# BRAVE Strategy
# Breast cancer Risk Assessment – achieving Equity

## STUDY PROTOCOL

## NCT05051631

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[redacted]

**Original Protocol Version: 09/28/2021**

****Vanderbilt will be <u>the only site recruiting, consenting interacting with participants, and following this study protocol</u>.**

# STUDY PROTOCOL

## 1. Study Summary

Breast cancer mortality disparities in young women result in increased early loss of life amongst women from low socioeconomic status, those dwelling in rural areas, and those from racial minority groups. Access to care, delays in diagnosis and treatment, and differences in tumor biology partially explain these disparities. Identifying racially, geographically, and socioeconomically diverse young women at high risk for breast cancer offers an opportunity to reduce cancer disparities through early screening and detection of breast cancer. Integrating the use of existing breast cancer risk assessment (RA) tools into clinical care is a means to identify these young women.

## 2. Rationale

While RA is recommended for all women no later than age 30, this has not yet been translated to clinical practice and thus women are not receiving RA prior to the age of 50 years when screening is recommended for those at average risk. Women at high risk, in contrast, should start screening as young as age 25 (e.g., for those identified to have a *BRCA1* or *BRCA2* mutation). As most women ages 25-49 years of age do not now receive RA, and breast cancer in these women presents with a more aggressive phenotype at later stage associated with inferior outcomes, implementation strategies for RA in this age group should be developed. If women age 25-49 receive RA and are identified as high-risk, they can be screened earlier than age 50 to diagnose cancer at an earlier stage, when the disease is most successfully treated.

## 3. Objectives

The central goal of this study is to test strategies to implement evidence-based breast cancer RA in healthcare clinics in Tennessee. The strategies that we will test include engaging a site champion at each clinic, offering tailored provider education, and offering tools to increase patient awareness of breast cancer RA. The BRAVE study aims to assess the feasibility, reach, acceptability, and appropriateness of these select customized strategies to increase uptake of breast cancer RA. We will achieve these aims through a conducting a stepped-wedge trial employing a mixed methods study design. The primary outcome is the proportion of women age 25-49 having RA. Secondary outcomes include the numbers of women: 1) identified as high-risk; 2) pursuing risk-adherent screening; and 3) diagnosed with breast cancer. Implementation outcomes include reach, feasibility, acceptability, and appropriateness. Data collected will inform a future multi-site cluster randomized clinical trial to test the implementation strategies on a larger scale over a longer duration, enriched for underserved populations such as minority and rural dwellers.

## 4. Personnel

[redacted]

## 5. Research Design and Methods

### *5.1 Feasibility*

5.1.1 Purpose

Test the feasibility of implementing strategies to increase uptake of breast cancer RA.

5.1.2 Feasibility Assessment

Presentation of Potential Strategies:
The Vanderbilt study team will give a short presentation demonstrating the proposed strategies to increase breast cancer RA. Strategies include engaging a site champion, offering provider education, and offering methods to increase patient awareness of breast cancer RA. The presentation will be either in person or virtual as necessary per COVID restrictions. The presentation is expected to take approximately 15 minutes and will demonstrate strategies such as how a site champion will engage with the research team to share information with clinics, how provider education can be offered to the sites, and how patient awareness materials could be presented.
Following the presentation, the Vanderbilt team will distribute a web-based voluntary, anonymous REDCap survey to clinic providers and staff. This survey is an adapted version of the validated Feasibility of Intervention Measure (FIM), a 4-item scale that measures provider perception that a given practice can be easily or conveniently performed. Questions are asked on a Likert-like scale (1, Completely Disagree – 5, Completely Agree) with both FIM sum and mean scores calculated. Higher scores indicate higher feasibility. **[see REDCap Survey - Feasibility]**

Following completion of the survey, clinic providers and staff will be invited to participate in a brief listening session to share their thoughts on the strategies presented. **[see Listening Session Guide - Feasibility]**

Recruitment and Eligibility: The Vanderbilt study team will perform the Feasibility Assessment in up to 10 clinics in Tennessee. The Vanderbilt team will recruit clinics to participate in the Feasibility Assessment leveraging existing relationships through the TBCSP to identify potential participants **[see Recruitment Email – Feasibility]**. The Vanderbilt team will respond via email or phone to answer additional questions potential clinics may have. The Vanderbilt team will recruit individuals at each participating clinic at the time of the feasibility presentation to participate in the Feasibility Assessment **[see Information Sheet – Feasibility]**. The Vanderbilt team will answer any questions potential participants may have. The survey sample will consist of approximately 60 individuals. Sample size at individual clinics may vary due to differences in the number of providers and staff at each clinic. Eligible individuals will be age 18 and older and will be a provider, staff, or administrator employed in a clinic enrolled in the study.

Data Collection Methods: Data from the anonymous, voluntary survey will be collected and stored via REDCap, a secure online data collection tool. The listening sessions will be digitally recorded via audio recorders with participant permission, transcribed verbatim, and coded by two research team members using a codebook. If participants choose not to be recorded, the interviewer will take notes on their responses. Any identifying information that are part of the participants' responses will be removed from the transcriptions. Original listening session recordings will be destroyed once transcribed. The responses to all the listening sessions will be summarized. When the specific responses from individual organizations are quoted, the organization or person's name will not be identified.

Consent: We will request a Waiver of Consent for the Feasibility Assessment. Consent will be implied by completion of the survey and participation in a listening group.

5.1.3 Data Analysis

Continuous measurements will be summarized using mean + standard deviation or median/interquartile range. tables and graphs will be created to describe and visualize data. Qualitative data will be analyzed using inductive coding to identify emerging themes.

### *5.2 Reach*

5.2.1 Purpose

Conduct a trial to evaluate the impact of breast cancer RA implementation strategies on the proportion of eligible women receiving RA (reach). The intervention in this trial is the use of implementation strategies including identifying a site champion, offering provider education, and providing tools to increase patient awareness of RA. The working hypothesis is that implementing this bundle of selected strategies to increase utilization of breast cancer RA will increase the proportion of eligible women (age 25-49) having RA performed when compared to usual care.

5.2.2 Design

The BRAVE trial is a real-world cross-sectional trial. The trial intervention is the implementation of the bundle of selected strategies to increase uptake of breast cancer RA (Fig. 1). No clinics are exposed to the intervention at the beginning of trial. Subsequently, each clinic will receive the intervention. Data will be collected before and after intervention, so that each clinic contributes observations under both control and intervention conditions. Ultimately, all clinics will receive the same intervention. The primary outcome is the proportion of eligible women (women age 25-49) who receive breast cancer RA.

5.2.3 Implementation Periods (Control, Implementation, Maintenance)

Control: Baseline data on reach will be collected through electronic health record or data collection forms (see section 5.2.6 - Data collection methods).
Implementation: During the implementation period, the research team will identify and engage the site champion and the research team. The research team will deliver tailored in-person provider education and provide clinics with tools to increase patient awareness of breast cancer risk assessment. The research team will also participate in clinic staff meetings to answer questions about breast cancer RA, discuss barriers to performing RA, and provide feedback on the clinic's use of RA. Final versions of education and awareness materials have been submitted and approved by the IRB.
Maintenance: Implementation strategies will no longer be offered. The maintenance period will consist of data collection only.

5.2.4 Recruitment and Eligibility

The Vanderbilt team will recruit 10 individual clinics to participate in the trial. We will apply eligibility criteria to purposively select geographically diverse clinic sites serving racially diverse populations. First, clinics must be located within approximately 2-hour driving distance of Nashville, Tennessee, where the program coordinator is housed to maintain frequent contact with the clinics. Second, clinics must identify a champion to work with the research team and serve as the primary contact. Third, the clinic must serve a racially diverse population of women. Fourth, the clinic must have an electronic health record. We will recruit two back-up clinics meeting these selection criteria in case a site drops out during the early phase of the study. The Vanderbilt team will reach out to potential clinics with the guidance of our established relationship with the TBCSP via email or in person and provide a study information sheet for potential clinics **[see Recruitment Email – Clinic, Information Sheet – Clinic]**. The Vanderbilt team will respond via email or phone to answer additional questions potential clinics may have regarding enrollment.

At the clinics enrolled in the study, we will collect data retrospectively from individual health records on patients who are seen by the clinic. We anticipate that we will collect clinical data on approximately 3,000 women during the time of the stepped-wedge trial. Inclusion criteria for individual records will be women, age 25-49. Exclusion criteria will include personal history of breast cancer.

### 5.2.5 Remuneration

Clinics will be offered compensation for the administrative time and effort and IT efforts necessary to participate in the study. [redacted]

### 5.2.6 Data Collection Methods

Data collection will be performed preferentially through clinic electronic health records. Data will be extracted from the electronic health records through automated reports and through manual chart review. Manual chart review will be performed by individuals affiliated only with the clinic site that the chart is being reviewed for. Individuals will have appropriate data access credentials and IRB approval. VUMC personnel will not directly access any medical records. Data extracted by chart review will be de-identified and entered into the **Clinic Data Collection Form – REDCap**.

If an enrolled clinic does not have a reliable electronic health record, paper data collection forms or via REDCap will be used **[Clinic Data Collection Form – Paper, Clinic Data Collection Form - REDCap]**. These clinic data collection forms will be distributed to clinic sites by the research team prior to the initiation of the stepped-wedge trial. Research team personnel will provide instruction to clinic site personnel on how to use the forms. Clinic sites will store the data collection forms in a secure pre-determined location within the clinic. Forms will be electronically scanned and sent to the research team or collected by the research team bi-weekly.

Data collected will include the date of the patient encounter, provider name, demographic information (age, race/ethnicity); was breast cancer RA offered/performed with the Tyrer-Cuzick tool? (yes/no), result of breast cancer RA, was further testing was recommended? (y/n), and what further testing was recommended on the clinical data collection forms. For clinics with reliable electronic health records, this information will be obtained from the electronic health record by participating clinics, deidentified, and provided to the Vanderbilt team. We will obtain data use agreements with the enrolled clinics for the data transfer.

The numerator for the primary outcome (number of women receiving breast cancer RA by Tyrer-Cuzick model) will be extracted by study team members from the electronic health record or data collection form. Study team members will establish the denominator for the primary outcome (number of patients eligible for breast cancer RA) by extracting data on the number of eligible women seen for medical visits at each clinic site from the clinic's electronic medical record or scheduling database.

Data collection for secondary outcomes will include the number of women offered RA, but declining; number of high-risk women identified; number of high-risk women pursuing risk-stratified screening; number of abnormal screening studies; number of cancers identified; and types of cancers identified. Data on these secondary outcomes will be obtained from the electronic health record. This data will be collected for 6 months following the completion of the stepped wedge trial.

Additional secondary outcomes of adoption and maintenance will be extracted from the electronic health record or data collection forms (described in section 5.2.6) by Vanderbilt research team members. Adoption outcomes will include the total number of clinics offering RA and the total number of providers offering RA during the implementation phase. Maintenance outcomes will include the total number of clinics offering RA and the total number of providers offering RA six months after the completion of the implementation period.

Data will be collected during the control, implementation, and maintenance time periods of the stepped-wedge trial.

### 5.2.7 Consent

As enrollment will occur at the clinic level, rather than the individual level, and the study intervention is considered usual care, consent from individual participants will not be obtained. We will use a data use agreement to obtain data from the electronic health record and the clinic data collection forms from the enrolled clinics.

### 5.2.8 Data Analysis

Data will be summarized using mean +/- standard deviation. Generalized linear mixed models for binary outcome will be used to assess difference in the proportion of participants receiving breast cancer RA between control and intervention groups, stratifying by clinic size, rural vs. urban location, race/ethnicity, socioeconomic status, and time, with a nested random-effect for subjects within clinic clusters. Adjusted odds ratio (OR) with 95%

confidence interval (CI) will be reported. Interaction between intervention and time will be assessed. All tests of statistical significance will be two-sided. Findings will be considered significant if $p<0.05$.

### *5.3 Acceptability and Appropriateness*

5.3.1 Purpose

Assess acceptability and appropriateness with an integrated mixed-methods analysis including surveys and interviews of patients and healthcare team members recruited from the 10 clinic sites enrolled in the stepped-wedge trial.

5.3.2 Healthcare Team Survey

Healthcare Team Survey: During the maintenance phase of the stepped-wedge trial, we will distribute a web-based REDCap survey via email to providers, staff, and administrators in the enrolled clinics to obtain data on acceptability, appropriateness, and intent to continue using the breast cancer RA tool. We will use adapted versions of the Acceptability of Intervention Measurement (AIM) and the Intervention Appropriateness Measure (IAM) scales. Up to 4 weekly email reminders will be sent weekly to non-responders to increase response rate. **[see REDCap survey – Approp, Accept]**

Recruitment and Eligibility: The Vanderbilt team will perform recruitment for the Healthcare Team Survey via email with the guidance of the clinic site champions **[see Recruitment Email – Survey]**. The Vanderbilt team will respond via email or phone to answer additional questions potential survey respondents may have. The survey sample will consist of approximately 10 individuals per clinic (N = 100). Sample size at individual clinics may vary due to differences in the number of providers and staff at each clinic. Eligible individuals will be age 18 and older and will be a provider, staff, or administrator employed in a clinic enrolled in the study.

Data Collection Methods: Data will be collected and stored via REDCap, a secure online data collection tool.

Consent: We will request a Waiver of Documented Consent for the Healthcare Team Survey. Consent will be implied by completion of the survey. Participants will be provided with study information at the beginning of the survey.

5.3.3 Healthcare Team Interviews

Healthcare Team Interview: We will conduct semi-structured interviews during the maintenance phase with key informants. Interview guides will explore in more detail the results of the provider survey. We will elicit information about the acceptability and appropriateness of implementing our selected breast cancer RA strategies **[see Interview Guide – Healthcare Team]**. These interviews may be performed via telephone. Interviews are anticipated to last approximately 45-60 minutes.

Recruitment and Eligibility: The Vanderbilt team will recruit Healthcare Team members from the enrolled clinics with the guidance of the site champion for interviews via email, phone, or in person **[see Recruitment Email - Interview, Recruitment Script –Interview, Interview – Information Sheet].** The Vanderbilt team will recruit approximately 5 key informants per clinic (N=50) including individuals such as administrators, site champions and clinic providers (i.e. nurses and physicians). Site champions will help to identify participants for the Healthcare Team Interviews. Recruitment will stop when the team feels that we have reached data thematic saturation. Participants in these interviews may have complicated the Healthcare Team Survey, but that will not be a requirement. Eligible individuals will be age 18 and older and will be a provider, staff, or administrator employed in a clinic enrolled in the study.

Remuneration: Healthcare team members participating in interviews will be offered a $50 incentive in appreciation of their time.

Data Collection Methods: Interviews will be digitally recorded via audio recorders with participant permission, transcribed verbatim, and coded by two research team members using a codebook. If participants choose not to be recorded, the interviewer will take notes on their responses. Any identifying information that are part of the participants response will be removed from the transcriptions. Original interview recordings will be destroyed once transcribed. The responses to all the interviews will be summarized. When the specific responses from individual organizations are quoted, the organization or person's name will not be identified.

Consent: We will request a Waiver of Documented Consent for the Healthcare Team Interviews. Consent will be implied by participation in the interview. Written consent will not be obtained. Interview participants will be provided with a study information sheet. **[Interview – Information Sheet]**

5.3.4 Patient Interviews

Patient Interview: We will conduct semi-structured interviews with patients who recently had breast cancer RA. Site champions will help to identify appropriate patient participants. These interviews will help us to understand the patient perspective on breast cancer RA. **[see Interview Guide – Patient]**. These interviews may be performed via telephone, in person, or via computer. Interviews are anticipated to last one hour or less.

Recruitment and Eligibility: Clinic sites will identify potential participants for interviews via telephone, email, or in person **[see Patient Interview - Recruitment Email (for clinic), Patient Interview - Recruitment Script (for clinic)]**. Clinic staff will identify these potential participants through their own electronic health record or word of mouth. Clinical staff will ask potential patient participants if they 1) prefer to provide their contact information so the Vanderbilt team can contact them directly or 2) if they prefer to contact the Vanderbilt team themselves. At the participant's preference, the clinic sites will either 1) obtain patient's preferred method of contact (phone call [with an introductory text message] or email) and contact information or 2) provide contact information for the study team to patients.

The Vanderbilt research team will store this participant contact information (name, email address, phone number) in a password protected file on an institutional secure server such as OneDrive. This information will not be connected in any way to participant interview data. This information will be destroyed at the earliest time possible **[**see **Patient Interview - Contact Information Form]**. Once the participant and the Vanderbilt team are connected, the team will share more information about the study and enroll those who are interested.

For patients preferring a phone call, a text message will be sent prior to the phone call to familiarize the participant with the phone number of the caller **[**see **Patient Interview - initial text message before recruitment phone call]**. If the Vanderbilt research team member calls the patient's phone and does not reach the patient, the research team member will leave a voice mail [see **Patient Interview - voicemail before recruitment script**]. When the research team member reaches the patient on the phone, they will describe the study [see **Patient Interview - Recruitment Script (for research team)**]. For patients preferring an email, an email will be sent [see **Patient Interview – Recruitment Email (research team)**].

The Vanderbilt research team member will discuss the study with the patient by email or phone call. If the patient agrees to participate in the interview, the Vanderbilt research team member will schedule the interview and then send the patient the Patient Information Sheet via email or text message [see **Interview - Information Sheet**, see **Patient Interview - Provision of patient study information sheet via email or text message**]. The day before and the day of the interview, the Vanderbilt research team member will send the patient a reminder text message or email about the interview [see **Patient Interview - reminder text message or email**].

We will recruit approximately 50 patients for interviews. Recruitment will stop when the team feels that we have reached data thematic saturation. Eligible individuals will be women who were age 25-49 and had breast cancer RA performed at a clinic site that was enrolled in the BRAVE study during the study time period.

Remuneration: Patients participating in interviews will be offered a $50 incentive in appreciation of their time. In order to provide remuneration, the research study team will collect the patient's preferred method of receiving remuneration (email, standard mail). The Vanderbilt research team will store this participant contact information (name, email address, mailing address phone number) in the password protected file described above on an institutional secure server such as OneDrive. This information will not be connected in any way to participant interview data. This information will be destroyed at the earliest time possible.

Data Collection Methods: Interviews will be digitally recorded via audio recorders with participant permission, transcribed verbatim, and coded by two research team members using a codebook. If participants choose not to

be recorded, the interviewer will take notes on their responses. Any identifying information that are part of the participants response will be removed from the transcriptions. Original interview recordings will be destroyed once transcribed. The responses to all the interviews will be summarized. When the specific responses from individual organizations are quoted, the organization or person's name will not be identified.

Consent: We will request a Waiver of Documented Consent for the Patient Interviews. Consent will be implied by participation in the interview. Written consent will not be obtained. Interview participants will be provided with a study information sheet. **[see Interview - Information Sheet]**

5.3.5 Data Analysis

We will use descriptive statistics to examine quantitative outcomes of reach, acceptability, and appropriateness. Continuous measurement will be summarized using mean ± standard deviation or median and interquartile range. The AIM and IAM scores with 95% confidence intervals will be calculated. Summary tables and graphs will be created to describe and visualize the data. Qualitative data will be analyzed using inductive coding to identify emerging themes.

## 6. Total Recruitment

### *6.1 Feasibility*

The Vanderbilt team will recruit approximately 60 participants from healthcare clinics across the state of Tennessee to participate in the Feasibility Assessment. Recruitment of clinics to participate in this assessment will occur via email through established local connections. Eligible individuals will be age 18 and older and employed in a healthcare clinic providing breast care services in the state of Tennessee.

### *6.2 Reach*

The Vanderbilt team will recruit and enroll a total of 10 healthcare clinics across the state of Tennessee to participate and will collect data on reach and clinical outcomes. Recruitment will occur via email and via personal contact using established local connections. Individual women will NOT be enrolled in the study or consented as the study intervention is considered usual care. At the clinics enrolled in the study, we will collect data from individual health records on women patients who are seen by the clinic. We anticipate that we will collect clinical data on approximately 3,000 individual women ages 18-49 during the time of the stepped-wedge trial. We will obtain a HIPAA waiver to collect data from the electronic medical record.

### *6.3 Acceptability and Appropriateness*

Healthcare Team Survey: The Vanderbilt team will recruit approximately 100 individuals from the 10 clinic sites enrolled to complete the Healthcare Team survey. Eligible individuals will be age 18 and older and will be a provider, staff, or administrator employed in a clinic enrolled in the study.

Healthcare Team Interview: The Vanderbilt team will recruit approximately 50 individuals to participate in Healthcare Team Interviews. These individuals may have completed the Healthcare Team Survey, but this will not be a requirement. Eligible individuals will be age 18 and older and will be a provider, staff, or administrator employed in a clinic enrolled in the study. Participants will be offered $50 remuneration for participation.

Patient Interview: The Vanderbilt team will recruit approximately 50 individuals to participate in a Patient Interview. Eligible individuals will be women who were age 25-49 and had breast cancer RA performed at a clinic site enrolled in the BRAVE study during the study time period. Participants will be offered $50 remuneration for participation.

## 7. Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

There are no greater than minimal risks anticipated for participating in this study. Breast cancer RA is considered usual care as a clinical offering.

Participants completing surveys and interviews could potentially face minimal discomfort answering questions. Participants have the option of not answering any questions that make them feel uncomfortable and are free to end their participation at any time. Participants will also be provided with a study information sheet explaining

the study and be given the contact information for the study PI and IRB so they may reach out with questions at any time.

The minimal risk of participating in this study is outweighed by the potential benefit. The information gathered through the study will collectively help to identify the challenges, gaps, and opportunities for providers and patients regarding use of breast cancer risk assessment tools. This information gathered will also help to test the implementation of breast cancer risk assessment tools.

No adverse events are anticipated for this study. Although no adverse events are anticipated for this study, the PI will report any adverse events to the IRB immediately.

## 8. Study Withdrawal/Discontinuation

Participants (including clinic sites) are free to stop participating at any time without penalty. Participants in surveys and interviews may choose not to answer any questions that make them feel uncomfortable.

## 9. Privacy/Confidentiality Issues/Data Safety Monitoring

There will be no hard copy signed consent forms for the surveys or interviews since a Waiver of Documentation of Consent will be requested and consent to participate will be implied by completing the survey or participating in the interview. Participants will be provided with study information.

Data from the electronic surveys will be stored in REDCap, a secure online platform. Deidentified, anonymous data downloaded from REDCap will be stored electronically in password protected VUMC Box folders.

The feasibility listening sessions and acceptability/appropriateness interviews will be recorded with digital audio recorders with participant permission. Recordings will be transcribed, and all identifiers will be removed from the transcription and notes. The responses to all the listening sessions and interviews will be summarized. When specific responses from individual organizations are quoted, the organization or person's name will not be identified. The recordings will be stored on password protected computers until they are transcribed, with access only available to study personnel. After the information is transcribed, the recording will be deleted.

Electronic data abstracted from clinic electronic medical records and the clinic data forms will be stored in password protected Box folders or within REDCap. Data will be deidentified at the earliest time possible. Any data on paper forms will be stored in a locked cabinet in a locked office at VUMC.

Contact information for the patient interviews will be stored in a password protected file on a secure server. This information will be destroyed at the earliest time possible.

Only study team personnel will have access to the data.

We will obtain a data use agreement with each enrolled clinic to obtain clinical data.

## 10. Follow-up and Record Retention

We will maintain the electronic data files on a password protected computer and paper data files in locked cabinets in locked offices, with access available to study personnel only. We will maintain the files for at least six years after the research is completed.