the protocol # in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand then select ECOG-ACRIN, and protocol number EAQ201.
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided.

  NOTE: For sites under the CIRB, IRB data will load automatically to the CTSU.

Requirements For EAQ201 Site Registration:

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- Site Registration Status for EA1151

Required Protocol Specific Regulatory Documents

1. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

2. A. CTSU IRB Certification Form
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:
   - Indicate 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

Checking Your Site's Registration Status:

Site's registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of your screen;
- Click on *Site Registration*; and

- Enter the site's 5-character CTEP Institution Code and click on Go
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

NOTE: The status shown only reflects compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Participant Enrollment

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of participant registration/randomization assignment. OPEN will populate the participant enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- Have an approved site registration for the protocol prior to participant enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a participant transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

Prior to accessing OPEN, site staff should verify the following:

- Participant has met all eligibility criteria within the protocol stated timeframes; and
- All participants have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and procedure/randomization information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Registration Demographics

The following information is to be provided at the time of registration to the trial:

4.1.1 Protocol Number

4.1.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.1.3 Participant Identification

- Participant's initials (first and last)
- Participant's Hospital ID and/or Social Security number
  - Sex
  - Birth date (mm/dd/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country

4.2 Eligibility Verification

Participants must meet all of the eligibility requirements listed in Section 3.1.

4.3 Additional Requirements

4.3.1 Participants must provide a signed and dated, written study informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.3.2 Sites must maintain a record of participant identification information.

4.3.3 ECOG-ACRIN Outcomes and Economics Assessment Unit (OEAU) data collection

4.3.3.1 ECOG-ACRIN Systems for Easy Entry of Participant Reported Outcomes (EASEE PRO):

EASEE-PRO is comprised of a group of systems, interfaces, and databases designed to aid in the management, providing information, and collection of PRO data from participants. While EASEE-PRO is a single entity, the security framework and data flow for the main system components are described later in this section. The PRIDE portal provides a single common interface for participants and CRAs whose access to system components restricted by role, location, and study specification (Similar to using Imedidata.com to access RAVE and its subcomponents).

Access to the study in EASEE-PRO is granted to all participants registered to the study through the OPEN registration system with a valid participant email address. Upon registration, an account verification email will be sent to the user with a link to activate their account. The user will be required to enter some verification information (e.g., DOB) in order to activate their EASEE-PRO account. Site personnel (e.g., CRAs) are granted limited access to the systems, which only allows them to view reports on survey completion and expectedness. Additionally, if required by the study, they may be granted special access (provided a special role in the system) that allows them to assist

participants completing questionnaires and viewing other study materials, as described in the PROVIDE system component below.

Neither participant nor CRA access allows them to view/retrieve participant identifying information or survey responses stored in EASEE-PRO databases.

EASEE-PRO Participant Access:

To enter data, the participant must have an active EASEE-PRO user account. This account is automatically created when the participant is registered to the study in OPEN. For all web participants, an account activation email will be sent to the address entered in the OPEN eligibility checklist. This email address must be a valid email address for the web participant. (If the email address was entered incorrectly in OPEN, the CRA must contact the OEAU (pro-help@stat.brown.edu to manually correct the error.) To activate their account, participant must access the Participant Reporting Interface for Data Entry (PRIDE) web portal (https://pride.stat.brown.edu/Participant-Login) (i.e., click the link in the activation email) and verify their account before they can login and complete surveys or view web education materials. Once the account is activated, participants may return to the PRIDE portal at any time and login. Upon login, users will be presented with any available surveys and materials they can view.

EASEE-PRO CRA Access:

To access EASEE-PRO, the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam). In addition, site users that are a member of ECOG-ACRIN must have the mapped ECOG-ACRIN roles or explicit Rave role (Rave CRA) in RSS at the enrolling site. Site users that are not members of ECOG-ACRIN must have the Rave role on the CTSU roster at the enrolling sites. The Site Administrator or Data Administrator at the enrolling site may assign the appropriate roles from the Site Roles tab on the CTSU website. To login, CRAs will use their CTSU (IAM) credentials on the OEAU-PRIDE web portal (https://pride.stat.brown.edu/CRA-Login) using the familiar IAM interface. No e learnings are required for use of this site.

The OEAU can be contacted for via email at pro-help@stat.brown.edu. An EASEE-PRO instructional guide for both sites and participants can be found on both the ECOG-ACRIN and CTSU websites.

EASEE-PRO Systems:

1) Participant Reporting Interface for Data Entry (PRIDE) web portal:

a) PRIDE (https://pride.stat.brown.edu) provides a front facing web portal for participants, CRA, monitors and investigators.

b) The interface between internet users and the EASEE-PRO data entry subsystems (outlined below).

c) A secure site using HTTPS encryption (2048-bit SSL/TLS; 256-bit encryption) and requiring a username and password login in order enter data or view materials.

d) A web portal to provide general study information, links, help and support.

2) Secure environment for control of user records, information, and transactions (SECURIT): Provides a secure – limited access point for entering data into the restricted secure PII Database, for management of user data, creating user accounts, and reporting. The SECURIT interface requires the secure hypertext transfer protocol (HTTPS) to ensure encryption of transmitted data and is not accessible outside the OEAU.

a) PII database: is a dedicated secure limited access database, used to store protected PII.

i. Secure: All communications to the PII database through SECURIT are encrypted. The database resides behind a firewall and cannot be reach from outside the OEAU.

ii. Limited access: this database is restricted not only by username and password but is also restricted to specified internal OEAU computers by IP address, so that only authorized users logging in at the OEAU from pre-specified computers may access/enter PII. At no time is outside access allowed to this database.

iii. Protected restricted PII (e.g., SSN) are encrypted at the time of data entry and double data entered for verification. All users regardless of their security level are blinded to this protected data, and it cannot be decrypted without the encryption key, housed in a safe, in a location separate from the OEAU. This type of data is generally collected for long term follow-up where it may be needed to be decrypted for select participants in order to search registries like the national death index to determine survival status of lost participants. In these instances, with appropriate approvals, the Database Administrator will decrypt this data in

accordance with the approved retrieval specification.

b) User records: This functionality allows OEAU personnel, using specific computers within the OEAU, to create user records, enter user information into the PII database, and manually establish user web accounts in the separate user database. Allows the management of users and their data, including the ability to update a participant's preferred contact method, address, and participation status (e.g., no longer wishes to be contacted with respect to the PRO component of the study).

c) Information: This functionality allows the OEAU to record all participant contact, document any changes to the participant, and make any important notes related to the participant.

d) Transactions: SECURIT provides a reporting and monitoring interface to the PRO database (separate from the PII database above), which is used to store non-PII data (e.g., participants reported survey responses.)

i. Allows OEAU to monitor per participants form completion status using the tracking management facility. This facility reports on what data is currently expected from participants, CRAs, and the OEAU interviewers.

ii. Aggregate reporting: this series of reports allows the OEAU to monitor the distribution of participants over data completion methods and form completion methods (both overall and by site).

3) Database utility and control environment (PRO-DUCE): This utility interfaces with the main clinical database containing CRF/trigger data (Medidata RAVE), monitors the clinical database for events (e.g., participant registrations, scheduled procedures, and other triggers) and establishes event scheduling. The system sets up e-mail reminders [and SMS text message and/or push notifications, when applicable to the study] to relevant parties (CRAs, participants, C-BAC, OEAU personnel, etc.) to ensure timely completion of surveys, follow-up, or other interventions.

4) Web entry subsystems (PROWESS):

a) On participant login to the PRIDE portal and selecting the survey to complete, PROWESS generates the survey and layout including instructions, approx. time for completion, the number of questions to be completed in this

session, any important information regarding this survey (including help and contact information), and the survey itself

b) Secure HTTPS communications requiring a username and password login.

c) PROWESS presents each survey question, collects entered responses, and pushes the resulting data to the PRO-DB.

d) PROWESS is a one-way interface; data cannot be returned from the PRO-DB to the user. PROWESS cannot retrieve data from the PII-DB.

5) PRO Valet Interface and Data Entry System (PROVIDES).

a) The PROVIDES subsystem allows CRAs to act as a valet/scribe and enter a participant's responses to a survey into the PRO-DB.

- Allows CRAs to enter forms completed by the participant on paper (either on-site or completed remotely).
- Allows CRAs to act as scribes (if allowed), to read questions and enter data for participants.

b) Similar to PROWESs, PROVIDES is the linkage between EASEE-PRO and the PRIDE portal.

c) Secure HTTPS communications requiring a username and password login.

d) Which forms can be entered is restricted by username, site affiliation, and role, thus CRAs can only enter surveys predesignated as on-site data collection surveys and only for their own participants.

e) On login, user is presented with brief instructions; is requested to select the protocol, case number, time-point and verify the case Id by providing the participant birthdate.

f) PROVIDES presents each survey question, collects entered responses, and pushes the resulting data to the PRO-DB.

g) PROVIDES is a one-way interface; data cannot be returned from the PRO-DB to the user. PROVIDES cannot retrieve data from the PII-DB.

4.3.4 Data Integration Approach

Database Utilities and Control Environment (PRODUCE) sub-system allows for the collection and management of study critical events. This allows EASEE to interface with a variety of systems and use external APIs to retrieve data necessary for study operations.

4.3.5 Questionnaire Administration Process

At the time EASEE-PRO account activation, (or at the time of recruitment for subjects preferring paper surveys) participants will be asked to complete the Participant Contact Information Form. This form collects information used to maintain contact with the participant over the course of the study, including name, home address, phone number, and may include the name of a primary (or other) physician to whom requests for participant location may be made.

This form is retained in the study participant's chart at the site and is not entered in the RAVE clinical database; however, the completed form is faxed to the OEAU at Brown University. This information is necessary so that participants can be contacted by the OEAU for the Participant Reported Outcomes (PRO) portion of the study as required. The contact information is entered and stored in a dedicated SQL database (PII-DB) and IS NOT accessible by ECOG-ACRIN clinical database. The OEAU RA will not have access to the main ECOG-ACRIN database that contains clinical data.

At registration, participants will be asked to express a preference for on-line or paper administration of PRO forms. Participants may choose to complete questionnaires using a web-based application or paper at the site.

Participants will be prompted to complete web-based forms via an email prompt [push notifications or SMS as applicable to the study]. This notification will include a link to the PRIDE web portal for questionnaire completion. Questionnaires will be completed on line using a unique participant account. The web site will reference a toll-free phone number and email address that participants can use to reach the OEAU staff should they have questions or need assistance. All data will be stored on a secure server. Participants who do not complete the web questionnaires within 3 working days of the initial request e-mail will receive up to 3 additional reminders, each about 3 days apart. These reminders, like the initial notification, will provide a link to the current surveys, ask the participant to confirm that they have been able to access the web site, and provide both the e-mail address and the toll free help number for support.

If participants still have not responded within 12 days of the original e-mail, the OEAU Research Associate may attempt to telephone the participant and administer the questionnaire over the telephone. If participant requests that a paper questionnaire by mailed, the OEAU Research Associate may send out a paper questionnaire. If questionnaires are telephone-administered, they will be marked as such in the database. All surveys, while desired within 3 days of the event, will remain available for participants until either the surveys are completed or they are off-study. Since the completion date is recorded for all surveys, the study team will be able to make relevant determinations for inclusion of these data in specific analyses. However, after telephone follow-up, no additional or extraordinary means will be employed to collect overdue/missing questionnaires.

4.3.6 RAVE data collection

RAVE is the NCI-DCP approved Electronic Data Management System (EDM)

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

5. Methodology Plan

We will conduct an observational study to compare 1) the proportion of COVID-related participant factors (including financial hardship and distress among WOC who decline participation in TMIST (EAQ201 participants) compared to non-WOC EAQ201 participants; and 2) effects of federal-, state- and local-level COVID-19 factors on TMIST participation, in WOC vs non-WOC. The primary objective compares COVID-related financial hardship between WOC vs non-WOC EAQ201 participants (see **Table** 1 definition). Federal-, state-, local-, practice- and participant-level moderators (see Fig. 1 conceptual model) will be evaluated with hierarchical regression models. For the exploratory objectives, we will compare the effects of federal-, state- and local-level COVID-related factors on TMIST participation (secondary outcome), stratified by WOC vs non-WOC. Any woman 45-74 years old who is scheduled for breast cancer screening and is eligible for TMIST but declines will be approached by the TMIST site research associates (RAs). Enrollment for TMIST typically occurs immediately prior to the scheduled breast screening visit. Solicitation for participation in EAQ201 will occur at the same time for those who decline TMIST. TMIST site RAs will ask women who decline TMIST if they are interested in participating in EAQ201.

Sites participating in the parent study may approach potential participants using written materials, by phone or at the time of screening mammography. We will use the same enrollment processes. For those who are approached by phone and who decline to participate in TMIST will recruited for EAQ201 during the same call.

For those sites that use the written materials, it is up to the participant to actively respond to the site at which point they are additionally screened for eligibility for TMIST, usually by phone. Among those who respond to written materials and are additionally screened by phone, we will be able to approach the women who decline to participate in TMIST for EAQ201 recruitment.

Paper documentation of consent is required. It may be signed when the participant attends the schedule screening mammogram.

We will also compare the sociodemographic characteristics of women who complete the EAQ201 participant survey with women who agree to participate in TMIST over the same time period using only data collected as part of the TMIST study that have also been collected as part of the current study. No additional data will be collected from women who participate in the TMIST study.

No additional participant-level data will be collected from TMIST participants related to COVID-19 given the supplement scope. We elected to more completely understand the effects of COVID-19 on those who declined participation in TMIST.

Site characteristics and recruitment process: All sites will receive $30 per-case reimbursement for each eligible participant who registered to EAQ201. As with EAQ162CD, the study will provide some resources to assist the site, in particular: 1) site RA guides for engaging women who decline TMIST to enhance EAQ201 participation; 2) biweekly webinars/ phone calls for sites to check-in and discuss issues regarding recruitment and/or other study related issues, as needed. Sites that have implemented successful recruitment processes will be encouraged to attend and share their experiences.

Site Recruitment Plan: EAQ201 Study Chair or her designee will present the EAQ201 study to TMIST participating sites via standing TMIST Open Sites calls and through

direct email outreach to site TMIST PIs and lead TMIST research coordinators. This introduction to the study is expected to occur as close as possible to EA activation of the trial. The purpose of the study, site responsibilities, survey team responsibilities, and timeline will be presented on these calls. Along with materials to help support recruitment effort including phone script, study talking points, FAQs to help sites understand the study and to be able to communicate it to potential participants.

All EA1151 participating sites in the United States that are approved to enroll to EA1151 according to CTSU and actively recruiting and enrolling new participants to EA1151 based on at least one new enrollment attributed to the site in the most recent CTSU monthly enrollment report will be cleared to activate EAQ201 by ECOG-ACRIN upon obtaining EAQ201 NCI CIRB approval.

EAQ201 project manager will create a list of eligible sites based on EA1151 recruitment and enrollment status and will notify CTSU of ECOG-ACRIN clearance of this site qualification criteria. Site submission of required IRB documentation to NCI CIRB will be monitored in RSS weekly by the EAQ201 project manager who will report site activation clearances in CTSU weekly to the EAQ201 study chair by [define weekly communication mechanism you prefer here]. All sites that plan to open EAQ201 are strongly encouraged to activate EAQ201 within 30 days of ECOG-ACRIN activation of the trial as there will be no maximum number of subjects that can be enrolled in the trial at any one site and enrollment is expected to be completed within a few months.

EAQ201 project manager will reach out weekly to all eligible EA1151 sites to remind them about the EAQ201 study and obtain IRB approval through NCI CIRB. This outreach will occur by email to TMIST PI and TMIST lead coordinator until the site opens EAQ201, declines to participate, or EAQ201 enrollment reaches 50% of planned enrollment, 500.

Participant Recruitment Plan: All participating EAQ201 TMIST sites will be expected to approach at least 20 women per month in person or over the phone as part of their TMIST recruitment effort while EAQ201 is open to participant enrollment with at least 5 women approached that are classified as Women of Color [definition] according to information documented in the site's electronic medical record system.

All women presenting for screening mammography who meet the eligibility criteria for EA1151 but ultimately decline to participate in EA1151 should be immediately invited to participate in EAQ201 by EA1151 site designated recruiters.

All EAQ201 TMIST sites are expected to keep local TMIST recruitment logs for duration of EAQ201 enrollment period. The first two weeks of local TMIST recruitment logs for each site are to be submitted to the EAQ201 project manager to confirm that recruitment effort is happening for TMIST and to monitor number of WOC TMIST declines at the site. This information will be summarized across all sites for reporting to the EAQ201 central trial team to compare to EAQ201 enrollment rates at each site to determine if site is on track to complete within timeline planned and that overall WOC versus non-WOC participation ratio is within 10%-25% range planned.

Survey administration and data collection: We will use the ECOG-ACRIN Systems for Easy Entry of Participant Reported Outcomes (EASEE-PRO), our online survey platform supplemented by paper and/or telephone surveys using methods successfully employed in EAQ162CD financial burden assessment in colorectal cancer (Carlos co-PI) and E4112 prospective study of MRI and multiparameter gene expression assay in DCIS (Carlos co-I). Proxies are not allowed to complete questionnaires on behalf of participants. However, participants may use assistance and other accommodations to

complete questionnaires, including: CRAs, participant navigators/advocates, family members, and/or other individuals or aids that allow the participant to understand and record their answers to the survey questions (for example, visually impaired individuals may have questions read to them and their responses recorded). The surveys are available only in English.

TMIST site RAs will collect contact information at EAQ201 enrollment using Participant Contact Information Forms (name, home address, phone number and e-mail) and fax it to the central ECOG-ACRIN OEAU at Brown University. The COVID factors survey may be completed at the screening visit by paper or online. We assume that 40% will opt to complete the survey after the screening visit based E4112 patient preferences. Those who elect to complete the survey after the screening visit will only be able to do so online to conform to the scope of a supplement. These women will receive an invitation and account activation email from the central ECOG-ACRIN Outcomes and Economic Assessment Unit (OEAU) within 7 days to complete the online survey. Each online participant will use a unique account to complete the survey.

Women who choose to complete their survey online either during or after the screening visit will use our EASEE-PRO web-based participant-facing system. Through EASEE-PRO, study staff communicate with participants about study participation (e.g., email solicitations to logon and complete the survey using unique links and reminders). All study participants can access EASEE-PRO with a valid email address. Upon enrollment into the study, women will be able to activate their account using their email address, either in person or remotely. Activation requires entry of verification information (e.g., DOB) in order to complete activation. TMIST site RAs with the appropriate study roles will be granted access allowing them to assist participants who experience any difficulty. The web site includes a study-specific toll-free phone number to contact OEAU staff for assistance. All data will be stored on a secure server. Participants who do not complete the web surveys within 3 working days of initial e-mail request will receive up to 3 additional e-mail reminders, each 3 days apart. These reminder e-mails provide a link to the current surveys, ask the participant to confirm that they have been able to access the web site and provide both the e-mail address and the toll-free help number for support. All surveys will remain available for participants until either completed or participants are off-study. Since the completion date is recorded for all surveys, the study team will determine appropriate inclusion of these data in specific analyses. If a participant is non-compliant, the OEAU may contact the site CRA and/or the participant in an effort re-establish contact, remove barriers, and obtain the survey responses. These efforts may include email, mail, and phone contact with no more than 3 attempts by any method (i.e., three failed recovery attempts, at least 3 days apart, will be considered participant refusal.)

Women who choose to complete their surveys on paper at the site, should be provided with a paper copy of the survey to complete. The site personnel may then enter the answers into EASEE-PRO. Alternatively, the questionnaire may be faxed to the OEAU. Also, the CRA may have the participant complete the questionnaire on a site-provided tablet or computer.

Outcome and moderator measures are summarized in Table 1 and 2. Participant survey burden in EAQ162CD was 3.25–5.18 questions per minute. The approximately 60 item survey is estimated to take 12-18 minutes.

TABLE 1 : Participant-completed items	
Primary Endpoints	Measure (collected from EAQ201 participants)
COVID-related financial hardship among EAQ201 participants	Composite outcome, defined as answering in the affirmative to any of the following personal changes due to COVID: layoff or furlough, insurance loss, work hours reduction, new job/increased hours to increase income, food or housing insecurity (items used in EAQ162CD) OR answering in the affirmative to any of the following household changes due to COVID: ≥20% income lose, savings use for living expenses, home sale/refinance, increased debt, declared bankruptcy (items used in EAQ162CD)
Secondary Endpoints	Collected from EAQ201 participants
Material condition composite measure	Self-reported material condition of any of the following: >20% income loss, savings use, home sale or refinance, loans, reaching credit limits, becoming subject to a collection agency, or bankruptcy in the last 3 months (binary) (1 item, used in EAQ162CD)
COVID-specific perceived financial distress	Adapted from the summary item from COST measure.[16,17] (continuous) "COVID-19 has been a financial hardship to my family." (1 item)
Exploratory Endpoints	Collected from EAQ201 participants
Employment change	Self-reported work hours reduction, layoff or furlough, sick time or vacation time use or new job/increased hours to increase income (binary) (1 item, used in EAQ162CD)
COVID-specific perceived distress	Adapted from Penedo (personal communication) to capture the emotional response to COVID related to fear of infection, financial anxiety, housing and food insecurity (single items). (categorical)(11 items)
Perceived susceptibility to disease	Single items for breast cancer and COVID-19, modified from previous studies of intention to undergo breast cancer screening and used in EA2185 and EAQ162CD. (categorical) (2 items)
Distress coping behavior that increase breast cancer risk	We previously demonstrated that risky behaviors (e.g., cancer screening adherence, not smoking and seatbelt use[22, 23]). Alcohol[24] use has been described a risk factor for breast cancer. Smoking[25,26] has been raised as a risk factor. We will assess change in frequency or amount of tobacco or alcohol use during COVID compared to before COVID. We will not assess absolute amount of use. (categorical) (2 items)
HRQL	Participant-Reported Outcomes Measurement Information System (PROMIS)-10[18] 10-item physical and mental health assessment. Sum of item responses (continuous) (10 items)
General anxiety	PROMIS Anxiety 4-item Short Form. Sum of item responses (continuous) (4 items)
Depression	PROMIS Depression 4-item Short Form. Sum of item responses (continuous) (4 items)
Covariates	
Sociodemographics collected from EAQ201 participants	Race/ethnicity, age, education, marital status, annual household income, insurance, ZIP+4* to estimate neighborhood SES the using the Area Deprivation Index[15]
Sociodemographics collected from women who participate in TMIST	Race/ethnicity, age, insurance, and ZIP

TABLE 1 : Participant-completed items	
Provider-initiated delay	Participant-reported provider-initiated service delay or reduced access for any health service and for screening mammography in the last 3 months due to COVID
TABLE 2: Study team collected items	
Federal-, State- and local-level	Medicaid coverage policies, COVID burden and shelter-in-place policies (initiation, duration and extent of implementation) including any changes during the study period. Local unemployment rates[19] during shelter-in-place estimated from ZIP+4 using Local Area Unemployment Statistics from the Bureau of Labor.

State-level variables: COVID burden is assessed as:

1) Maximum new cases and deaths reported in one day as of registration of the first participant in that state;
2) Total case numbers in the 3-month period following the World Health Organization classification as a pandemic on 3/11/20 (raw and population-adjusted values);
3) Number of days from 3/11/20 to peak single-day report of new cases;
4) Occurrence of a “second peak” defined as a subsequent wave of new cases from the previous maximum number of new cases;
5) Cumulative death/infection rates at the time of study activation.

This data will be derived from the states’ departments of health and the Centers for Disease Control and Prevention. We will also examine state statutes and regulations including:

1) Timing of initiation of shelter-in-place policies (defined as the number of days from 3/11/20);
2) Duration of policies (number of days from initiation to any relaxation of shelter-in-place policies); and
3) Medicaid coverage of COVID-related care.
4) Shelter-in-place policy extent will be categorized as high (closure of all businesses except essential services e.g., grocery stores and pharmacies) or low (any business closure less complete than the above definition).
5) State legislation/regulation searches through Lexis-Nexis will be conducted using methods we previously employed to describe Medicaid coverage of trial participation costs[20].

6. Study Calendar

Survey is collected at baseline. See below for number of questions in the study assessment.

Table 3	Baseline
Participant questionnaires	(min/max # questions based on skip pattern)
Sociodemographics	Max 3q*
Insurance and COVID-related change	Min 4q/ Max 8q
Distance traveled for mammogram	Max 1q
Reason for refusing to participate in TMIST	Max 1q
Employment and COVID-related change	Max 2q
Financial situation and COVID-related change	Max 7q
COVID testing or infection	Max 2q
Participant reported COVID-related delays in care	Min 3q/Max 4q
COVID-specific distress	Max 10q
Change in smoking and alcohol use	Max 2q
Preference for delaying screening due to COVID	Max 1q
Perceived susceptibility to disease	Max 2q
PROMIS-10 Overall quality of life	Max 10q
PROMIS ASF	Max 4q
PROMIS DSF	Max 4q
Assistance needed questions	Min 1q/Max 3q
Minimum/Maximum number of items	Min 57q/64q

*Some of the sociodemographic questions are collected at registration and entered into the OPEN database and not listed here.

7. Statistical Considerations

7.1 Study Design and Objectives

7.1.1 Primary Objectives

In a population of women who decline participation in TMIST (EAQ201 participants), we will compare the proportion of WOC vs non-WOC with respect to who experience COVID-related financial hardship, a composite endpoint defined as any psychological response (financial distress, food/housing insecurity) or change in their material condition.

Hypothesis: Compared to non-WOC, WOC will experience more COVID-related financial hardship.

7.1.2 Secondary Objectives

7.1.2.1 Compare the proportions of WOC vs non-WOC EAQ201 participants with COVID-related change in their material condition, a composite measure.

Hypothesis: Compared to non-WOC, WOC will experience more COVID-related change in their material condition.

7.1.2.2 Compare the proportions of WOC vs non-WOC EAQ201 participants with COVID-specific perceived financial distress.

Hypothesis: Compared to non-WOC, WOC will experience more COVID-specific perceived financial distress.

7.1.2.3 Compare the proportion of WOC in TMIST participants vs EAQ201 participants.

Hypothesis: The proportion of WOC should be higher in the TMIST decliners than that in TMIST agree-ers.

7.1.3 Exploratory Objectives

7.1.3.1 Compare the proportion of WOC vs non-WOC EAQ201 participants with COVID-related employment change, a composite measure.

7.1.3.2 Compare the proportions of WOC vs non-WOC EAQ201 participants with COVID-specific perceived distress and perceived susceptibility to COVID and breast cancer.

7.1.3.3 Compare the proportions of WOC vs non-WOC EAQ201 participants with relative increase in smoking and alcohol use, risk factors for breast cancer.

7.1.3.4 Compare participant-reported quality of life, anxiety and depression between WOC and non-WOC EAQ201 participants.

7.1.3.5 Assess the effects of sociodemographic characteristics, and federal-, state- or local-level COVID-19 factors on TMIST participation, in WOC vs non-WOC.

7.2 Primary Objective

The primary objective is to compare the proportion of WOC EAQ201 participants who experience COVID-related financial hardship vs non-WOC EAQ201 participants. The results, with and without adjustment for missing values (see 7.5), will be compared as a sensitivity analysis. Logistic regression models, with and without stratification by WOC status, will be fit with financial hardship as the response variable to investigate other sociodemographics (e.g., age, marital status, insurance status) and state- and local-level factors (e.g., state COVID severity, shelter-in-place policies, state and local unemployment during shelter-in-place) as moderators.

Sample Size Considerations for the Primary Objective (7.1.1):

The primary objective is to compare the proportion of WOC EAQ201 participants who experience COVID-related financial hardship (see **Table 1** for definition) with the proportion of non-WOC EAQ201 participants who experience COVID-related financial hardship. The National Bureau of Economic Research estimated unemployment rates by race and ethnicity in April 2020, around shelter-in-place regulations[7]. Unemployment in African-American and Latinx populations averaged 18% compared to Whites (13%). At a sample size of 1000 women who decline TMIST participation, we expect to recruit at least 10-25% WOC into this study. Assuming alpha of 0.05, we estimated power over a range of differences across various proportions (see **Table 4**). For instance, at a sample size of 1000 with 10% of WOC, we have 77% power to detect a minimum difference of 0.10 between two proportions (0.2 vs. 0.1); at a sample size of 1000 with 25% of WOC, we have 88% power to detect a minimum difference of 0.08 between two proportions (0.18 vs. 0.1). Please note that based on DCP-001, 16% of the women who declined TMIST were WOC. Accrual onto TMIST is expected to continue for another 4.4 years. Also based on DCP-001 and extrapolating to the Non-NCORP US sites, accruing 1,000 women to this study is achievable. We do not envision any danger that this study will close due to lack of accrual.

Table 4: Estimated power for a two-sample proportions using Fisher's Exact test (two-sided). N1: # of WOC; N2: # of non-WOC

Sample size (N)	N1/N2	P1 (WOC)	P2 (non-WOC)	Delta	Alpha	Power
(Sample size: 1000; N1/N2=1/9, i.e.,10% of WOC)						
1000	1/9	0.200	0.100	0.100	0.05	0.77
1000	1/9	0.225	0.100	0.125	0.05	0.90
1000	1/9	0.250	0.100	0.150	0.05	0.96
1000	1/9	0.250	0.150	0.100	0.05	0.66
1000	1/9	0.275	0.150	0.125	0.05	0.83
1000	1/9	0.300	0.150	0.150	0.05	0.92
(Sample size: 1000; N1/N2=1/3, i.e.,25% of WOC)						
1000	1/3	0.180	0.100	0.080	0.05	0.88
1000	1/3	0.200	0.100	0.100	0.05	0.97
1000	1/3	0.220	0.100	0.120	0.05	0.99
1000	1/3	0.230	0.150	0.080	0.05	0.79

1000	1/3	0.250	0.150	0.100	0.05	0.92
1000	1/3	0.270	0.150	0.120	0.05	0.98

7.3 Secondary Objectives

Two-sample proportion tests (e.g., Z-test based on normal approximations or Fisher's exact test) will be used to compare the proportions of WOC vs non-WOC EAQ201 participants with 1) COVID-related change in their material condition; 2) COVID-specific perceived financial distress. Logistic regressions may be performed to adjust for potential confounders during the comparisons. Missing data will be managed as below (See 7.5).

The proportion of WOC in EAQ201 participants will be compared to the proportion of WOC in TMIST participants using the one-sample proportion test. Based on the TMIST data, the proportion of WOC in TMIST participants is around 25-%. Then we will have 80% power to detect a difference of 3.9% using a two-sided exact test with a significant level of 0.05.

7.4 Assess the effects of sociodemographic characteristics, and federal-, state- or local-level COVID-19 factors on TMIST participation, in WOC vs non-WOC.

For the exploratory objective (7.1.3.5), we will compare the effects of sociodemographic characteristics, federal-, state- or local-level factors (e.g. maximum number of COVID-19 cases, state unemployment during shelter-in-place, local unemployment during shelter-in-place) on TMIST participation, stratified by WOC vs non-WOC. We will fit a logistic regression model with TMIST participation status (EAQ201 participant or TMIST participant) as the response variable to investigate other sociodemographic (e.g., marital status, neighborhood SES, insurance type), federal-, state- or local-level factors (see **Table 2**). Regression modeling will be conducted with and without stratification by WOC vs non-WOC.

The analysis set will include the 1000 EAQ201 participants from this study and a corresponding number of TMIST participants, who will be randomly selected from the enrolled participants in the main TMIST study. The selection will be stratified by site and enrollment time. Assuming that the proportion of overall EAQ201 participants is from 0.20 to 0.50, **Table 5** below shows the power analysis of testing for the odds ratio in the logistic regression. The variables of interest can be continuous or categorical (binary). For instance, 2000 women (1000 EAQ201 participants versus 1000 randomly selected TMIST participants) achieves 90% power at a 0.050 significance level to detect a change in the proportion of EAQ201 participants from 0.50 at the mean of the testing variable to 0.538 when the value of the variable is increased to one standard deviation above the mean. This change corresponds to an odds ratio of 1.165. An adjustment was made since a multiple regression of the independent variable of interest on other independent variables in the logistic regression obtained an R-Squared of 0.10.

Table 5: Tests for the Odds Ratio in Logistic Regression (Wald Test)									
A. X is continuous									
Power	**N(EAQ201 participants)**	**N(TMIST participants)**		**P0**	**P1**	**Odds Ratio**	**R-SQRD**	**Alpha**	**Beta**
	(50% EAQ201 participants)								

0.9	1000	1000		0.5	0.538	1.165	0.1	0.05	0.1
0.9	1500	1500		0.5	0.531	1.133	0.1	0.05	0.1
	(40% EAQ201 participants)								
0.9	1400	2100		0.4	0.429	1.125	0.1	0.05	0.1
0.9	2100	3150		0.4	0.423	1.101	0.1	0.05	0.1
	(20% EAQ201 participants)								
0.9	1200	4800		0.2	0.218	1.117	0.1	0.05	0.1
0.9	1800	7200		0.2	0.215	1.094	0.1	0.05	0.1
B. X is categorical (binary)									
Power	**N**		**% N X=1**	**P0**	**P1**	**Odds Ratio**	**R-SQRD**	**Alpha**	**Beta**
	(50% EAQ201 participants)								
0.9	1000	1000	50	0.5	0.576	1.359	0.1	0.05	0.1
0.9	1500	1500	50	0.5	0.562	1.284	0.1	0.05	0.1
	(40% EAQ201 participants)								
0.9	1400	2100	50	0.4	0.457	1.263	0.1	0.05	0.1
0.9	2100	3150	50	0.4	0.447	1.21	0.1	0.05	0.1
	(20% EAQ201 participants)								
0.9	1200	4800	50	0.2	0.236	1.239	0.1	0.05	0.1
0.9	1800	7200	50	0.2	0.23	1.192	0.1	0.05	0.1

7.5 Handling Missing Data

As stated above, we will closely monitor the participant attrition and determine whether the dropout is informative or not. If the missing is random, we may implement a method like multiple imputation to impute the missing values. In case the missing is not random (e.g., participants who are lost to follow up may experience more financial burden), we will implement various methods for the adjustment in our analysis, e.g., Bayesian modeling with informative priors. Analysis under different scenarios will be conducted to explore sensitivity to different missing data assumptions[21].

7.6 Gender and Ethnicity

Based on TMIST data from participants enrolled in September 2020, at sites in the United States, the anticipated accrual in subgroups defined by gender and race is:

Racial Categories	Not Hispanic or Latino Female	Not Hispanic or Latino Male	Hispanic or Latino Female	Hispanic or Latino Male	Total
American Indian/ Alaska Native	2	0	0	0	2
Asian	19	0	0	0	19
Native Hawaiian or Other Pacific Islander	1	0	0	0	1

Racial Categories	Not Hispanic or Latino Female	Not Hispanic or Latino Male	Hispanic or Latino Female	Hispanic or Latino Male	Total
Black or African American	196	0	2	0	198
White	742	0	30	0	772
More Than One Race	6	0	2	0	8
Total	966	0	34	0	1,000

7.7 Study Monitoring

This study will be monitored by the Data Safety Monitoring Committee (DSMC). The DSMC will meet twice each year. For each meeting, the study is reviewed for safety and progress toward completion. These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document.

This protocol will be monitored under the jurisdiction of the EA1151 (TMIST) DSMC.

The Brown office of the Statistics Center has extensive and long-term experience in monitoring large screening trials, including ACRIN 6652 (Digital Mammography Imaging Screening Trial), ACRIN 6654 (National Lung Screening Trial), ACRIN 6664 (National CT Colonography Trial), and ACRIN 6666 (Screening Breast Ultrasound in High-Risk Women). Established approaches and practices for study monitoring in our organization will be followed and adapted to meet the monitoring needs of this protocol.

We will learn from the experiences of the ongoing SWOG 1417CD trial investigating financial burden in metastatic disease.

In addition to site visits and available phone and email support, as outlined above, the EASEE-PRO system will send email notifications and up to 3 follow-up reminders to notify web-based participants to complete surveys. If a participant is non-compliant, the OEAU may contact the site CRA and/or the participant in an effort re-establish contact, remove barriers, and obtain the survey responses. The efforts may include email, mail, and phone contact with no more than 3 attempts by any method (i.e., three failed recovery attempts, at least 3 days apart, will be considered participant refusal.)

8. Electronic Data Capture

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

Please refer to the study parameters (Section 7) for the forms submission schedule. Clinical data collection will be performed in Medidata Rave. Survey data will be collected in EASEE-PRO.

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

9. Participant Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

If a participant wishes to withdraw from all aspects of the trial including medical record review and registry searches, the withdrawal must be in writing (on paper or via email) and state their desire to withdraw from passive data collection: medical record review and registry search. If documentation is created in a language other than English, a copy of the original source document as well as a translated English version must be submitted. Women are not allowed to rejoin the trial after they withdraw from all aspects of the trial.

10. References

1. Society AC. Breast Cancer Facts & Figures 2019-2020. 2019; https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf. Accessed 6/15/2020, 2020.
2. Wenzel JA, Mbah O, Xu J, et al. A Model of Cancer Clinical Trial Decision-making Informed by African-American Cancer Patients. *J Racial Ethn Health Disparities.* 2015;2(2):192-199.
3. Nahleh Z, Otoukesh S, Mirshahidi HR, et al. Disparities in breast cancer: a multi-institutional comparative analysis focusing on American Hispanics. *Cancer Med.* 2018;7(6):2710-2717.
4. Lee CI, Lehman CD. Digital Breast Tomosynthesis and the Challenges of Implementing an Emerging Breast Cancer Screening Technology Into Clinical Practice. *J Am Coll Radiol.* 2016;13(11S):R61-R66.
5. Cutler D. How Will COVID-19 Affect the Health Care Economy? https://jamanetwork.com/channels/health-forum/fullarticle/2764547. Accessed 6/15/2020, 2020.
6. T CPaH. Rolling Shock as Job Losses Mount Even With Reopenings. 2020. Accessed 05/24/2020, 2020.
7. Fairle RW CK, Xu H. The Impacts of COVID-19 on Minority Unemployment: First Evidence from April 2020 CPS Microdata. 2020; https://www.nber.org/papers/w27246. Accessed 06/23/2020, 2020.
8. National Cancer Institute (NCI) CCTGC. Digital Tomosynthesis Mammography and Digital Mammography in Screening Patients for Breast Cancer. In: National Institute of Health; 2017.

9. Sateren WB, Trimble EL, Abrams J, et al. How sociodemographics, presence of oncology specialists, and hospital cancer programs affect accrual to cancer treatment trials. *J Clin Oncol.* 2002;20(8):2109-2117.
10. Adams-Campbell LL, Ahaghotu C, Gaskins M, et al. Enrollment of African Americans onto clinical treatment trials: study design barriers. *J Clin Oncol.* 2004;22(4):730-734.
11. Williams DR, Kontos EZ, Viswanath K, et al. Integrating multiple social statuses in health disparities research: the case of lung cancer. *Health Serv Res.* 2012;47(3 Pt 2):1255-1277.
12. Langford AT, Resnicow K, Dimond EP, et al. Racial/ethnic differences in clinical trial enrollment, refusal rates, ineligibility, and reasons for decline among patients at sites in the National Cancer Institute's Community Cancer Centers Program. *Cancer.* 2014;120(6):877-884.
13. Charkhchi P, Omotoso,K, Fendrick,A, Gomez-Hassan,D, Carlos,R,. Financial Burden of Advanced Imaging in Radiology (FAIR Study). *Radiological Society of North America 2019 Scientific Assembly and Annual Meeting,.* 2019. http://archive.rsna.org/2019/19018702.html. Accessed 06/23/2020.
14. Comstock CE, Gatsonis C, Newstead GM, et al. Comparison of Abbreviated Breast MRI vs Digital Breast Tomosynthesis for Breast Cancer Detection Among Women With Dense Breasts Undergoing Screening. *JAMA.* 2020;323(8):746-756.
15. Department of Medicine UoWSoMaPH. Neighborhood Atlas. https://www.neighborhoodatlas.medicine.wisc.edu/. Accessed 06/15/2020, 2020.
16. de Souza JA, Yap BJ, Hlubocky FJ, et al. The development of a financial toxicity patient-reported outcome in cancer: The COST measure. *Cancer.* 2014;120(20):3245-3253.
17. de Souza JA, Yap BJ, Wroblewski K, et al. Measuring financial toxicity as a clinically relevant patient-reported outcome: The validation of the COmprehensive Score for financial Toxicity (COST). *Cancer.* 2017;123(3):476-484.
18. Cella D, Yount S, Rothrock N, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first two years. *Med Care.* 2007;45(5 Suppl 1):S3-S11.
19. Statistics UBoL. Local Area Unemployment Statistics. In:2020.
20. Obeng-Gyasi S, Kircher SM, Lipking KP, et al. Oncology clinical trials and insurance coverage: An update in a tenuous insurance landscape. *Cancer.* 2019;125(20):3488-3493.
21. Daniels MJaH, Joseph W. *Missing Data in Longitudinal Studies: Strategies for Bayesian Modeling and Sensitivity Analysis* 1st ed: Chapman and Hall/CRC; 2008.
22. Carlos RC, Fendrick AM, Patterson SK, Bernstein SJ. Associations in breast and colon cancer screening behavior in women. *Acad Radiol*. 2005;12(4):451-458. doi:10.1016/j.acra.2004.12.024
23. Carlos RC, Fendrick AM, Abrahamse PH, Dong Q, Patterson SK, Bernstein SJ. Colorectal cancer screening behavior in women attending screening mammography: longitudinal trends and predictors. *Womens Health Issues*. 2005;15(6):249-257. doi:10.1016/j.whi.2005.06.001
24. Howell A, Anderson AS, Clarke RB, Duffy SW, Evans DG, Garcia-Closas M, Gescher AJ, Key TJ, Saxton JM, Harvie MN. Risk determination and prevention of breast cancer. Breast Cancer Res. 2014 Sep 28; 16(5):446.
25. Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Cogliano V, WHO International Agency for Research on Cancer Monograph Working Group. A review of human

carcinogens--Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol. 2009 Nov; 10(11):1033-4.

26. Kispert S, McHowat J. Recent insights into cigarette smoking as a lifestyle risk factor for breast cancer. *Breast Cancer (Dove Med Press)*. 2017;9:127-132. Published 2017 Mar 7. doi:10.2147/BCTT.S129746