

Social and Behavioral Sciences Human Research Protocol

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PROTOCOL TITLE

Improving utilization of supplemental breast MRI screening for women with extremely dense breasts

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INTRODUCTION AND PURPOSE

Women with dense breasts have 3-5-fold increased risk for breast cancer as women without dense breasts.^{1,2} Dense breast tissue can “mask” small tumors, leading to reduced mammography sensitivity. Recent randomized controlled trials demonstrate that supplemental breast MRI screening improves detection of small, invasive cancers that are not detected by mammography.³⁻⁵ The DENSE trial randomized over 40,000 women with dense breasts to breast MRI screening or mammography alone, and found that MRI reduced the interval cancer rate by 50%.⁴ The American College of Radiology’s 2021 Appropriate Use Criteria specifies that supplemental breast MRI screening “may be appropriate” for all women with dense breasts, and is “usually appropriate” for women with dense breasts and high risk based on other factors.⁶ In January 2022, a Pennsylvania law went into effect mandating insurance coverage of supplemental screening for women with extremely dense breasts.⁷ Currently only a small fraction (<8%) of eligible women with extremely dense breasts at Penn Medicine are receiving supplemental breast MRI screening. Clinical pathways to identify patients who are eligible for insurance coverage of supplemental breast MRI screening and communicate this option to patients and providers are needed. We therefore propose a stepped wedge cluster randomized clinical trial to determine whether electronic health record (EHR) and secure text message nudges increase utilization of supplemental breast MRI screening among eligible women with extremely dense breasts.

OBJECTIVES

Aim 1. To develop provider-and patient-directed nudges for supplemental breast MRI screening for women with extremely dense breasts.

Aim 2. To test the effect of provider-and patient-directed nudges on ordering and/or scheduling of supplemental breast MRI screening among women with extremely dense breasts. Secondary outcomes will include ordering of MRI and scheduling of MRI analyzed separately, receipt of breast MRI screening, false-positive rate and cancer detection rates.

Aim 3. To compare the effect of nudges on utilization of supplemental breast MRI screening for Black and White women.

Aim 4. To determine the sustainability of changes in MRI engagement behavior following the removal of study interventions. This aim solely involves data review; no individuals will receive an intervention.

Primary Outcome Variable

The primary outcome is ordering or scheduling of supplemental breast MRI within 6-months of receiving a nudge.

Secondary Outcome Variables

The secondary outcomes will include ordering of MRI, scheduling of MRI, completion of a supplemental breast MRI, as well as clinical measures for those who complete MRI screening, including cancer detection rate and false-positive rate.

BACKGROUND AND RATIONALE

Significance

Among 38,077 women screened across Penn Medicine in 2021, 2,670 (7.0%) had extremely dense breasts (**Table 1**), but only 204 (7.6%) received breast MRI through the end of 2021. This represents clear underutilization of supplemental breast MRI screening and a missed opportunity to improve early detection among high-risk women. Furthermore, utilization of breast MRI screening is abysmally low for Black women. Among 390 Black women with extremely dense breasts, only 11 (2.8%) received an MRI, compared with 9.2% of White women with extremely dense breasts. Black women have 40% higher breast cancer mortality than White women, and higher incidence of triple negative breast cancer, which is less likely to be detected by mammography than other subtypes.⁸ Thus, breast MRI screening may be particularly beneficial for Black women. With the recent passage of the PA supplemental screening law, now is an opportune time to develop and test tools to raise awareness of supplemental breast MRI screening among both providers and patients in order to increase breast MRI screening utilization overall, and particularly for Black women.

Table 1: Negative Mammograms, Breast Density and MRI utilization at Penn Medicine in 2021			
	Negative/ Benign Mammo	Extremely dense breasts	MRI among extremely dense
	N	N (%)	N (%)
HUP	12,034	549 (4.6%)	79 (14.4%)
PAH	12,009	1422 (11.8%)	43 (3.0%)
PMC	4,258	111 (2.6%)	1 (0.9%)
Radnor	9,776	588 (6.0%)	81 (13.8%)
Total	38,077	2,670 (7.0%)	204 (7.6%)
White	19,271	1,764 (9.2%)	167 (9.5%)
Black	13,964	390 (2.8%)	11 (2.8%)

Innovation

We will employ an innovative, multilevel intervention to quickly disseminate information regarding supplemental screening to both providers and patients. Our pilot will occur in the setting of recent clinical implementation of abbreviated MRI screening (AB-MR). Full breast MRI screening is time consuming and costly. While insurance coverage is now mandated, copays can still create a financial barrier. AB-MR screening protocols take less than 10 minutes and have similar sensitivity as full protocol MRIs which take almost 30 minutes, reducing the cost of the procedure. A trial in the U.S. and Germany found that sensitivity for breast cancer was 95.7% for AB-MR compared with 39.1% for digital breast tomosynthesis (3D mammography, DBT) among women with dense breasts.³ Dr. Conant's recent study found the cancer detection rate for AB-MR at Penn Medicine was 27.4 per 1000 among women with dense breasts and a recent negative or benign DBT screen⁵, a clinically significant increase over DBT screening alone. Penn Medicine is a national leader in AB-MR, and it has built clinical capacity to expand AB-MR to all women who qualify.

Specific biases exhibited by patients and clinicians can reduce engagement with and recommendation of supplemental breast MRI screening, including *focusing effect bias* (placing greater weight on past experiences, informing our future expectations with them) and *availability bias* (placing greater importance on readily available examples in our minds than what applies to

reality). Thus, complex and overlapping behavioral economic constructs play a significant role in determining referral and engagement decision-making, and therefore targeting these constructs could significantly improve the endeavor of increasing engagement of patients with dense breasts with supplemental breast MRI screening.

This study will be one of the first in the oncology setting to compare effectiveness of nudges to clinicians and patients as implementation strategies to improve supplemental breast MRI screening referral and engagement. It builds upon our prior work and targets biases among both clinicians and patients, addressing known barriers to undergoing and making referrals to supplemental screening in women with dense breasts, who are at higher risk for later detection of breast cancer and thus worst outcomes. The intervention is designed to minimize interference with established workflow while incorporating attention to the motivation needed to make behavior changes in regards to supplemental screening.

CHARACTERISTICS OF THE STUDY POPULATION

1. Target Population and Accrual

To be eligible, patients must be women with dense breasts, aged 40 to 74, who have had a non-actionable mammographic screening event within the past six months at one of four centers: Penn Center for Advanced Medicine, Penn Presbyterian Hospital, Pennsylvania Hospital, or Radnor. Based on data from mammograms between January 2022 and December 2022, an estimated number of 1,600 patients will be randomized to one of four arms (Table 2), with about 400 patients per arm. We have identified about 1,100 clinicians who are eligible to be included in this study. Based on the above data on mammograms, we estimate that in the 12 months following the closure of the intervention period, an additional 1,600 patients will fulfill eligibility criteria and will be appropriate for Aim 4 (data review of patients identified during the sustainment period).

Patient Interviews

We will conduct structured interviews with approximately 30 patients purposively sampled to assure variation in ethnicity/race, study arm, and study outcome. Patients will be sampled from the patients accrued over the course of the study.

Clinician Survey

After patient enrollment into the trial concludes, we will survey participating clinicians to gather feedback on the implementation strategies and understand more about barriers and facilitators to engagement with supplemental screening for breast cancer. Clinicians will be sampled from those who accrued over the course of the trial. Approximately 100 have been identified as eligible, and we anticipate a response rate of about 40%, resulting in a target of about 40 respondents to the clinician survey.

2. Key Eligibility Criteria

Patient participants must meet the following criteria for enrollment:

Key Inclusion Criteria

- Women aged 40-74
- Recent non-actionable mammogram of less than 6 months
- Mammogram performed at Penn Center for Advanced Medicine, Penn Presbyterian Hospital, Pennsylvania Hospital, or Radnor
- Valid mobile phone number

Key Exclusion Criteria

- Prior history of breast cancer
- No breast MRI within the past 2 years
- No prior actionable mammogram within 6 months
- No recent or concurrent ultrasound

Provider participants must meet the following criteria for enrollment:

Key Inclusion Criteria

- Provider needs to have ordered the initial screening mammogram
- Employed by Penn Health System and access to Penn Chart
- To be contacted for survey recruitment, providers must have authorized at least three mammogram orders for patients with extremely dense breasts within the study window

Key Exclusion Criteria

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3. Subject Recruitment and Screening

We will seek a waiver of informed consent. The trial is pragmatic in nature, assessing the impact of implementation strategies delivered to clinicians and patients through minor adjustments to existing workflow delivered through the electronic health records (EHR). Changes to workflow are by necessity systematically applied to all clinicians within the practices, as well as their patients. We will obtain a waiver of informed consent for clinicians and patients for pragmatic trial activities accomplished for Aims 1 & 2. Aim 3 will not require additional participants; it will include data from all randomized provider practices, as well as patient-level EHR data for all patients treated by the clinicians in the sample set during the study period. Aim 4 involves reviewing data from the electronic health record and no interventions or patient interaction with the study team. We will seek a waiver of informed consent for this aim as well. Please see the “Informed Consent” section below for additional detail.

We view this project as a quality improvement initiative (with data collection to allow for corresponding evaluations of the initiative). As a result, the changes introduced to the EHR (i.e., nudges to promote utilization of supplemental breast MRI screening in women with extremely dense breasts) will be considered standard of practice within the healthcare system, thereby allowing for a waiver of informed consent for both clinicians and patients. It is important to note that clinicians and patients involved in the project will not be assigned a change in treatment; clinicians are still free to refer or prescribe, or not refer or not prescribe, as they see fit. Instead, they are being reminded of an evidence-based practice (EBP) guideline and offered an opportunity to review pertinent information and refer to and/or prescribe the EBP (or not) as clinically appropriate. Thus, the implementation strategies offer minimal risk to clinicians and patients. This approach to informed consent and data collection will also aid implementation integrity and generalizability by avoiding behavior changes related to being observed (i.e., the Hawthorne effect). In other words, this initiative could not practicably be carried out without the waiver as obtaining consent would introduce significant bias into the work, preventing the ability to achieve the aims and achieve the study goal: improving evidence-based supplemental breast MRI screening within cancer care. We see this study as similar to those which have received waivers from our Institutional Review Board before.^{10, 11, 12, 13}

Patient Interviews:

Following enrollment in the study, patients who have completed the 6-month follow up window will be randomized to be recruited for qualitative interviews. Eligible interview participants will be identified through EHR data pulls that are occurring as part of screening for the larger study. Recruitment will include an initial letter sent to their main address, followed by up to three phone calls from the research coordinator. The patient will be asked to consent to participation. If consent is obtained, a 30-minute interview time slot will be scheduled through Penn's Mixed Methods Research Lab. If the patient declines participation in the qualitative interviews, they will no longer be contacted.

Clinician Survey

After patient enrollment into the trial concludes, we will recruit clinicians who accrued over the course of the trial to share feedback on the implementation strategies and describe barriers and facilitators to engagement with supplemental screening for breast cancer. The recruitment plan will involve partnering with service line leaders to share an announcement about an upcoming survey, followed by automated emails to individual clinicians with a personalized email containing a link to a REDCap survey. All clinicians will be directed to a consent form outlining the survey and its goals; the voluntary nature of participation; risks, benefits, and strategies for preserving confidentiality; and compensation for participation. We will send reminders via email for clinicians who do not respond to the initial invitation.

As this survey will be implemented electronically, we seek a waiver of written consent, as we have obtained for similar REDCap surveys (e.g., IRB 844846). Additional detail can be found in the "Informed Consent" section of this protocol.

4. Early Withdrawal of Subjects

We are requesting a waiver of informed consent, so the option to early withdraw from this study is not applicable for Aims 1, 2 and 3 of this project.

Patient Interviews

The steps to withdraw early from participation in patient interviews will be outlined during the consent process. See the Consent Process section below for more details.

Clinician Survey

If clinicians elect not to participate, they can choose not to click on the link to the REDCap survey.

5. Vulnerable Populations

Children, pregnant women, fetuses, neonates, or prisoners are not being targeted in this research study.

6. Populations Vulnerable to Undue Influence or Coercion

We will not be targeting participants who are likely to be vulnerable to undue influence or coercion. Clinicians employed by Penn may experience undue influence to take part in this study and, as outlined in <https://irb.upenn.edu/sites/default/files/IRB%20SOP%20V.11.1-06.2019-Clean.pdf>, efforts are needed to prevent against this potential. To this end, we will send a formal general notification to all clinicians regarding the proposed study, indicating that it will involve data ascertainment from the EHR, that they can opt out, and that decision to opt out will

be confidential. All practices will be informed of the study through their leadership figures. Since this study includes only best practice recommendations, the providers can opt out of the research simply by not following these recommendations and not referring their patients to supplemental breast MRI screening.

STUDY DESIGN

1. Study Design

Aim 1. We will develop provider-directed and patient-directed nudges to notify them about the recommendation of supplemental breast screening MRI screening for women with extremely dense breasts.

Aim 2. We will test the effect of provider-and patient-directed nudges on ordering and/or scheduling of supplemental breast MRI screening among women with extremely dense breasts. Secondary outcomes will include ordering of MRI and scheduling of MRI analyzed separately, receipt of breast MRI screening, false-positive rate and cancer detection rates.

Aim 3. We will explore the effect of the provider-direct and patient-directed nudges on the utilization of supplemental breast MRI screening between Black women and White women.

Aim 4. We will determine the sustainability of changes in MRI engagement behavior following the removal of study interventions. We will assess outcomes used for Aim 2 (e.g., MRI ordering) in the period after the nudges were removed.

2. Study Duration

The nudges and EHR phenotyping algorithm will be developed over 4 months. The deployment of the intervention will be 12 months total, with participants receiving nudges within two weeks of their appointment. These will be followed by a follow-up period of 6 months over which outcomes will be ascertained and analyzed. Data review for Aim 4 (“sustainment”) will begin during the 6-month follow-up period and will continue for an additional 6 months, resulting in patients being identified over 12 months total. As with the patients enrolled during the intervention period, patients identified during the “sustainment” period will have their outcomes ascertained over the ensuing 6 months.

METHODS

1. Study Instruments

Any study instruments will be submitted to the IRB as a modification prior to use.

Patient Interviews:

Patients will be invited to complete a qualitative interview. The interview questions were developed in conjunction with implementation science and qualitative analysis experts. Generally, patients will be asked questions about their experience receiving breast cancer screening at Penn Medicine, their knowledge of breast density and supplemental MRI, their recollection and opinions

of this study's intervention, and the barriers they faced when scheduling or completing supplemental breast MRI. These interviews are expected to take less than 30 minutes.

Clinician Survey

Clinicians will be invited to complete a brief survey (expected time of ~10 minutes) with questions developed in partnership with clinicians and implementation science experts. Clinicians will be asked about their current practices associated with supplemental screening for breast cancer, their understandings of strategies to promote supplemental screening, and barriers and facilitators to engaging with breast MRI.

2. Administration of Surveys and/or Process

Aim 1, 2, 3, & 4. No surveys will be administered to patients as part of the main pragmatic trial or as part of the sustainment period. A follow-up survey will be implemented for clinicians upon the conclusion of patient enrollment.

Clinician Survey

Clinicians will be sent a personalized link to a REDCap survey and will be able to complete the survey on their own time. If clinicians elect to participate, they will be directed to a consent form, where they can review the logistics of the survey and confirm their understanding and interest in participating. Once they have provided consent, clinicians can answer the questions online and submit responses when they are ready. Upon submission, study staff will provide compensation to respondents.

Patient Interviews:

Patients will be contacted to schedule a time to conduct the interview with a member of Penn's Mixed Methods Research Lab. Once the interview is scheduled, the participant will complete the interview via phone or video call. Participants will be consented before any interview activities occur. All interviews will be audio recorded and transcribed. See the Informed Consent section for more details regarding this process.

3. Data Management

To minimize the risk of breach of data and confidentiality, we will use secure, encrypted servers to host the data and conduct the analysis. The Penn Medicine Academic Computing Services (PMACS) will be the hub for the hardware and database infrastructure that will support the project. The PMACS is a joint effort of the University of Pennsylvania's Abramson Cancer Center, the Cardiovascular Institute, the Department of Pathology, and the Leonard Davis Institute. The PMACS provides a secure computing environment for a large volume of highly sensitive data, including clinical, genetic, socioeconomic, and financial information. PMACS requires all users of data or applications on PMACS servers to complete a PMACS-hosted cybersecurity awareness course annually, which stresses federal data security policies under data use agreements with the university. The curriculum includes Health Insurance Portability and Accountability Act (HIPAA) training and covers secure data transfer, passwords, computer security habits and knowledge of what constitutes misuse or inappropriate use of the server. We will implement multiple, redundant protective measures to guarantee the privacy and security of the participant data. All investigators and research staff with direct access to the identifiable data will be required to undergo annual responsible conduct of research, cybersecurity, and HIPAA certification in accordance with University of Pennsylvania regulations. Data will be stored, managed, and

analyzed on a secure, encrypted server behind the University of Pennsylvania Health System (UPHS) firewall. All study personnel that will use this data are listed on the IRB application and have completed training in HIPAA standards and the CITI human subjects research. Data access will be password protected. Whenever possible, data will be deidentified for analysis.

4. Subject Follow-up

Subjects will be followed for approximately 6 months after enrollment. A separate pool of patients, identified after the close of the intervention period, will be reviewed for fulfilling eligibility criteria for a period of 12 months. All patients deemed eligible during this 12-month “sustainment” period will be followed for 6 months to ascertain outcomes.

STUDY PROCEDURES

1. Detailed Description

We will employ a stepped wedge cluster randomized clinical trial to test the independent and joint effects of provider and patient nudges on MRI utilization. We will cluster randomize ordering providers by clinic group and individually randomize patients, resulting in four study arms described in **Table 2**. Based on data between January 1st, 2022, and December 31st, 2022, we expect approximately 1,600 women with extremely dense breasts to be randomized, approximately 400 per arm. We currently have identified an estimated 1,139 distinct ordering providers within this period practicing in the specialties of family medicine, internal medicine, and OB/GYN: 1,058 primary care providers (both internal medicine and family medicine) and 81 OB/GYN providers. Clinics across the four sites will be aggregated in 10 steps. The steps determine the order in which the cluster will make the transition from standard care to clinician nudge. We will refine our study design (e.g., exclude practices with small numbers of referred patients) as needed in consultation with the ISC3 statistical core. Nudges will be deployed outside of a clinic visit within two weeks of receiving a mammogram. Text messages will be sent via Penn’s secure Way to Health platform. Prior to receiving the nudge, patients will confirm their identity and express interest in learning more. Nudge message content was developed with input from patient and clinician partners and subject matter experts in behavioral economics. Rapid cycle testing was implemented to test three patient-directed nudges with 180 patients prior to launching the study intervention. The patient nudge targeting availability bias and the endowment effect was chosen, as it correlated with more clinician communication and improvements in MRI ordering. A provider nudge was chosen following discussion between the ISC3 team, practicing clinicians, behavioral economic experts, and radiology leadership. Provider nudges will be embedded within the mammogram report.

Sustainment analysis

After the intervention period closes and all nudges are removed, new patients that fulfill eligibility criteria will be tracked to determine whether behavior change is sustained beyond the trial period. In a retrospective data analysis at the end of this “sustainment” period, the same outcomes as in the main trial (i.e., MRI ordering, scheduling, completion) will be pulled for eligible patients. Patients will be screened for eligibility for 12 months, with an additional 6 months allotted for completing all outcomes. In line with estimated enrollment during the trial period, we anticipate 1,600 patients will fulfill eligibility criteria during the “sustainment” period. No interactions will be had with these patients or their providers, and no one will receive any study interventions during

this time. Data will be collected and securely stored in accordance with the procedures previously approved for use as part of the main trial.

Table 2: 2x2 factorial design

Table 2 Study Design		Providers (cluster randomized by clinic group)	
		No nudge	Nudge
Patients (Individually randomized N~3000)	No nudge	Usual care (no nudge)	Provider nudge only
	Nudge	Patient nudge only	Patient and provider nudge

Development of message content

For Aim 1, we developed nudges to be deployed to women with a recent mammography report of extremely dense breasts and to the ordering provider. To develop nudge content, we consulted with a wide range of stakeholders. Three patient-directed nudges were drafted that varied in terms of bias being targeted and contained a link with additional information and how to contact their provider. We conducted an RCA study with 180 mammography patients to assess the content of the patient nudges and delivery method in motivating uptake of supplemental breast MRI screening. The nudge with the most engagement and MRI scheduling was selected and will be deployed as the patient nudge. A provider-directed nudge was developed after consulting with our stakeholders and will be embedded in the impression section of mammogram reports.

EHR phenotyping

We will work with the ISC3 team to develop an EHR phenotyping algorithm to prospectively identify women with extremely dense breasts with no prior history of breast cancer and who had a recent negative mammogram to whom we will deploy the intervention. Patients will be excluded if they received supplemental screening in the past 12 months. Notification of breast density to patients is federally mandated.^{7,9} Breast density is available as a hard coded field through the EPIC Radiant Radiology Information System, which we will use to obtain breast density. We will include women undergoing mammography at the Penn Center for Advanced Medicine, Penn Presbyterian Hospital, Pennsylvania Hospital, and Radnor. Aim 2 will explore the effect of the provider-directed and patient-directed nudges on supplemental breast MRI screening among women with extremely dense breasts. The primary measure of implementation is the ordering or scheduling of supplemental MRI screening following the distribution of the nudge. The secondary measures are ordering of MRI, scheduling of MRI, completion of an MRI within 6 months of receiving the nudge, cancer detection rate and the false-positive rate among those women who undergo supplemental breast MRI screening. Lastly, Aim 3 will explore how the nudges affects the utilization of supplemental breast MRI screening in White women in comparison to Black women.

Patient Interviews

Recruitment for patient interviews will begin in the eighth month of the study. Patients will be purposively sampled from the entire study population. Initially, 60 patients will be recruited. If 30 interviews are not reached, another round of recruitment will commence. Recruitment includes an initial letter sent to a patient's main address. This letter outlines the study, asks the patient to participate in the interview, and provides contact information to our study team. Following the letter, the research coordinator will call the patient to follow up. If the patient consents to participate, a 30-minute interview time slot will be scheduled through Penn's Mixed Methods Research Lab. If the patient declines participation in the qualitative interviews, they will no longer

be contacted. Recruitment will continue until we reach ~30 total participants. The interview includes questions about the perceptions of breast cancer screening at Penn, views on supplemental breast cancer screening, recollection of this study's intervention, and barriers that impacted their ability to get supplemental breast MRI.

Chart Review

The study team will conduct reviews of study patients' charts to evaluate conversations that happen between patients, nurses, and clinicians about supplemental breast cancer screening. We will identify trends of how providers and patients view supplementing mammography with breast MRI for women with extremely dense breasts. Furthermore, we will identify barriers and facilitators for supplemental MRI.

Clinician Survey

Following the conclusion of patient enrollment, clinicians who have authorized the ordering of mammograms will be recruited to participate in a brief survey on their current practices associated with supplemental screening for breast cancer, their understandings of strategies to promote supplemental screening, and barriers and facilitators to engaging with breast MRI (such as those identified in the chart review noted above). An initial announcement about the survey will be followed by individual emails outreach and reminder messages.

Plan for future investigation

Pilot study results will support an R01 targeted to NIH Program Announcement PAR-21-190 Modular R01s in Cancer Control and Population Sciences, which would expand the intervention to women with heterogeneously dense breasts. This requires ascertainment of additional breast cancer risk factors, exploring barriers and adapting our intervention to further increase utilization of supplemental breast MRI screening.

2. Data Collection

The EMR and other Penn Medicine secondary databases will be used to collect information on practices, providers, and patients. These systems are used to routinely collect this information for patient care. Once collected, data are maintained on password-protected computers. The data will be maintained in spreadsheets, access databases, and REDCap, with access limited to study staff.

For ordering providers, we will extract the following information: First Name; Last Name; Site and location; Region; Practice; Practice type and specialty; NPI; Patient panel size; Patient mammogram referral; Extremely dense breast patients; Ordering provider type and specialty; Authorizing provider, first name, last name, provider type and specialty; provider NPIs.

For patients, we will extract the following information: MRN; Referring Clinician; First Name; Last Name; DOB; demographic information; Street Address; City; State; Zip; Preferred Phone Number; Alternate Phone Number; Email; Primary Health Insurance; Secondary Health Insurance; breast density; Mammogram Report Date; site of primary care MRI scheduling information/date; MRI completion/date. Breast MRI result; false positive MRI; Biopsy recommendation; Biopsy date; Biopsy result; Cancer diagnosis; cancer diagnosis date; and any additional variables related to breast imaging procedures, dates, and outcomes.

The above data from the EMR and other Penn Medicine databases will continue to be collected during the "sustainment" period to facilitate data review.

Patient Interviews:

All interview data will be collected via phone or video call and audio recorded. Audio recordings will be kept on a secure, password-protected file and transcribed by a HIPAA-compliant transcriptionist. The transcriptions will be redacted for any identifiable information and saved on a secure file for analysis by the Mixed Methods Research Lab (MMRL). The MMRL is a research lab that is dedicated to fostering the use of qualitative and mixed methods research methodologies with a focus on integrating key stakeholder perspectives and goals into research design. The MMRL will oversee the transcription of all audio recordings to ensure all activities are consistent with Penn IRB and HIPAA guidelines and regulations. All MMRL staff involved in the project will be listed as study personnel on this protocol.

Patient names, contact information and demographics will be extracted from the medical record and shared securely with the study team for interview recruitment. During all recruitment activities with all potential participants, the research teams will make clear that participation in the research project is 100% voluntary and not mandatory. We will also ensure that leaders are aware that they cannot mandate that employees participate or that patients participate and that any involvement (or decision not to participate) in the proposed work will not have an adverse impact on their employment or care. All language used during the consenting process will incorporate required elements of consent and thoroughly describe the procedures to be followed in the study. All language used during the consent process and participant facing documents will be submitted to the Penn IRB prior to use.

Chart Review:

Patient-provider messages will be extracted from Electronic Health Records and entered into a spreadsheet. All patients who are enrolled in the study will be eligible for chart review. The spreadsheets will be accessible to the minimum necessary staff.

Clinician Survey

Data collected in this survey will be stored in REDCap, a HIPAA-compliant survey platform. Upon conclusion of the survey, data will be exported from REDCap onto secure servers administered by study personnel, which will allow for analysis. Access to these data will be limited to study staff.

3. Genetic Testing

Not applicable.

4. Use of Deception

Not applicable.

5. Statistical Analysis

We will evaluate the effectiveness of provider and patient nudges with an intention-to-treat analysis using logistic regression with generalized estimating equations (GEE) with the outcome of ordering and/or scheduling of breast MRI as the primary outcome with binary predictors for the patient nudge and provider nudge, adjusted for patient characteristics, provider specialty, and mammography site and with robust standard errors to account for clustering of patients within

practices. We will evaluate the interaction of patient and provider nudges. We will then perform analyses stratified by race, and test for interaction of race and the interventions. Secondary outcomes will also be modeled as binary outcomes using logistic regression with GEE. The proposed study timeline is provided in **Table 3**.

Table 3: Proposed Timeline	Month 1-4	5-8	9-12	13-16	17-20	21-24
Development of EHR nudges	X					
Development of EHR phenotyping algorithm	X					
Deploy Intervention		X	X	X		
Assess utilization of MRI screening					X	X
Data analysis						X
Manuscript writing and future grant planning						X

Following the above timeline, a “sustainment” period will be added during which no interventions will be active. During the “sustainment” period, patients will be screened for eligibility (i.e., aged 40-74, having extremely dense breasts, etc., as in the main trial) over the course of 12 months following the conclusion of the intervention period. These patients will be tracked for 6 months to ascertain the outcomes from the main trial (i.e., MRI engagement). After all patients have had 6 months to complete outcomes, data will be exported from the EMR for data analysis. In sum, this “sustainment” period will last for 18 months – 12 months for patient identification and 6 months for patient follow-up.

Power and Sample Size

Based on preliminary assessments via electronic phenotyping in the EHR, the target population will consist of approximately 1,600 patients at the four sites in our health system who may benefit from supplemental breast MRI screening. We calculated power requirements by simulation using Stata 17, assuming a logistic regression model fitted using generalized estimating equations (GEE), and found our sample gives us 80% power to detect 6% improvement in our primary outcome (e.g., from current 8% referral rate to 14%) for patient nudges, using a two-sided type 1 error rate of 5%, for planned comparisons between each sequence. The analysis provides similar power to detect 7% improvement from provider nudges, and a 10% difference representing the interaction between patient and provider nudges.

Qualitative Analysis of Patient Interviews and Chart Review:

This qualitative analysis is not designed to assess statistical significance, but rather to use innovative mixed methods approaches to generate hypotheses and identify frequently cited themes across individuals. We will use convergent mixed-methods analysis to code contextual conditions (e.g., facilitators and barriers to screening associated with individuals’ surroundings) and implementation conditions (e.g., characteristics of communication strategies). The constant comparative method, guided by grounded theory, will be used to iteratively identify *a priori* domains of interest (guided by the 5 CFIR domains, including biases from behavioral economics) and to inductively explore emergent themes. Our goal is to identify common themes in individuals’ experiences with breast cancer screening and our interventions to better understand the process of achieving our overall study outcomes. Quantitative ratings will be assessed using t-tests to compare averages (e.g., evaluating the extent to which each barrier is believed to have impacted decisions to get screening), and these comparisons will be integrated with the qualitative coding as part of mixed-methods analyses.

Clinician Survey

Descriptive statistics will be used to characterize the sample and identify the most common barriers and facilitators. We will conduct regression analyses to determine if responses differ based on demographic characteristics, experience level, and/or site.

Sustainment Period

The same quantitative analyses used to assess outcomes in the main trial will be used to assess outcomes during the sustainment period, with the exception that no evaluations will be made based on study arm because all interventions will have been removed. The purpose of the sustainment period is to determine the maintenance of engagement behavior without the reminders provided by the interventions.

RISK/BENEFIT ASSESSMENT

1. Risks

There are minimal risks to participants in this trial. Regardless of nudges, the intervention provided is FDA approved, providers routinely order screening as part of their standard of care, and patients routinely use MRI screening. The interventions could increase the time spent discussing supplemental breast MRI screening for high-risk women with extremely dense breasts. Shared-decision making is a high priority and evidence-based practice for cancer care and increased time on this topic is likely valuable. In our prior studies, nudges in the EMR were associated with minimal burden on practice staff and clinicians. There is a risk of breach of data and confidentiality; however, we described the precautions in place to securely manage this data in the “Data Management” section of this protocol. No additional risks are associated with the “sustainment” aim. New patients identified during the “sustainment” period will not receive any interventions, and as in the trial period, data collected will be securely managed as outlined in the “Data Management” section of this protocol.

Patient Interviews:

Potential harms to participants are minimal and there is no known physical, financial, or legal risks to participating in the study. However, participants will be asked about their perspectives and experiences at their respective sites. Participants may feel temporarily uncomfortable while participating in the interview. An additional risk is the potential for loss of confidentiality. Sensitive personal information may be revealed during this process. All information shared during interviews will be kept private and confidential. No identifiable information from patients will be shared with any individuals outside of the study procedures outlined in this protocol. We described the precautions in place to securely manage this data in the Data Management section of this protocol.

Clinician Survey

While there is some risk associated with potential loss of confidentiality for survey respondents, we will maximize security using strategies we have implemented for prior survey-based studies (e.g., IRB #844846) and the “Data Management” section of this protocol.

2. Benefits

Clinicians and patients will receive no direct benefits from participating in this study. Participants who are part of this trial will benefit from the knowledge that they are contributing in an important way to potentially furthering scientific knowledge concerning ways to improve evidence-based

practice. The knowledge gained on how to increase evidence-based practice could be applied to other populations and implemented at other health systems. Patients may benefit from being more likely to undergo supplemental breast MRI screening.

3. Subject Privacy

Privacy will be given utmost consideration and is highly valued in the proposed research. No research activities involve any direct interaction with subjects that would pose risk to their privacy.

4. Subject Confidentiality

Confidentiality refers to the subject's understanding of, and agreement to, the ways in which identifiable information will be stored and shared.

How will confidentiality of data be maintained?

- ☐ Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.
- ☒ Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.
- ☒ Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.
- ☒ Whenever feasible, identifiers will be removed from study-related information.
- ☐ A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.
- ☒ A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)
- ☒ Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.
- ☐ Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.
- ☐ Other (specify):

To protect participant confidentiality, only the research team outlined in HSERA will have access to review identified research records. Confidentiality will be protected to the fullest extent allowable under the law. See the Data Management section for more details.

If any data needs to be transmitted, it will be done through a Penn-approved secure encrypted file transfer solution as is described in Penn IRB's Guidance on Electronic Data Protection Requirements for Research Involving the Use of PHI. Records will not be released without the participant's consent unless required by law (e.g., imminent risk of harm to self-suspected) or court order. When results of the research are presented at scientific meetings or published, no identifying information will be included.

All identifiable data, including the master list linking identifiers to the ID number and recordings, will be destroyed in 2031, seven years after the conclusion of the study.

5. Protected Health Information

- Name
- Address
- Date of birth
- Phone number(s)
- Email address
- Medical record number
- Accession numbers of images
- Dates of breast imaging and follow-up procedures
- Dates of breast cancer diagnosis

6. Compensation

Aims 1, 2, 3 & 4. Participants will not be compensated for participating.

Patient interviews:

Participants will be compensated with a \$50 gift ClinCard after completing the interview.

Clinician Survey

Participants will be compensated with a \$25 gift card upon completing the survey.

7. Data and Safety Monitoring Board

The nature of the project poses minimal risk to participant safety and privacy. Yet, we will constitute a formal Data Safety Monitoring Board. The specific aspects of the DSMB for this study are as follows:

The DSMB will consist of 4 members who will perform several duties. First, they will review and approve research protocols and plans for data and safety monitoring prior to any study commencement. Second, they will evaluate the progress of any eligible trial. This will include assessment of data quality, participant recruitment, accrual and retention, participant risk versus benefit, and study outcomes. This assessment will be performed at meetings every six months during eligible trials, and more frequently if decided by the DSMB. Third, they will make recommendations to ensure that all of the issues above are appropriately addressed. The corresponding project teams will be responsible for responding to all recommendations of the DSMB and submitting DSMB reports to the University of Pennsylvania IRB.

8. Data and Safety Monitoring Plan

Oversight and evaluation will be accomplished using standard University procedures for safety monitoring. The specific elements of our oversight plan are as above: 1) all project staff will

complete certification in the protection of research participants; 2) the principal investigator will supply the IRB with annual progress reports, or more frequently as determined by the IRB, which may in turn suspend, terminate or restrict the study as appropriate; and 3) any serious adverse events will be reviewed in real time by the PI and reported to the IRB as required. Individual-level data for participants will be kept confidential and will only be stored on highly secure servers available for patient-level data. Only authorized project personnel will have access to the data and the data will only be stored on servers and not stand-alone PCs or laptops. All data will be reported at units of aggregation which make impossible the identification of individual patients or clinicians.

The data and safety monitoring plan will have 3 parts. First, the study MPIs, biostatistician, and Director of the Data Management Unit will develop and implement methods of verifying entered data and of quality control. Second, the MPIs will be directly responsible for identifying and reporting all adverse events, protocol deviations/violations and unanticipated events to the IRB and funding agency promptly, as appropriate. The PIs will also report all adverse events, accrual rates, retention rates, and all other logistical issues to the DSMB (described above) at least biannually (and more frequently if there are serious adverse events). Third, there will be a DSMB responsible for monitoring the trial.

A written research protocol will undergo formal institutional scientific and institutional review board (IRB) review at the University of Pennsylvania (Penn) to ensure protection of the rights and welfare of human research subjects. Specifically, the MPIs and the IRB will be responsible for ensuring risks to human subjects are minimized, risks are reasonable, subject selection is representative, the research team has access to adequate resources to conduct the study, the informed consent process (or waiver) meets regulatory and ethical requirements, adequate provision is made to protect human subjects by monitoring the data collected and there are adequate provisions to protect subject privacy per HIPAA regulations and confidentiality of data.

All senior/key personnel and research staff who will be involved in the design and conduct of the study must receive education in human research subject protection from a training program that is approved by a properly constituted independent Ethics Committee or Institutional Review Board. The MPIs will be responsible for ensuring project faculty and staff have the equipment and training required to protect privacy and confidentiality and will monitor and document that these individuals are properly certified. If new senior/key personnel and staff become involved in the research, documentation that they have received the required education will be included in the annual progress reports. The UPENN Office of Regulatory Affairs currently requires HIPAA training upon designation as research investigator/staff and recertification in human subjects research protection every three years.

The Penn IRB will serve as the IRB of record for any external ethics review boards or IRBs applicable to researchers from other institutions who may have access to human research subjects identified data.

9. Investigator's Risk/Benefit Assessment

This study presents minimal risk that is balanced by the potential benefits of the research to society.

INFORMED CONSENT

1. Consent Process

Aims 1, 2, 3, 4, and Chart Review. Since this is a pragmatic trial focused on improving implementation of higher-value evidence-based practices with minimal risk to patients, we are requesting a waiver of informed consent from providers and patients. We have received this in the past for these types of trials. We will identify providers at the practice sites and their patients using the EMR. Aim 4 (analysis of the sustainment of nudges) involves only data review. As there is no active intervention or patient interaction, and there is minimal risk to patients, we similarly request a waiver of informed consent for this aim as well.

Patient Interviews:

For patient interviews we are requesting a waiver of **written** documentation of consent. Potential participants will receive a link to a brief questionnaire in REDCap prior to the start of their interview. When the potential participant clicks the link, they will be directed to a page within REDCap that outlines the required elements of informed consent. If they agree to participate, participants will indicate consent by clicking the I AGREE button. If they do not want to participate, they will simply close the window. Before the interview is conducted, the research team will confirm that the consent form was completed. Before the interview, potential participants will be encouraged to ask questions about the project. All participants will be provided with an electronic copy of the IRB approved consent document for their records. All potential participants will be informed that participation is voluntary and provided with the information that they need to make an informed choice. We will provide contact information to all potential survey respondents in case they have any questions before, during, or after completing the survey. Potential interview participants will be asked if they have any questions and if they agree to participate before any research questions are asked. All participants will be informed that their decision to participate or not will not impact their relationship (i.e., services or employment) with their employer/provider.

Clinician Survey

As with the patient interviews, clinician survey participants will provide consent via an online survey platform (REDCap). As such, we are requesting a waiver of **written** documentation of consent. Procedures for gathering consent will follow the initial steps of the patient interview consent process – potential participants will receive a link to the REDCap consent form and survey via email, and upon clicking the link, they will be directed to a page outlining the required elements of informed consent. If they agree to participate, they will indicate this by clicking “Yes”, while those who do not want to participate can click “No” or simply close the window. Contact information is provided in the consent form to allow potential participants to ask any questions.

2. Waiver of Informed Consent

We are requesting a waiver of informed consent and HIPAA authorization from providers and patients (see attached request for waiver of HIPAA authorization). A waiver of informed consent is requested for the following reasons. First, it is not feasible to consent every patient and provider and as mentioned this initiative would occur with or without the study of it. Second, if members of the control (Usual Care) group were consented, they would know they were being studied and this could change their behavior. This could potentially disrupt the design of the study and make

interpretation of the findings challenging. Third, clinicians are not forced to recommend additional breast MRI screening to their patients, and patients are not being forced to undergo the additional MRI screenings. In all arms, providers can still engage or refrain from recommending additional breast MRI screening according to their best clinical judgment, and patients can refuse to undergo the screening, even when engaged by their provider. Instead, they are being reminded of evidence-based guidelines and offered an opportunity to review pertinent information and decide to refer to additional screening or not. This is no different than standard of care in which a provider would review the same information and decide to offer such recommendation. The initiative is simply a reminder for the clinician and makes their standard of care process easier to conduct.

Patient Interviews:

Waiver of Written Documentation of Consent for patient interviews. Participants will receive a link to complete a brief questionnaire via REDCap prior to the interview or be able to review all required elements of consent electronically via the consent form which is emailed to them prior to the interview and then be asked to provide verbal consent. Before the interview begins, participants will be encouraged to ask any additional questions, and interview administrators will confirm that the participant has provided consent. We anticipate most if not all interviews will be completed remotely and audio-recorded, and as such, it is infeasible to obtain written consent. This research activity presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

Clinician Survey

It is impractical to collect written documentation of consent from survey participants, as they will be completing the survey remotely, on their own time, via an electronic survey. Participants will be able to ask questions of the research team by following up to the invitation email and/or using the contact information included in the electronic consent form. This research activity presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

Sustainment Analysis

For the data pulls being conducted for the sustainment analysis, we are requesting a waiver of informed consent and HIPAA authorization, in line with the waivers that were approved for prior study aims. As patients are not directly being seen by members of the study team, it is not feasible to consent every patient who fulfills the eligibility criteria. Further, there are no interventions being enacted, we are merely reviewing how individuals interacted with MRI (i.e., ordered or not), so this research poses no more than minimal risk. The use of protected health information involves minimal risk to individuals and their privacy due to the plan to securely store and manage all data on password-protected servers (please see the *Data Management* section above for additional detail). In line with other trial data, data pulled for this aim will be destroyed within a reasonable time period following the conclusion of the study. Individual-level identifiable data will not be disclosed outside the study except as required by law. As with the data collected during the main trial, it would be impractical to conduct this study aim without a waiver, as data will be entered into the electronic health record without engagement from the study team. Finally, without such data, we would not be able to achieve the study aim of determining whether behavioral change is sustained after the removal of nudges because the primary outcome (MRI engagement) is collected via the electronic health record.

RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION

Adequate facilities are available at the ACC. The members of the research team are outlined in HSERA and include appropriate personnel to successfully implement this project. The entire team will be overseen by the PI. All personnel will complete required training before being granted access to any identifying information. This includes training on confidentiality through the Collaborative IRB Training Initiative (CITI) course. All personnel will be trained in the procedures for reporting unintentional breaches in confidentiality to the PI. All personnel will be aware that violations of participants' confidentiality, either unintentional or deliberate, may result in termination of hire. The PI will conduct training with all research personnel regarding data, limits of confidentiality, maintaining confidentiality and proper study procedures.

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