AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN PA 4006

Comparison of Full-Field Digital Mammography with Digital Breast Tomosynthesis Image Acquisition in Relation to Screening Call-Back Rate

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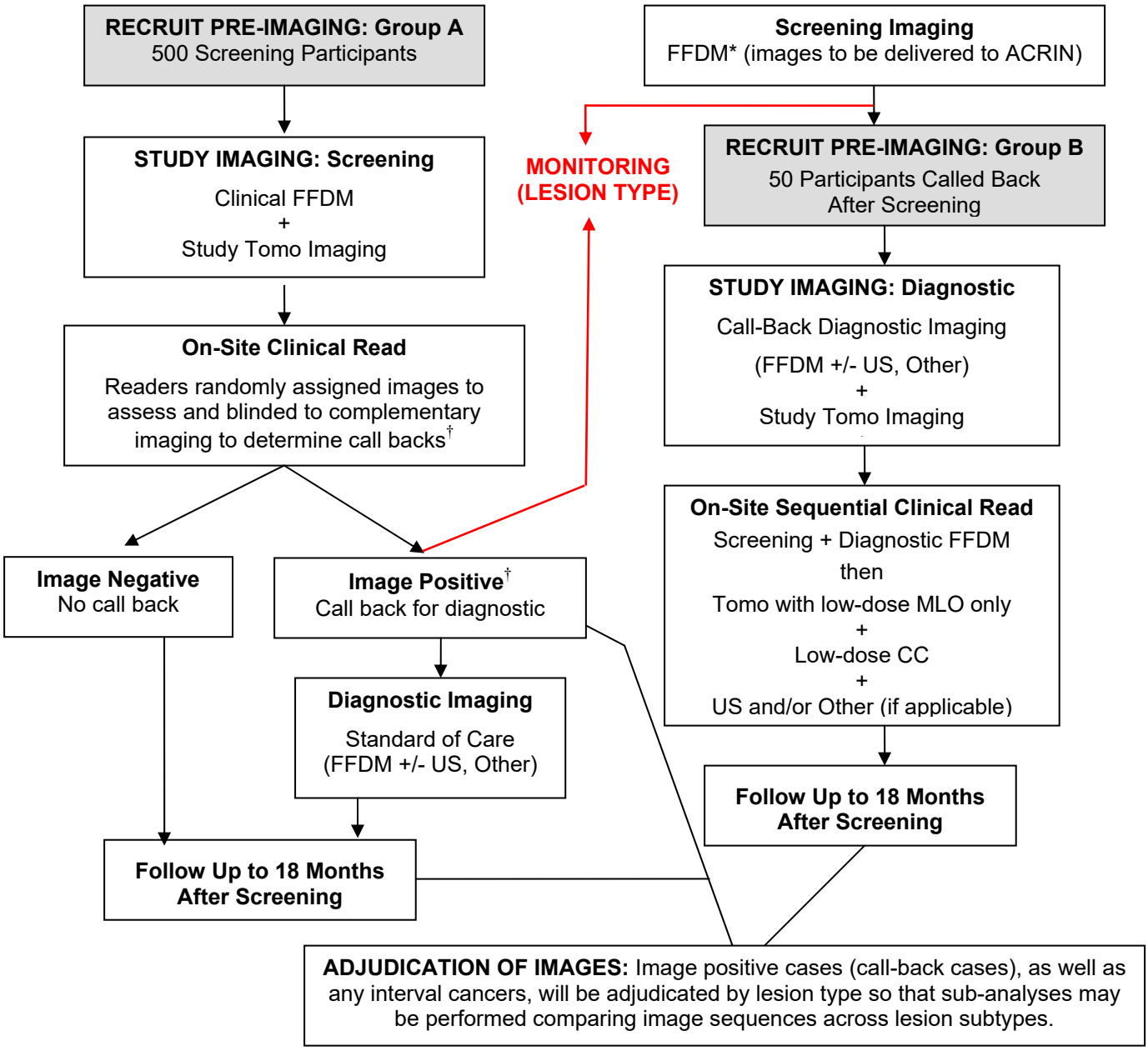
SCHEMA



Clinical FFDM, full-field digital mammography; Study Tomo Imaging, two-view tomosynthesis plus low-dose MLO (mediolateral oblique) and low-dose CC (cranial caudal) views; US, ultrasound.

* The screening digital mammography that prompted the recommendation for call back for potential Group B participants will have to be available for submission to ACRIN for patients to qualify for participation in the Group B arm.

† "Image Positive" abnormal findings from either FFDM or tomosynthesis image set on-site clinical reads will be used to trigger call back of participants for diagnostic assessment.

SPECIFIC HYPOTHESES

This multicenter trial using Hologic digital mammography units will evaluate the specificity of 2-D full field digital mammography (FFDM) versus a combination of 2-D and 3-D tomosynthesis imaging in breast cancer screening. Specificity, in this study, will be measured by the participant call-back rate by each modality. Varying combinations of 2-D mammography and tomosynthesis projections will be evaluated to optimize the screening paradigm and limit radiation exposure when tomosynthesis is incorporated. Both prospective and retrospective imaging data will be assessed.

1. Digital breast tomography (DBT) will improve the specificity of breast cancer screening as measured by a reduction in the call-back rate while maintaining the sensitivity of cancer detection. This improved accuracy will be achieved by the optimization of the imaging sequence and number of views obtained at a capped radiation dose in the combined DBT and 2-D screening sequence.

ELIGIBILITY *(see Section 5.0 for details)*

Asymptomatic women 25 years and older with no history of breast cancer will be recruited from a prospective population of patients scheduled for screening mammography (Group A). A similar population of women called back from screening for 2-D FFDM-detected abnormalities will also be recruited to provide an enriched population of true-positive and false-positive 2-D FFDM and tomosythesis cases (Group B). Pregnant women, women unable to tolerate compression of the breast associated with mammography, women with implants, and women with breasts too large to accommodate adequate positioning of the breast for DBT are excluded from trial participation.

SAMPLE SIZE

A total of 500 participants will be recruited for collection of prospective imaging data in this trial (Group A); 50 additional participants, recalled for diagnostic assessment after positive screening findings, will be recruited for DBT imaging data collection and retrospective image analysis (Group B). Participating institutions for this trial will be clinical research institutions in Pennsylvania with Hologic tomosynthesis units.

1.0 ABSTRACT

This protocol for human research study is conducted according to United States and international standards of Good Clinical Practice (International Conference on Harmonisation [ICH] Guidelines), applicable government regulations (e.g. Title 45, Part 46 Code of Federal Regulations) and the American College of Radiology Imaging Network (ACRIN) research policies and procedures.

The incorporation of tomosynthesis, a novel 3-D reconstruction of multiple low-dose digital mammographic images may reduce the number of diagnostic examinations (call-back visits) needed by providing many of the benefits of diagnostic imaging during screening. The results of early studies of tomosynthesis technology are promising and indicate that the specificity of screening mammography can be improved with the incorporation of digital breast tomosynthesis (DBT) without concomitant loss in overall sensitivity.[1–3] Unfortunately, the peer-reviewed publications evaluating DBT in the screening setting are limited and consist of single institution/single manufacturer studies with a small number of patients. Additionally, the optimal procedural metrics in DBT have not been fully defined. Manufacturers have different platforms that offer different combinations of tomosynthesis projections (mediolateral oblique [MLO] only versus MLO plus cranial caudal [CC]), different tomosynthesis image acquisition geometries (angular range, number of projections, dose distribution across projections, detector and tube motion, etc.), and different radiation dose levels (one to two times the dose of a mammogram). Controversy continues over the use of tomosynthesis in combination with 2-D FFDM or as a stand-alone—tomosynthesis only—screening method without concomitant 2-D imaging. This disparity in image number and image acquisition parameters may alter the balance between specificity and sensitivity and significantly affect radiation dose.

Studies have shown that tomosynthesis is effective in characterizing possible masses, focal asymmetries, and areas of architectural distortion seen on 2-D mammography. However, the lower conspicuity of calcifications with tomosynthesis than on 2-D mammography has been a concern and may stem from several factors that need to be explored.[1,4] Standard 2-D FFDM projection images summate all the calcifications in a cluster in a single-image presentation, potentially allowing improved detection and characterization of calcified lesions. In DBT, calcifications are presented on individual image slices rather than as a summated cluster and may therefore be more difficult to detect and characterize than on conventional projection imaging. While post-processing algorithms including slab reconstruction and novel 3-D computer aided detection (CAD) programs may potentially improve the conspicuity of calcifications in tomosynthesis, these programs are still under development.[1,3,4] In addition, movement of the tube during tomosynthesis image acquisition may lead to blurring of the fine detail of calcifications necessary for accurate characterization.[1] Similarly, long total scan time may result in patient motion which can blur the fine detail of calcifications.

This study will assess variations in DBT image acquisition while limiting radiation dose to participants with varying breast sizes and densities. The expected outcome of this research is to show, with the incorporation of tomosynthesis in the screening paradigm, a reduction in the number of false-positive interpretations without a loss of cancer detection. This improvement in screening specificity can be gained while limiting both the number of imaging views and the radiation dose to the participant.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 Current Breast Screening and the Tomosynthesis Advantage

With competing parameters of specificity and sensitivity, breast cancer screening must limit both missed cancers and false-positive call-backs (with potential to biopsy) to reduce cost and unnecessary anxiety in patients. FFDM has been shown to provide improved sensitivity over analog mammography in the detection of breast cancers, particularly in women with dense breasts.[5] Unfortunately, the call-back rates for both digital and analog screening mammography remain elevated with similar rates of approximately 10%.[5] This results in many women receiving additional imaging of "pseudo-lesions" or suspicious-looking superimpositions of glandular tissue on 2-D projection imaging that additional imaging later proves to be normal. Advanced techniques have been proposed that make use of the additional capabilities of digital image processing inherent to digital mammograms.[6]

Screening mammography examinations are performed currently by taking 2-D projection images of the breast, while tomosynthesis involves taking multiple low-dose images at sequential angles that are reconstructed and presented as a 3-D image set of the breast. DBT has been proposed for both diagnostic and screening applications since the 3-D image set provides a presentation in which the effects of tissue superposition are largely removed from the image, as superimposed tissue may hide breast cancers. The ability to "scroll through" the sequential slices of the 3-D reconstructed breast images in DBT can contribute to improved conspicuity of cancers and avoid the creation of spurious lesions due to superposition of overlying and underlying tissue structures. The reduction of superimposed tissue should allow the detection of cancers that may be hidden by superimposed normal breast tissue.[1–4,6]

The radiation doses from tomosynthesis can be similar to those from conventional projection (2-D) imaging, thus tomosynthesis has the potential to replace conventional mammograms while improving both sensitivity and specificity of cancer detection. A screening tomosynthesis examination may reduce the number of diagnostic exams needed by essentially providing many of the benefits of diagnostic imaging in the screening examination.

2.2 Screening and Diagnosis With FFDM and/or Tomosynthesis: Disparities, Unanswered Questions, and the Need for Further Evaluation

Studies have shown that tomosynthesis is effective in identifying masses and areas of architectural distortion. However, visibility of calcifications, an early indicator of breast cancer, with tomosynthesis has been a concern and stems from several factors that need to be explored.[1,4] Standard 2-D projection images summate all the calcifications in a cluster in a single-image presentation, potentially allowing improved detection and characterization of calcified lesions. In a tomosynthesis image set, calcifications are presented on individual image slices rather than as a summated cluster and may therefore be more difficult to detect and characterize than on conventional projection imaging. In addition, during tomosynthesis image acquisition, incremental movement of the tube over an angle may lead to blurring of the fine detail of calcifications necessary for accurate characterization. Multiple images of calcifications, taken over a large angular range, may reduce the fine detail or edge characteristics of calcifications.

Two general techniques are currently used for acquiring the tomosynthesis image set. One technique acquires images with the tube in continuous motion over an arc of approximately 15 degrees. The approach requires very rapid x-ray exposures so that blurring of the tomosynthesis image is minimized. In this scenario, the length of time the patient's breast is in compression is minimized, thereby reducing

patient motion. The second technique is a "step and shoot" technique where the tube stops along the arc for each image acquisition. This approach eliminates blurring from the x-ray source/tube, but requires longer breast compression, resulting in the potential for greater breast motion, also causing blurring.[1] The first feature that may be lost with blurring is the visibility of calcifications.

Full-Field Digital Mammography. Rothenberg et al[7] reviewed records from the Blue Cross Blue Shield Association Technology Evaluation Center after updates from the Oslo II study[8] and ACRIN 6652 Digital Mammographic Imaging Screening Trial (DMIST),[5,9] a trial providing more than 42,000 cases of FFDM and film-screen mammography. These studies found the two modalities to be largely equivalent in screening accuracy, but with greater cancer detection with FFDM among specific populations of women for whom breast cancer is more difficult to detect with film-screen mammography. FFDM appeared to have greater accuracy among women stratified for age (ACRIN 6652 DMIST: women younger than 50; Oslo II: women ages 50 to 69), menopausal status (pre-menopausal or perimenopausal), and breast density (heterogeneous or extremely dense breasts). Both modalities face limitations from false-positive results. From a diagnostic point of view, Rothenberg et al infer FFDM detected more invasive carcinomas and medium-grade to high-grade ductal carcinomas in situ. FFDM has many other advantages over film-screen mammography which include: the ability to electronically archive and transmit images, the ability to post-process images to enhance the conspicuity of some lesions types, and the ability to apply computer-aided detection (CAD) algorithms to assist radiologists in the detection of breast lesions.

Tomosynthesis. The promise of DBT in the screening setting is its potential to reduce false-positive call-back examinations, without a loss of sensitivity over conventional digital mammography. The results of early studies are promising and indicate that the specificity of DBT is improved without concomitant loss in overall sensitivity.[1–5] In 2007, Poplack et al[1] compared the image quality of tomosynthesis imaging as an adjunct to diagnostic imaging with film-screen mammography for participants who had been called back from screening. In this reader study, the tomosynthesis images were considered "comparable-to-superior" in image quality to the diagnostic 2-D imaging in 89% of cases. In addition, it was determined that approximately half (52%, or 52 of 99) of these women would not have been called back for diagnostic imaging had their screening been conducted using FFDM supplemented with tomosynthesis. After adjustment, reduction in call back was determined to be 40%. Further assessment determined significant correlation between call back and tumor type ($p = 0.004$). In addition, tomosynthesis performed better than 2-D mammography for the detection and characterization of all lesions types except for calcifications. The 2-D mammography outperformed tomosynthesis in the evaluation of calcific lesions on the basis of better conspicuity and better discrimination of calcium particle number and morphology. This finding was thought to be due to a combination of image blur and image presentation in DBT, where slices were reconstructed at too thin a slice to allow the observer to perceive the clustering of the calcifications.[1]

Few published trials on breast cancer screening with tomosynthesis exist, partly because the optimal procedural metrics for tomosynthesis have not been fully defined. A multi-institutional screening trial was presented in 2007 (in abstract form only) by Rafferty[2], which recruited 1,083 women from five clinical sites for 2-D FFDM plus DBT. From the data set, 316 imaging data sets were selected randomly to create an enriched reader study with 12 radiologists. The receiver operating characteristic (ROC) for all 12 radiologists was superior for FFDM plus DBT that for FFDM alone. The specificities for the reader increased from 84.1% to 89.2%, and the sensitivity improved from 65.5% to 76.2%. A mean

reduction in call-back rate of 42.6% was also observed.[2] In this combination of 2-D FFDM plus DBT, the combined radiation dose per breast is estimated to be approximately 5.8 mGy, which is twice the dose of a routine mammogram performed on the same equipment and significantly higher than the national average dose for routine two-view mammogram (3.4 mGy).

The optimal procedural metrics for DBT have not been fully defined, thus limiting scientifically sound, practice-guiding results. Manufacturers have different platforms that offer different views (MLO only versus combination MLO plus CC), different tomosynthesis image acquisition geometries, and different radiation dose levels. The exact number of tomosynthesis views of MLO only or combination MLO-and-CC tomosynthesis views varies. Controversy continues over the use of tomosynthesis with 2-D FFDM or its use as a stand-alone screening method. This disparity in image number and image acquisition parameters may alter the balance between specificity and sensitivity and significantly affect radiation dose. The current study design focuses on optimizing image quality with reduced call-back rates while limiting radiation dose.

2.3 Screening With FFDM and/or Tomosynthesis: Collecting Beneficial Images While Limiting Radiation Exposure

The disparity in image number and image-acquisition parameters may alter the balance between specificity and sensitivity, and significantly affect radiation dose. While tomosynthesis shows promise in its potential to more accurately diagnose questionable lesions as malignant or not, the potential increase in radiation exposure from this technology in comparison with ultrasound or magnetic resonance imaging (MRI) calls into question the risk over benefit of this imaging advance.

The national average dose per breast for two-view 2-D mammography is 3.4 mGy. The exact dose varies by manufacturer and technology (film-screen, computed radiology, and direct radiology). We propose to investigate the use of a dose for the complete tomosynthesis image set (two-view tomosynthesis at approximately 1.2 mGy each, plus two simultaneously-acquired, low-dose 2-D combination tomosynthesis plus set views at approximately 1.0 mGy each) of 4.4 mGy, which is comparable to conventional mammography. The dose for the "limited tomosynthesis set" of two-view tomosynthesis plus low-dose 2-D MLO only is approximately 3.4 mGy, equal to routine two-view mammography. The addition of the CC view—the added benefits of which will be assessed in the course of this trial—contributes approximately 1.0 mGy of exposure. This trial will limit the potential radiation exposure to determine the quality of the images obtained with these varying combinations of views. Local reader evaluations, as well as an adjudication process, will include assessment for image quality and completeness for analysis.

2.4 Defining the Questions to Determine the Answers

The potential of tomosynthesis cannot be clearly defined until optimal, standardized technical parameters, angle views, and low-dose radiation exposure can be determined. Among asymptomatic women being screened with FFDM, this trial will assess the combinations of views between variations—two-view tomosynthesis with a low-dose 2-D MLO with and without CC view in comparison with institutional standard-of-care two-view FFDM—to determine prospective call-back rates at the sites of accrual.

Among an enriched population of women called back for diagnostic imaging based on positive findings during previous screening with FFDM, diagnostic imaging will include DBT (to both breasts, even if

only a single breast was found suspicious during screening assessment) to determine its impact on defining true-positive and false-positive disease findings. Lesions types based on screening FFDM findings will be characterized at a basic level to classify them for monitoring—as calcification-only or as soft-tissue lesions (masses, asymmetries, architectural distortions, or masses with calcification)—to evaluate DBT's capacity to characterize "calcification only" lesions as compared to FFDM. The assumption is that most Group A call-back cases will comprise soft-tissue lesions. Therefore, the enrollment to the Group B enriched population will be targeted to first accrue calcification-only lesion cases. Recruitment to Group B may be adjusted to include soft-tissue cases to achieve target accrual while targeting a final 75/25-to-50/50 ratio (e.g., 75 soft-tissue to 25 calcification-only lesions; ratio based on ACRIN 6652 DMIST data; see Section 6.4 for more detail).

An analysis will be performed to compare the appropriate combination of images for the tomosynthesis set to cap the per-breast dose at approximately 3.4 mGy (equivalent to 2-D mammography). Determining the quality and value of tomosynthesis image sets with limited radiation exposure is an integral part of the trial's objectives. The potential benefit of tomosynthesis imaging within the appropriate population of people at risk for breast cancer can be achieved only by proving the value of characterization of suspicious findings using tomosynthesis and reducing the risk associated with higher radiation doses currently associated with the technology.

Because this trial is limited to Pennsylvania-based institutions—and therefore to Hologic imaging technology only—due to funding requirements, subsequent assessment of technical parameters across manufacturers will need to follow in a multi-center national trial.

3.0 STUDY OBJECTIVES/SPECIFIC AIMS

ACRIN PA 4006 is designed to answer questions related to image combinations and quality in pursuit of reduced radiation exposure from tomosynthesis technology.

3.1 Primary Aim

3.1.1 To compare recall rates of FFDM to the limited DBT set (digital breast two-view tomosynthesis with low-dose MLO) [Group A].

3.2 Secondary Aims

3.2.1 To compare sensitivity of FFDM to the limited DBT set (digital breast two-view tomosynthesis with low-dose MLO) [Groups A and B].

3.2.2 To assess lesion-type characterization:

3.2.2.1 To compare the sensitivity and specificity by lesion-type characterization (calcification-only lesions versus soft-tissue lesions, as well as lesion subgroups: masses, calcifications, architectural distortions, asymmetries) in FFDM versus DBT (two-view tomosynthesis set with low-dose MLO) [Group A call-back cohort and Group B];

3.2.2.2 To estimate the agreement of FFDM and DBT with the determination of the adjudication committee on lesion-type characterization.

3.2.3 To use the sequential interpretation results [Groups A and B] in order to compare the two-view limited tomosynthesis set (with low-dose MLO view alone) with the tomosynthesis plus set (low-dose MLO view plus addition of low-dose CC view) on the basis of:

- Call-back rate;
- Identification of new lesion(s);
- Lesion characterization; and
- Triangulation.

3.2.4 To calculate and compare the radiation dose of the FFDM and the DBT sets.

3.2.5 To identify the determinants of participant radiation dose and clinical image quality, including factors such as kVp, mAs, target/filter combination, and breast thickness and composition.

4.0 STUDY OVERVIEW

All participants will be consented and registered prior to their screening or diagnostic evaluation, which may be same day. If an eligible patient decides not to join the trial, her reason should be documented on a Screening Log to assist in identifying recruitment barriers. Participants will undergo both routine screening full field digital mammogram (FFDM) and the tomosynthesis imaging set (DBT) comprising: FFDM only (from screening in Groups A and B), as well as diagnostic imaging (FFDM, +/- ultrasound and other) when obtained on call-back in Group A and on all Group B patients; low-dose DBT—two-view limited tomosynthesis set with low-dose 2-D MLO view (limited tomosynthesis set) and low-dose low-dose CC view (tomosynthesis plus set). However, the timing of the study-related imaging visits will be segregated into two cohorts, screening (Group A) and diagnostic (Group B).

4.1 Group A: Screening Tomosynthesis

Group A comprises 500 asymptomatic women with no history of breast cancer who are scheduled for routine screening of the breasts with FFDM. The Group A component of the trial is powered to show a 30% reduction in call-back rate from screening including DBT. Participants in Group A will undergo both FFDM and DBT. Initial interpretation from local readers will determine call back for diagnostic evaluation based on positive (abnormal) findings from either the conventional two-view digital mammography study—"FFDM only"—or the tomosynthesis imaging sets (limited tomosynthesis set and then a sequential read with the low-dose CC view added for the tomosynthesis plus set). Participants will be biopsied or followed as recommended by the physician who evaluated the participant at diagnostic call back. Local readers will be randomly assigned images to assess per institutional standard procedures and are blinded to the results of the complementary image set for the participant. Local readers also will be asked to assess image quality. Any necessary diagnostic evaluation from positive screening findings should be conducted within 30 days after screening visit. Follow up will include medical record review, review of conventional imaging results, and images collection at approximately 1-year post-screening assessment. Follow-up data may be collected up to 18-months post-screening depending on participant's scheduling; data may be collected over a shorter time period due to funding constraints.

4.2 Group B: Diagnostic Tomosynthesis in an Enriched Population

Approximately 50 asymptomatic women with no history of breast cancer who have been informed of positive (abnormal) findings from a recent (within 30 days) FFDM screening will be recruited to Group B prior to their diagnostic imaging (e.g., diagnostic FFDM and/or ultrasound and/or other). Group B participants will consent to DBT of both breasts as part of their diagnostic imaging work up; all screening and diagnostic images will be collected for study-related analysis. Participants will be biopsied or followed as recommended by the physician who evaluated the participant at diagnostic call back. Study-related follow up will include medical record review and images collection at approximately 1-year post-screening assessment. Follow-up data may be collected up to 18-months post-screening depending on participant's scheduling; data may be collected over a shorter time period due to funding constraints.

Enrollment to Group B will concentrate initially on calcification-only lesions (based on the report of the initial screening study), under the assumption that Group A will comprise predominantly soft-tissue lesions. Recruitment of call-back cases based on lesion type will be monitored to achieve 75%-to-50% soft-tissue lesions and 25%-to-50% calcification-only lesions within the enriched cohort. See Section 6.4 for additional details.

The enriched Group B population is designed to increase the number of true-positive and false-positive cases for comparison of the two imaging modalities at the lesion level. Images for lesion level analysis will comprise approximately 100 image-positive cases collected from both study cohorts (all of Group B and approximately 50 cases from Group A that result in call backs for diagnostic assessment). Analysis of the images performed at the lesion level will also assess the added contribution of the low-dose CC view when added to the two-view tomosynthesis plus low-dose MLO view image set.

4.3 ACRIN PA Trials and Hologic

Potential participants will be recruited from Pennsylvania institutions with Hologic tomosynthesis units. While an important outstanding obstacle to routine use of tomosynthesis involves differences in technical parameters (radiation exposure in particular) used across competing scanner types, this study is limited to Pennsylvania-based sites only due to funding, and Hologic is the only manufacturer approved for use in Pennsylvania. The results of this trial are aimed at setting the stage for a larger screening trial where best-practices related to quality under specific technical parameters (radiation dose, image angle) across manufacturers might be better assessed.

5.0 PARTICIPANT SELECTION/ELIGIBILITY CRITERIA

The trial's study population comprises two cohorts: asymptomatic women ages 25 and older with no history of breast cancer 1) who are scheduled for screening mammography (Group A) or 2) who are recalled for additional diagnostic imaging based on image-positive findings from recent screening with FFDM (Group B). If an eligible patient decides not to join the trial, their reason should be documented on a Screening Log to assist in identifying recruitment barriers.

5.1 Inclusion Criteria

5.1.1 Women 25 years of age or older;

5.1.2 No history of breast cancer;

5.1.3 **Group A only:** Asymptomatic and scheduled for screening mammography;

5.1.4 **Group B only:** Asymptomatic and recalled for diagnostic testing due to positive findings on recent screening using FFDM, completed within 30 days prior to registration (BI-RADS 0: additional imaging needed);

5.1.5 Willing to provide a written informed consent.

5.2 Exclusion Criteria

5.2.1 Pregnancy or intent to become pregnant;

5.2.2 Unable or unwilling to tolerate compression associated with mammography;

5.2.3 Breast implants;

5.2.4 Breasts too large to allow for adequate positioning for the DBT examination;

5.2.5 **Group B only:** Patients with FFDM taken at screening who are unwilling or unable to submit images to ACRIN;

5.2.6 **Group B only:** Unwilling to undergo tomosynthesis on both breasts as well as potentially additional diagnostic imaging based on tomosynthesis findings;

5.2.7 Unable or unwilling to complete screening and (as necessary) diagnostic imaging at same facility;

5.2.8 Tomosynthesis or mammography within 11 months prior to registration.

5.3 Recruitment and Screening

The research team at each participating site includes the radiologist principal investigator (PI), local radiologists for local reads in Group A, mammography and DBT technologists, and research associate(s). The local radiologists also will interpret the tomosynthesis image sets at the time of diagnostic imaging for Group B participants. The PI and other research staff will be responsible for the screening, review of participant medical records, and investigator-designated data submission. A total of 3 to 4 readers at each site experienced in both digital mammography and tomosynthesis will be recruited to participate in this trial.

5.4 Inclusion of Women and Minorities

The ACRIN-qualified participating institutions will not exclude potential participants from participating in this or any study solely based on ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible participants into this protocol and therefore address the study objectives in a patient population representative of the entire English-speaking population at risk for breast cancer screened by the institution.

Women of all ethnic groups are eligible for participation in this study.

6.0 SITE SELECTION

6.1 Institution Requirements

The potential sites for this study are ACRIN-participating institutions in Pennsylvania that meet qualifications for participating in this study. Each institution must complete a Protocol Specific Application (PSA) (available online at www.acrin.org/4006_protocol.aspx) and undergo ACRIN-qualification for digital mammography and tomography equipment and software to be used for the trial prior to the institution participating in the study (Appendix II).

Detailed information for Digital Mammography and Tomography Qualification Procedures and the application to become ACRIN qualified, as well as the PSA, can be accessed at www.acrin.org/4006_protocol.aspx. All qualification documentation must be submitted to ACRIN Headquarters for review and approval.

6.2 Local Reader Qualifications

6.2.1 All digital mammogram and tomosynthesis readers must be accredited under the Mammography Quality Standards ACT (MQSA) and have tomosynthesis experience (defined as 30 previous reads or more).

6.3 IRB Approval and Informed Consent Form

The study will be approved by the appropriate institutional review boards (IRBs) and the appropriate institutional review committees. All study participants will provide written informed consent (see the Informed Consent Form Template in Appendix I).

All institutions must have site-specific, initial full-board IRB approval for the protocol and informed consent form (ICF) for this study. (A sample ICF is included in this protocol as Appendix I and may be adjusted for local IRB submission.) The investigator and the investigator-designated research staff must follow OHRP-approved consent procedures (Title 45, Part 46 Code of Federal Regulations), as well as those set by the local IRB at the institution. A copy of the IRB approval letter, a copy of the IRB-approved, site-specific ICF, evidence of completion of the OHRP Human Subjects Assurance Training (or institution-specific equivalent), and FDA Form 1572 Statement of Investigator and CVs and medical licensure for all research staff listed in Form 1572 must be submitted to the ACRIN study monitor for review and to keep on file at ACRIN Headquarters (fax: 215-717-0936, ATTN: ACRIN PA 4006 Study Monitor) prior to registering the first participant.

6.4 Accrual Goals and Monitoring

The ACRIN Biostatistics and Data Management Center (BDMC) will monitor participant accrual. Total target accrual for this study is 550 participants. During the first year, the accrual goal will be 550 participants. If the target is not reached, a review will be conducted with the intention of discovering and resolving any recruitment barriers.

Accrual and safety information will be presented to the ACRIN PA (Pennsylvania) Data and Safety Monitoring Board (DSMB) at regularly scheduled meetings thereof; the PA DSMB may, at its discretion, re-evaluate the study with respect to feasibility or the need for additional participating institutions.

In Groups A and B, monitoring of lesion type will be necessary to ensure inclusion of an appropriate number of calcification-only lesions for meaningful assessment by lesion type. Under the assumption that the majority of cases called back from Group A screening FFDM and tomosynthesis will be soft-tissue lesions, the trial will focus on recruiting participants to Group B who are called back for diagnostic work-up based on calcification-only lesions seen on screening FFDM. Recruitment of call-back cases based on lesion type will be monitored throughout the study. Group B will not be closed to accrual of soft-tissue cases during the trial, but recruitment will focus on calcification-only lesions.

Based on ACRIN 6652 DMIST data, the target accrual by lesion type is 75%-to-50% soft-tissue lesions to 25%-to-50% calcification-only lesions.

7.0 DATA MANAGEMENT/ONLINE REGISTRATION

7.1 General

7.1.1 The ACRIN web address is www.acrin.org**.**

7.1.2 Data collection and management will be performed by the Biostatistics and Data Management Center (BDMC) of ACRIN under the direction of Dr. Constantine Gatsonis. The Biostatistics Center (BC) is located at Center for Statistical Sciences at Brown University in Providence, RI, and the Data Management Center (DMC) is located at ACRIN in Philadelphia, PA.

7.1.3 Participant enrollment and data collection occurs through a series of programmed screens accessed through the ACRIN web site to register/randomize participants, collect participant data, and maintain calendars of data submissions for each participant. By using the World Wide Web, ACRIN has made participant registration, data entry, and updated calendar information available to clinical sites 24 hours a day, seven days a week. Each successful case registration is confirmed through receipt of an e-mail containing a registration/randomization confirmation and a case specific calendar identifying timelines for data and image submission. If the confirmation e-mail is not received, the enrolling person should contact the DMC before attempting a re-registration. A DMC contact list is located on the ACRIN web site for each protocol.

7.2 Clinical Data Submission

7.2.1 Upon successful participant registration to Group A (screening) or Group B (diagnostic), a confirmation e-mail containing the registration and case specific calendar is sent to the research staff enrolling the participant via the web. In addition, the investigator-designated research staff may download the participant specific data submission calendar, which lists all forms and designated reports required by protocol, along with the form due dates at the DMC. These calendars will be updated as the study proceeds to reflect data that have been received, reply deadlines for queries about unclear data, deadlines for follow-up reports of adverse events, or changes in the protocol that change the data being collected or the timeframe. Updated calendars for each participant can be obtained 24 hours a day from the ACRIN web site. The research associate may use the calendar as a case management tool for data submission and follow-up scheduling.

7.2.2 The investigative site is required to submit data according to protocol as detailed on each participant's calendar, as long as the case status is designated as open/alive or until the study is terminated. The case is closed when all data have been received, reviewed, and no outstanding data query exists for the case.

7.2.3 To submit data via the ACRIN web site, the appropriate investigator-designated research staff will log onto the ACRIN web site and supply the pre-assigned user name

and password. Case report forms will be available on the web site through a series of links. Each web form is separated into modules; each module must be completed sequentially in order for the internal programming to be accurate. The user selects the link to the appropriate form and enters data directly into the web-based form. As information is entered into the web form application, various logic checks will be performed. These logic checks look for data that are missing, data that are out of range, and data that are in the wrong format (e.g. character data in a field requiring numeric responses). Such errors will be detected as soon as the user attempts to either submit the form or move to the next data element. They must be corrected before the form is transmitted to the DMC. The user will not be able to finalize form transmission to the DMC until all data entered pass these logic checks. Forms that are not completed in one sitting can still be submitted and completed at a later date. The form will remain available on the web until the "Complete Form Submission" button is depressed.

7.2.4 Once data entry of a form is complete, and the summary form is reviewed for completeness and accuracy, the investigator or the research staff presses the "Complete Form Submission" button on the form summary screen and the data are transferred into the clinical database. No further direct revision of the submitted data is allowed after this point. E-mail confirmation of web data entry is automatically generated and sent to the site investigator or research associate listing all of the data generated and just submitted. Should a problem occur during transmission and the e-mail confirmation of data submission is not received, the investigator or research associate should contact the DMC for resolution of the submission.

7.2.5 If a temporary problem prevents access to the Internet, all sites are notified of the event and estimated down time through an ACRIN broadcast message. The investigative site should wait until access is restored to submit data. The site research associate or investigator should notify the DMC of the problem and the DMC will give an estimated time when access will be restored. If access will be unavailable for an extended period, sites must seek another Internet Service Provider (ISP). On a short-term basis, ACRIN can serve as an ISP.

7.3 Registration Protocol

Once the patient has been found to be eligible to participate in the trial, the potential participant will be consented (see Informed Consent Form Template in Appendix I). Upon obtaining a signed ICF, the research staff will register the participant by logging onto the ACRIN web site (www.acrin.org), and selecting the link for Data Center Login.

The registration screen begins by asking for the date on which the eligibility review was completed, identification of the person who completed the review, whether the potential participant was found to be eligible on the basis of the review, and the date the study-specific informed consent form was signed.

After completing the registration, the system assigns a participant-specific case number. The system then moves to a screen, which confirms that the participant has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the participant's record.

Participants will be identified according to their study group assignments (Group A—screening—or Group B—diagnostic).

7.3.1 Unsuccessful Registrations

Any problems or questions regarding registration of participants should be directed to the ACRIN DMC. Never re-register a participant as this may lead to duplicate case numbers.

7.4 Data Security

The registration and data collection system has a built-in security feature that encrypts all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of identification codes and passwords.

7.5 Electronic Data Management

7.5.1 Data received from the web-based forms are electronically stamped with the date and time of receipt by the ACRIN server. The data are then entered into the database. A protocol-specific validation program is used to perform more extensive data checks for accuracy and completeness. Complementary validation programs are initiated at the Brown BC and the ACRIN DMC. The logic checks performed on the data at this point are more comprehensive than those built into the web-based data entry screens. They include checking that answers are logical, based on data entered earlier in the current form and the more thorough checks. Data elements that fail validation are followed up by the DMC. The validation program generated by BC produces a log of errors, which is sent to the DMC for resolution. The program is frequently updated to incorporate exceptions to rules so that subsequent validity checks minimize the time the DMC needs to spend resolving problems. Additional data review will take place once the data are transferred to the BC. The BC will run thorough cross-form validations, frequency distributions to look for unexpected patterns in data, and other summaries needed for study monitoring. Any errors found at the BC will be reported to the DMC for resolution. All BDMC communication with the participating sites is normally done through the DMC.

7.5.2 If checks at DMC or BC detect missing or problematic data, the DMC personnel assigned to the protocol sends a Request for Information (Z1 query letter) to the site research associate or investigator specifying the problem and requesting clarification. The DMC updates the participant's data submission calendar with the due date for the site research associate or investigator's response.

7.6 Missing and Delinquent Data Submission

In addition to providing the investigator a data collection calendar for each case, the DMC periodically prompts institutions for timely submission of data through the use of a Forms Due Report. Distributed at intervals via the electronic mail system directly to both the research associate and the investigator at each site, this report lists data items (e.g. forms, reports, and images) that are delinquent and those that will be due before the next report date. In addition to prompting clinicians to submit overdue data, the Forms Due Report helps to reconcile the DMC's case file with that of the research associate and/or investigator. Future Due Forms Reports may be sent on an as needed basis in addition to past due

reports. The site investigator or research associate may use the Forms Due and Future Due Reports as a case management tool.

7.7 Data Quality Assurance

7.7.1 The BC at Brown University will maintain a study database at its site for monitoring data quality and for performing analyses. These data are drawn directly from the permanent database of the DMC. The transfer of data between the DMC and the BC has been validated through a series of checks consisting of roundtrip data verification in which data are sent back and forth to verify that the sent data are equivalent to the received data. These checks are repeated at random intervals during the course of a given study. Any discrepancies and other data quality issues will be referred to DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.

7.7.2 A goal of the monitoring of data is to assess compliance with the protocol and to look for unforeseen trends that may be indicative of procedural differences among clinical sites. If patterns are discovered in the data that appear to arise from causes specific to an institution, the BDMC will apprise the ACRIN Headquarters and the site of the problem, and work with the site, along with ACRIN Protocol Development and Regulatory Compliance (PDRC) department, until the problem has been resolved. If the BDMC, along with the PDRC, cannot find a resolution to the problem, it will be brought to the ACRIN Quality Assurance (QA) Committee for further discussion and resolution.

8.0 STUDY PROCEDURES

8.1 PRIOR TO IMAGING: Eligibility & Registration

8.1.1 Obtain a signed informed consent form;

8.1.2 Baseline assessment to determine eligibility based on details in Section 5.0 will comprise the following:

- Obtain medical history including:
  - Demographic risk assessment form;
- Obtain pregnancy test, if woman is of childbearing potential, per institutional standard of care;

8.1.3 Collect contact information for participant and proxy for site staff to make telephone contact only in the event that approximate 1-yr follow up medical record extraction and images collection is unavailable from known treating physician;

8.1.4 Register the eligible participant to Group A (screening) or Group B (diagnostic);

8.1.5 Screening or diagnostic imaging should occur same day as scheduled previously (unless the potential participant requests additional time to consider joining the trial, in which case delays in rescheduling should be minimized).

NOTE: If an otherwise eligible patient decides not to join the trial, their reason should be documented on a Screening Log to assist in identifying recruitment barriers.

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8.2 Group A Only Procedures

8.2.1 GROUP A IMAGING: Screening (FFDM with DBT)

Participants enrolled to Group A, a cohort of asymptomatic women ages 25 and older with no history of breast cancer and no implants, will undergo the following procedures during routine breast cancer screening:

- Confirm/collect current participant and proxy contact information;
- FFDM per institutional standard of care;
- Study-related tomosynthesis imaging sets (limited and tomosynthesis plus sets) according to parameters provided in the ACRIN PA 4006 Imaging Manual (available at www.acrin.org/4006_imagingmaterials.aspx);
- Assessment for AEs.

8.2.2 Local Reader Clinical Assessment

Local radiologists (see Section 6.2 for qualifications) will be responsible for the clinical read of screening FFDM and DBT under the following restrictions:

- Site PI will randomly assign images to local readers;
- Readers will be blinded to the complementary imaging for a participant (i.e., no local radiologist will read both FFDM and DBT for an individual);
- Images will be assessed for clinical significance, lesion(s) location and type (broadly as soft-tissue or calcification-only lesions for monitoring purposes, as well as subgroup analysis of mass, asymmetry, architectural distortion and calcifications), and quality;
- Image-positive results from either FFDM or DBT, or both, will require call back for diagnostic imaging follow up (BI-RADS = 0, additional imaging needed).

8.2.3 Diagnostic Imaging (Positive Screening Results Only) Within 30 Days After Screening

- Follow-up diagnostic imaging and possible biopsies will be per institutional standard of care (diagnostic FFDM, ultrasound, and/or other procedures);
- Follow-up diagnostic imaging must be completed within 30 days after screening imaging is completed;
- Further evaluation or follow-up procedures will be conducted per institutional standard of care;
- Results of diagnostic assessment and follow up will be submitted to ACRIN.

8.3 Group B Only Procedures

8.3.1 Pre-Trial Screening: Collection of Images

The initial screening study from which the call-back recommendation was generated must have been completed within 30 days prior to the call-back diagnostic imaging visit. The initial screening FFDM that led to the patient call back will need to be submitted to ACRIN for study-related assessment.

8.3.2 GROUP B IMAGING: Call-Back Diagnostic Imaging (Standard-of-Care Imaging, Including FFDM, and DBT) Within 30 Days After Screening

Participants enrolled to Group B, a cohort of asymptomatic women ages 25 and older with no history of breast cancer and no implants who have had image-positive screening results (abnormal findings, BI-RADS = 0, additional imaging needed), will undergo the following procedures on both breasts during routine call-back diagnostic imaging:

- Diagnostic FFDM and/or ultrasound (and any other standard imaging and procedures) per institutional standard of care;
- Confirm/collect current participant and proxy contact information;
- Study-related tomosynthesis imaging sets (limited and tomosynthesis plus sets) according to parameters provided in the ACRIN PA 4006 Imaging Manual (available at www.acrin.org/4006_imagingmaterials.aspx);
- Assessment for AEs.

8.3.3 Local Reader Clinical Assessment: Sequential Reads

Local radiologists (see Section 6.2 for qualifications) will be responsible for the clinical read of diagnostic imaging under the following restrictions:

- Diagnostic images will be read sequentially:
    1. FFDM (screening and diagnostic; historical patient imaging will be available per institutional standard of care);
    2. Two-view limited tomosynthesis image set with low-dose MLO view only;
    3. Two-view tomosynthesis plus image set with low-dose MLO and addition of low-dose CC view;
    4. Any other standard imaging and procedures (e.g., ultrasound).
- Images will be assessed for clinical significance, lesion(s) location and type (broadly as soft-tissue or calcification-only lesions, as well as subgroup analysis of mass, asymmetry, architectural distortion and calcifications), and quality;
- Further evaluation or follow up procedures will be conducted per institutional standard of care.

8.4 GROUPS A and B FOLLOW UP: Medical Records Review and Images Collection at Approximately One (1) Year Post-Screening

8.4.1 Follow-Up Responsibilities

Sites will be responsible for follow-up data collection at approximately one (1) year post-screening for Groups A and B. Study-related follow up may be necessary up to 18 months post-screening depending on participant accessibility and clinical follow-up scheduling. Study-related follow up may be truncated due to funding and related trial-completion limitations.

8.4.2 Follow-Up Procedures

- Participant status will be determined at approximately one (1) year post-screening;

- Research staff will contact the participant's treating physician for medical records extraction and to assist in submission of follow-up images to ACRIN;
- If treating physician is no longer overseeing participant care, telephone contact will be made with the participant or proxy to facilitate contact with new treating physician or to determine current breast cancer-related status at minimum;
- A Follow-Up Manual detailing the specifics of contact and other procedures is available at www.acrin.org/4006_imagingmaterials.aspx
- All participant data from image-positive call-back cases and interval cancers will be reviewed in adjudication to classify them as calcification-only or soft-tissue lesions (further delineated by subtype—e.g., mass, asymmetry, architectural distortion); this classification will serve as basis for comparison with local reader results (see Sections 9.3 and 15.5).

8.5 Study Procedures Table

Study Procedures	PRIOR TO IMAGING: Eligibility and Registration (BOTH GROUPS)	GROUP A (SCREENING) (30 Days Between Screening and Diagnostics)				GROUP B (DIAGNOSTIC) (30 Days Between Screening and Diagnostics)			FOLLOW UP: Approximately One (1) Year Post-Screening (BOTH GROUPS)
		IMAGING: Screening	Local Reader Clinical Assessment	Positive Screening Cases: Diagnostic Assessment	MONITORING (BY LESION TYPE)	Pre-Trial Screening*	MONITORING (BY LESION TYPE)	IMAGING: Diagnostic Imaging	Local Reader Sequential Clinical Read	
Informed Consent Form	X									
Eligibility/Registration	X									
Medical History	X									
Collect/Confirm Participant and Proxy Telephone Contact Information	X	X						X		
Pregnancy Test for Women of Childbearing Potential	X									
Standard Screening FFDM		X				X*				
Tomosynthesis Image Sets (see Section 9.0)		X						X		
Standard Diagnostic FFDM and/or Ultrasound				X				X		
Local Clinical Images Read			X	X		X			X	
Images Submission to ACRIN		X		X		X*		X		X
Reader Results Submission to ACRIN			X	X		X			X	X
Assessment for AEs		X						X		
Medical Records Extraction										X
Contact with Treating Physician and/or Participant and/or Proxy										X

FFDM, full-field digital mammography.

* The screening FFDM that prompted the recommendation for call back for potential Group B participants will have to be available for submission to ACRIN for patients to qualify for participation in the Group B arm.

9.0 IMAGING AND READER STUDIES PROTOCOLS

9.1 Imaging Parameters

Imaging parameters for the tomosynthesis sets have been developed in accordance with Hologic's guidelines and the overall strategy of maintaining the tomosynthesis dose at approximately 1.2 mGy and the low-dose FFDM dose at approximately 1.0 mGy for a 5.0-cm thick breast in the combined tomosynthesis+FFDM acquisition. The thickness-dependent doses are to be posted online at www.acrin.org/4006_imagingmaterials.aspx.

Monitoring of radiation dose will be a part of the image quality assurance program for this trial, and sites with higher average doses will be given feedback by the core lab and PI concerning methods to reduce dose.

9.2 Images Submission

The protocol-required images must be in DICOM format on CD/DVD-ROM or submitted via the Internet using the TRIAD transfer system, which facilitates DICOM exchange processes. ACRIN can provide TRAID software for electronic image submission and anonymization to participating institutions. Images should be transmitted along with an Imaging Transmittal Worksheet (ITW) that can be found on the ACRIN PA 4006 web site at: www.acrin.org/4006_imagingmaterials.aspx. The required images must be submitted to the ACRIN core laboratory. Prompt submission of all image data is essential to ensure adequate quality control. For support in sending the images via the Internet using TRIAD, contact the representatives of the core lab via email at Triad-Support@phila.acr.org or via phone: 215-940-8820.

Instructions for image submission and anonymization, as well as information regarding Quality Control, are available at: www.acrin.org/4006_imagingmaterials.aspx.

9.3 Local Reads and Adjudication of Cases

9.3.1 Local Reader Assessments

For screening Group A, local reads will comprise quality and diagnostic assessments of the image sets—2-D FFDM and the tomosynthesis image sets. Two radiologists minimum at each site will be needed for the study; images will be randomly assigned by the site PI; and local readers will be blinded to the other radiologists' interpretation of the complementary images. Positive findings on either FFDM or tomosynthesis reads will be defined as "image positive" cases and lead to call-back for diagnostic assessment.

For diagnostic Group B, local reads will comprise successive reads of 1) screening and diagnostic FFDM images followed by 2) the limited tomosynthesis set (with low-dose MLO view only) followed by 3) the tomosynthesis plus set (low-dose MLO view with the addition of low-dose CC view). Finally, any additional diagnostic assessment (e.g., ultrasound) will be read. Positive (abnormal) findings from the tomosynthesis imaging sets may lead to additional diagnostic procedures for participants.

9.3.2 Adjudication of Cases Using All Participant Data

Further assessment of images will focus on lesion subtypes. Distinctions in lesion identification, characterization, and triangulation across imaging platforms will be made after adjudication of cases by Drs. Copit and Conant (see Section 15.5). This will allow comparison of call-back rates and sensitivities by lesion type across the image sets (FFDM versus limited tomosynthesis image set versus tomosynthesis plus image set,

which includes the low-dose CC view). Data from all interval cancers diagnosed during the follow-up period (up to 18 months after screening) will be adjudicated, as well.

9.4 Assessment of Tomosynthesis-Imaging Parameters

9.4.1 Radiation Exposure and Quality

Analysis will compare combinations of tomosynthesis sets on all cases to allow a cap of approximately 3.4 mGy of radiation exposure per breast on average. The 3.4 mGy exposure would be equivalent to the national average for two-view mammography radiation exposure. Additional assessments will allow for subsequent analyses of image quality and specificity as compared with the adjudication results (see Section 15.5).

In this evaluation, 500 image sets from Group A will be used to compare two-view FFDM with the tomosynthesis image sets in the following combinations:

- FFDM only (average dose per average breast = approximately 3.4 mGy).
- Two-view limited tomosynthesis image set with low-dose MLO view only (low-dose 2-D MLO and two-view DBT average dose = approximately 3.4 mGy).
- Two-view tomosynthesis plus image set with low-dose MLO and addition of low-dose CC view (low-dose projection CC and MLO plus two-view DBT average dose = approximately 4.4 mGy). FFDM plus all diagnostic mammographic imaging at call-back versus the tomosynthesis image sets. The approximate dose per breast for two-view, 2-D mammography is 3.4 mGy. The dose for the complete DBT (two-view tomosynthesis at approximately 1.2 mGy each, plus two simultaneously acquired low-dose 2-D CC and MLO views at 1.0 mGy each) is approximately 4.4 mGy which is comparable to conventional mammography.

9.4.2 Quality and Lesion Subtypes

In addition to comparison between imaging modalities, quality of images (including spatial completeness, linear and feature sharpness, etc) will be assessed based on local reader and adjudication assessments for lesion subtypes.

10.0 ADVERSE EVENTS REPORTING

10.1 Definition of Adverse Event

An **Adverse Event (AE)** is any untoward medical occurrence in a participant that does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or physiological finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event (SAE)
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

10.2 Definition of Serious Adverse Event

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:

- results in death, or
- is life-threatening (at the time of the event), or
- requires inpatient hospitalization or prolongation of an existing hospitalization, or
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect.

10.3 Adverse Event Grading

Grade denotes the severity of the AE. An AE is graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0:

1 – Mild
2 – Moderate
3 – Severe
4 – Life-threatening or disabling
5 – Fatal

A copy of the CTCAE can be downloaded from the CTEP web site (http://ctep.cancer.gov).

10.4 Adverse Event Attribution

Attribution determines whether an AE is related to a study treatment or procedure. Attribution categories are:

Definite – AE ***is clearly related*** to the study treatment or procedure.
Probable – AE ***is likely related*** to the study treatment or procedure.
Possible – AE ***may be related*** to the study treatment or procedure.
Unlikely – AE ***is doubtfully related*** to the study treatment or procedure.
Unrelated – AE ***is clearly NOT related*** to the study treatment or procedure.

10.5 Potential Expected and Unexpected Adverse Events

AEs may be **expected** or **unexpected**:

- An **expected AE** is one that is described in the protocol, the ICF, or the investigator's clinical brochure.
- An **unexpected AE** is one that has not been described in the protocol, the ICF, or the investigator's clinical brochure.

10.6 Expected Adverse Event(s) for Study Procedures (Groups A and B)

Only AEs with grades 3, 4, and 5 that are considered **possibly, probably,** or **definitely** related to the study-related tomosynthesis scan procedures require reporting to ACRIN. Please refer to your local IRB's policies regarding AEs.

10.6.1 Expected Adverse Events From Tomosynthesis

Likely

- Discomfort from breast compression that is similar to routine mammography;
- Bruising similar to routine mammography.

10.6.2 Expected Adverse Events Associated With Radiation Exposure From Tomosynthesis

The radiation dose from a tomosynthesis study of the breast varies depending upon patient size, scanner used, technique used, and the use of available methods for dose

reduction. The radiation dose will be matched to the breast size per the manufacturer's specifications, optimizing the dose for each participant.

Utilizing these techniques, the radiation dose associated with this tomosynthesis protocol will be an average of 4.4 mGy for a breast of 5.0-cm thickness. By comparison, the national average dose for mammography is approximately 3.4 mGy for the same breast size. Thus, the radiation risk from this study is little different from that of a standard mammogram.

The radiation dose of the study images doubles the participant's radiation exposure since the participant will undergo both mammography and tomosynthesis. However, the combined exposure is many orders of magnitude less than that associated with deterministic effects. Thus, no deterministic effects are anticipated.

Stochastic radiation effects can be estimated from the effective dose. The effective dose from the study images is 0.22 mSv assuming a tissue weighting factor (w_T) of 0.05.[10] By comparison, the national average ubiquitous background radiation is 3.1 mSv,[11] and more than 2.3 million people in the United States are exposed to more than 20 mSv per year without known detriment. For the purposes of radiation safety, a linear no-threshold model is assumed for solid cancer incidence. Based on this model, the current estimate of the lifetime risk of a fatal solid cancer is 0.05 per Sv (for the general public) or approximately 1.1×10^{-5} (1.1 in 100,000) for the study images.

10.7 Recording of Adverse Events

Prompt reporting of AEs is the responsibility of each investigator, clinical research associate (RA), and/or nurse engaged in clinical research. Please refer to Table A below and Sections 10.8 and 10.9 for specific details about reporting. Anyone uncertain about whether a particular AE should be reported should contact ACRIN headquarters at 215-574-3183 for assistance. However, an AE report should be submitted if there is a reasonable suspicion that the AE may be related to the study procedures.

Routine reporting is defined as documentation of AEs on source documents and the AE case report form (CRF), and submission to ACRIN for preparation of a report for DSMB review, and the final study report.

Expedited reporting is defined as immediate notification of ACRIN within the specified timeframe outlined in the protocol and in Table A below. Routine reporting requirements also apply.

TABLE A
Reporting Requirements for AEs occurring within 30 Days of the last use of a study-related device[1]

	Grade 1	Grade 2			Grade 3				Grade 4		Grade 5	
	Unexpected and Expected	Unexpected		Expected	Unexpected		Expected		Unexpected	Expected	Unexpected	Expected
		with Hospitalization	without Hospitalization		with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization				
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	**10** Calendar Days	Not Required	**10** Calendar Days	**10** Calendar Days
Possible Probable Definite	Not Required	Not Required	Not Required	Not Required	**10** Calendar Days	**10** Calendar Days	Not Required	Not Required	24-Hour; 5 Calendar Days	**10** Calendar Days	24-Hour; 5 Calendar Days	**10** Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to agent administration or other cause must be provided.

1 Adverse events that occur more than 30 days after the last exposure to the investigational device and have an attribution of possible, probable, or definite require reporting as follows:

24-hour notification followed by complete report within 5 calendar days for:
- Grade 4 and Grade 5 Unexpected Events

10 calendar day report:
- Grade 3 Unexpected Events with or without Hospitalization
- Grade 4 Expected Events
- Grade 5 Expected Events

At each contact (site visit and/or telephone) with the study participant, the investigator or investigator-designee must seek information on AEs through discussion and, as appropriate, by examination. Information on expected and unexpected AEs considered **possibly, probably,** and/or **definitely** related to the study components of the ACRIN PA 4006 trial with grades of 3, 4, or 5 should be recorded immediately into the source document (e.g. AE Log and/or progress notes of the study participant's chart) and retained at the site.

Study related AEs must be recorded in the AE CRF and reviewed by the principal site investigator in real time to determine grade and attribution of the event. If the AE meets the criteria for serious and requires expedited reporting, an ACRIN SAE Report will be completed (refer to Section 10.9 for detailed instructions).

AEs already documented in an AE CRF (i.e., at a previous assessment) and designated as 'ongoing,' should be reviewed at subsequent visits as necessary. If these have resolved, the documentation in the AE CRF should be completed including an end date for the event and not the date of the visit. If an adverse experience increases in frequency or severity during a study period, an up-to-date record of the experience will be documented. Each AE should be followed until resolution, stabilization, or until it has been determined that the study procedure or study participation is not the cause. Any SAE that occurs after the study period and is considered to be possibly related to the study procedures or study participation should be recorded and reported immediately.

10.8 When to Report

It is the responsibility of the investigator to document all AEs (as identified in Section 10.6) that occur during the course of the study including any unexpected AEs with grades 3, 4, and 5 with attributions of **possible, probable,** and **definite.** At each designated visit, the investigator will evaluate for any AEs. AEs not previously documented in the study will be recorded within the study participant's chart to identify any AEs potentially related to any study procedures. The nature of each event, date and time (when appropriate) of onset, outcome, frequency, maximum intensity, action taken, and attribution will be recorded.

10.8.1 When to Report

You must use the following AE reporting criteria for all protocol-specific AEs/SAEs:

1. Grade 3 unexpected AEs with hospitalization that are **possible, probable,** or **definite** require a complete SAE report to be submitted within **10 calendar days** of first knowledge of the event. **Routine reporting procedures also apply.**
2. Grade 3 expected AEs with hospitalization that are **possible, probable,** or **definite** will be reported by **routine reporting procedures only.**
3. Grade 3 unexpected and expected AEs without hospitalization that are **possible, probable,** or **definite** will be reported by **routine reporting procedures only.**
4. Grade 4 or 5 expected AEs that are **possible, probable,** or **definite** require a complete SAE report to be submitted within **10 calendar days** of first knowledge of the event. **Routine reporting procedures also apply.**
5. Grade 4 or 5 unexpected AEs that are **possible, probable,** or **definite** will be reported via phone report within a **24-hour** time period to ACRIN by the investigator or investigator-designee. In addition, a complete SAE report is due within **5 calendar days** of the initial 24-hour telephone report. **Routine reporting procedures also apply.**
6. Expedited AE reporting must be completed within **5 to 10** working days of first knowledge of the event according to the descriptions above.

10.8.2 Assignment of grades and attribution for each AE/SAE must be completed by the site principal investigator. All AEs/SAEs should be documented in the study participant's chart and CRFs. For expedited SAE reports, a copy of the report must be kept at the site. Significant new information on any on-going SAE should be promptly reported to ACRIN.

10.9 How to Report

10.9.1 An expedited AE report requires submission to ACRIN using the ACRIN SAE Report.

10.9.2 Completed expedited reports should be sent to:

Lia Worley, ACRIN AE Coordinator
Re: Serious Adverse Event Report
ACRIN PA 4006
1818 Market Street, 16th Floor

Philadelphia, PA 19103

10.9.3 A copy of all SAE reports should be sent to ACRIN by fax at (215) 940-8819. All deaths should be reported by telephone within 24-hours of first knowledge of the event. To make a telephone report to ACRIN, call (215) 717-2763, available 24 hours a day (recorder available Monday through Friday from 4:30 PM to 8:00 AM Eastern Time and on weekends).

10.9.4 All expedited AE reports should be sent to your local Institutional Review Board (IRB). Please refer to your local IRB's policies regarding AEs.

11.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice (International Conference of Harmonisation [ICH] guidelines), applicable government regulations, and ACRIN research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB) for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to ACRIN before implementation of the study.

The investigator will provide ACRIN with the institution's federal wide assurance (FWA) number, along with the IRB approval letter and copy of the IRB-approved informed consent form (ICF). The investigator will provide a copy(s) of IRB approval letter(s) for any amendment(s), and copy(s) of annual renewal(s).

All study participants in this study will be given an IRB-approved, site-specific ICF describing the study and providing sufficient information for participants to make informed decisions about their participation in this study (see Appendix I for an ICF template). The ICF will be submitted along with the protocol for review and approval by the local IRB. The study participant MUST be consented with the EC/IRB-approved ICF before the participant is subjected to any study procedures. The IRB-approved ICF MUST be signed and dated by the study participant or legally acceptable representative and the investigator-designated research staff obtaining the consent before the participant is subjected to any study procedures. Any revisions to the ICF at any time during the trial will need to be submitted to the IRB for approval, followed by submission to ACRIN PDRC.

12.0 CONFLICT OF INTEREST

Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest in accordance with ACRIN Conflict of Interest policies and applicable federal, state, and local laws and regulations.

13.0 PUBLICATION POLICY

Neither complete nor any part of the results of the study obtained under this protocol, nor any information provided to the investigator for the purposes of performing the study, will be published or passed on to any third party without the consent of ACRIN, the Study Chair, and/or the ACRIN

Publication Committee. Any investigator involved in this study is obligated to provide ACRIN with complete test results and all clinical data obtained from the participants in this protocol. Investigators will follow the ACRIN Publication Policy (available online at www.acrin.org/PublicationsPolicy.aspx).

14.0 INSTITUTIONAL MONITORING AND AUDITS

The investigator will permit study-related monitoring and auditing inspections of all study-related documents by the IRB, government regulatory agencies, and ACRIN. The investigator will ensure the capability for inspection of all participating sites' study-related facilities (e.g. imaging centers, satellite sites). The investigator will allocate adequate time for these activities, allow access to all study-related documents and facilities, and provide adequate space to conduct these visits.

14.1 Monitoring

Monitoring ensures protocol and regulatory compliance, participant's welfare and safety, and provides resources to sites for clarification to the protocol and guidance in completion of the case report forms. (CRFs). Monitoring of the protocol is implemented after the activation of the trial, and once participants have been enrolled into the study at each site. Each site will be informed when the monitoring of the protocol is implemented. Monitoring instructions will be sent to the site prior to the implementation of monitoring to aid in preparation for the monitoring. The instructions will specify regulatory documents and participant case records scheduled to be monitored. The ACRIN QA Monitor will review CRFs and source documents at several different time points: after first few participants enrolled and during the conduct of the trial, including staff changes at the participating sites. The QA Monitor will review the initial, annual, and any revised regulatory documents during each monitoring phase.

14.2 Auditing

All participating institutions that enroll participants will be audited. The timing of the initial on-site audit will depend upon several factors, including the rate of accrual (both study-wide and site-specific), the number of evaluable participants enrolled at an individual site, the status of the protocol and pending amendments, and monitoring status. Generally, audits will be conducted after the number of evaluable participants reaches 20% of targeted accrual, either study-wide and/or site-specific. Audits are typically scheduled to occur at least 3 months after an institution has been monitored, providing that monitoring did not identify issues that mandate immediate auditing. This schedule may be altered in the event of pending protocol amendments. Closure of the study to accrual will trigger auditing of all participating institutions not yet audited. Additionally, site-specific circumstances may prompt an audit at any time.

Subsequent audits will be scheduled per the outcome of the initial audit. Audits can be completed more frequently and conducted on a yearly basis depending on the outcome of the audit and monitoring. The audits will be conducted per procedures established by ACRIN for the audit visit will be sent to the site prior to the scheduled audit visit. These instructions will specify which participant case records will be reviewed during the audit. On-site records will be verified against the submitted form, and the findings will be recorded on specially-prepared audit reports. Major discrepancies will be forwarded to the appropriate oversight body within ACRIN. IRB procedures, approvals, and ICFs will also be reviewed at the time of the audit visit. The ACRIN Audit Manual is available online at www.acrin.org.

To help sites prepare for monitoring and audits and to assure that the investigator and the research staff maintain records appropriately, ACRIN Headquarters will offer training to sites. This training will cover all aspects of data collection, including special instructions to obtain and file the various source documents needed to verify the accuracy of submitted data for this trial. **Details in the study-specific Monitor Plan and Audit Plan will override procedures and timing described in the protocol.**

14.3 Source Documents

Source data are found in all information, original records of findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents represent the first recording of any observations made or data generated about a study participant while he or she is enrolled in a clinical trial. Source documents for each study participant substantiate the data that are submitted to ACRIN.

Source documents must verify the eligibility criteria and data submitted on all CRFs. If an item is not mentioned (e.g., history and physical examination alluding to a condition, but no mention of a psychological condition), it will be assumed it is not present.

Research records for each case should contain copies of the source documents for the data collected and reported to ACRIN. If data are abstracted from medical charts that are not filed at the investigative sites (e.g. hospital charts), copies of these records should be filed in the research chart. Every attempt must be made to obtain all records/charts that were used to abstract any study data for this protocol. This will prevent any discrepancies and the inability to verify the document and the data reported.

14.4 Case Report Forms

CRFs, both web-based and paper forms, are the primary data collection instruments for the study. All data requested on the CRFs must be recorded, and any missing data must be explained. If a space is left blank on paper CRFs because the procedure was not done or the question was not asked, "N/D" must be noted. If the item is not applicable to the individual case, "N/A" must be noted. All entries on paper CRFs must be printed legibly in black ink on the paper CRFs. In the event of any entry errors, corrections must be made by drawing a **single straight line** through the incorrect entry, writing **the initials of the person making the correction, recording the date** when the correction is being made, and entering the correct data above the strike through. Do not use white out or an eraser. Please refer to ICH Good Clinical Practice Guidelines.

Data elements that are extracted from the medical record (such as participant history or official clinical interpretations of images, pathology, or surgery results) and recorded on the CRFs will be reviewed against the appropriate component of the medical record. Data elements gathered from signed participant questionnaires must be available for review. Required study image interpretation data that are more detailed in information than the image and not typically documented in the standard radiology report may be documented on the CRF and are acceptable source documentation **if signed by the Investigator**. At the time of audit, the auditor will verify the occurrence of the imaging examination, the reader, and the date of the exam(s) from the medical record(s). Any use of approved CRFs as source documentation require a signature and date on the CRF with a reference to the information source (FFDM report, tomosynthesis report, medical record, etc.). Any use of CRFs as source documentation when the protocol has designated the source data will be medical record documentation will be considered a major protocol deficiency.

14.5 Institutional Review Board

Sites must obtain initial full-board, local IRB approval to participate in ACRIN trials. Prior to participant registration, a copy of the IRB approval letter for the protocol and the ICF must be sent to ACRIN, along with a copy of the IRB-approved, site-specific ICF. Investigator will provide a copy(s) of IRB approval letter(s) for any amendment(s), and copy(s) of annual renewal(s).

15.0 STATISTICAL CONSIDERATIONS

15.1 Study Design and Endpoints

Study participants will be recruited among those presenting for breast cancer screening using FFDM (Group A) or for diagnostic follow-up after positive findings on previous screening using FFDM (Group B) at ACRIN-qualified institutions in Pennsylvania that have a Hologic tomography scanner. Each participant will undergo both FFDM and DBT examinations. Each of the two tests will be interpreted separately by readers at the participating sites. Reference standard information on the presence or absence of cancer at the time of screening will be determined by pathology and the 1-year follow-up.

15.2 Specific Aims and Analysis Plans

15.2.1 Primary Aim

To compare recall rates of FFDM to the limited DBT set (digital breast two-view tomosynthesis with low-dose MLO) [Group A].

In this study, each participant will undergo imaging with both DBT and FFDM. To account for the paired nature of the design, McNemar's test will be used to make the comparisons of call-back rates.

15.2.2 Secondary Aims

15.2.2.1 To compare sensitivity of FFDM to the limited DBT set (digital breast two-view tomosynthesis with low-dose MLO) [Groups A and B].

The sensitivities of the two modalities will be compared using McNemar's test. The main analysis for this aim will be performed on the combined data from the two groups. In addition, data from each of the two groups will be examined separately. Exact p-values will be reported.

15.2.2.2 To assess lesion-type characterization:

15.2.2.2.1 To compare the sensitivity and specificity by lesion-type characterization (calcification-only lesions versus soft-tissue lesions, as well as lesion subgroups: masses, calcifications, architectural distortions, asymmetries) in FFDM versus DBT (two-view tomosynthesis set with low-dose MLO) [Group A call-back cohort and Group B].

15.2.2.2.2 To estimate the agreement of FFDM and DBT with the determination of the adjudication committee on lesion-type characterization.

The analysis for this aim will be performed at the lesion level. For the comparison of sensitivity and specificity, individual lesions will be grouped by lesion type as determined by the adjudication committee. For each group, sensitivity and specificity will be compared using McNemar's test, adjusted for correlation in the lesion data due to clustering within the participant.[12–14] For the assessment of agreement, the data on lesion-type determination of each modality will be tabulated against the determination by the adjudication committee. Percentages of agreement and kappa statistics appropriate for multiple categories will be estimated.

15.2.2.3 To use the sequential interpretation results [Groups A and B] in order to compare the two-view limited tomosynthesis set (with low-dose MLO view alone) with the tomosynthesis plus set (low-dose MLO view plus addition of low-dose CC view) on the basis of:

- Call-back rate;
- Identification of new lesion(s);
- Lesion characterization; and
- Triangulation.

The analysis of this aim will utilize reader responses during the local sequential interpretation of the two-view tomosynthesis set with low-dose MLO, followed by sequential read with addition of low-dose CC view [Groups A and B]. Rates of interest will be estimated and compared. For analyses at the lesion level, adjustment for clustering of lesions by participant will be implemented.

15.2.2.4 To calculate and compare the radiation dose of the FFDM and the DBT sets.

In the analysis for this aim, estimates of dose per participant will be computed. The radiation dose will be calculated in terms of the mean (average) glandular dose (MGD or equivalently AGD) from the kVp, mAs, target tube and filter, and other pertinent information derived from the DICOM header of the clinical images. The dose will be calculated per image and then summed to determine the total MGD per breast of the clinical FFDM images, and the total MGD per breast of the clinical trial-image DBT set. The distribution of radiation dose data will be explored graphically. Radiation doses from the two modalities will be compared non-parametrically, taking into consideration the paired nature of the design.

15.2.2.5 To identify the determinants of participant radiation dose and clinical image quality, including factors such as kVp, mAs, target/filter combination, and breast thickness and composition.

In the analysis for this aim regression modeling will be utilized to examine the relation between participant radiation dose and variables representing the factors listed above.

15.3 Sample Size/Accrual Rate

Study participants will be recruited to either Group A for breast cancer screening or Group B for diagnostic imaging following suspicious findings on previous breast cancer screening. A total of 550 participants (500 to Group A and 50 to Group B) will be enrolled over an accrual period of **12** months at two institutions.

15.4 Power Consideration

The sample size for the study was chosen to provide adequate power for addressing the primary aim of the study, which is the comparison of call-back rates in Group A. Available data on the comparison of FFDM to DBT in general screening populations suggest that the call-back rate for FFDM is about 10% and that of DBT is about 6% to 7% (a 30% to 40% reduction in call-back rate between FFDM and DBT). The following table presents sample size computations to achieve power of 80% using a two-

sided McNemar's test at level 0.05. Power and sample size are influenced by the actual difference in rates and by the proportion of cases in the off diagonal cells of the 2x2 table classifying call-back status as determined by FFDM and DBT.

The table shows that a total sample size of 500 cases will provide adequate power for many parameter combinations of interest. Because the power of the test depends critically on the proportion of discordant call-back determination, which is difficult to assess a-priori, we plan to monitor this proportion during the early part of the study and consider adjustments in the sample size, if necessary.

Power	Sample Size	Difference in Call Back Rates	Proportion of Discordant Determinations
0.80103	361	0.030	0.040
0.80077	463	0.030	0.050
0.80053	562	0.030	0.060
0.80001	645	0.030	0.070
0.80022	736	0.030	0.080
0.80049	830	0.030	0.090
0.80033	920	0.030	0.100
0.80057	258	0.035	0.040
0.80076	333	0.035	0.050
0.80071	410	0.035	0.060
0.80093	482	0.035	0.070
0.80062	543	0.035	0.080
0.80013	608	0.035	0.090
0.80046	676	0.035	0.100
0.80085	251	0.040	0.050
0.80079	307	0.040	0.060
0.80044	367	0.040	0.070
0.80022	421	0.040	0.080
0.80038	468	0.040	0.090
0.80010	517	0.040	0.100

15.5 Adjudication Committee Assessments

Study-related imaging results will be assessed for lesion type (soft tissue or calcifications only) and subtype (mass, architectural distortion, calcifications, asymmetry) as determined by breast imaging experts (Drs. Conant and Copit) familiar with all modalities used in breast screening and diagnostics (inclusive of FFDM, tomosynthesis, ultrasound, MRI and x-ray mammography).

15.6 Reporting Guidelines

Routine reports for this protocol will be provided to oversight bodies, including the ACRIN PA DSMB, for review during each of its quarterly teleconferences.

Routine reports will include:

- Accrual and participant characteristics;
- Timeliness and completeness, eligibility and protocol compliance, and outcome data;
- All reported adverse events.

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APPENDIX I

ACRIN PA 4006

INFORMED CONSENT FORM TEMPLATE

Comparison of Full-Field Digital Mammography with Digital Breast Tomosynthesis Image Acquisition in Relation to Screening Call-Back Rate

[Note: The American College of Radiology Imaging Network (ACRIN) complies with the privacy measures put forth by the Health Insurance Portability and Accountability Act (HIPAA). However, ACRIN does not monitor compliance with HIPAA; that is the responsibility of the local institutions and their Institutional Review Boards (IRBs). Local IRBs may choose to combine the authorization elements in the informed consent.]

The American College of Radiology Imaging Network (ACRIN) is conducting a research study known as a clinical trial. Research staff will explain to you the details of what is involved. This document is designed to help you understand what will happen in the study, why the study is being done, and what risks or benefits might be involved in the study. This informed consent form must be signed before any study procedures are performed and before you are registered into the clinical trial.

Clinical trials include only people who choose to take part. Please take your time in deciding whether you want to be involved. You are encouraged to discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you should ask your study doctor for more explanation. If you decide to do this study, you will be asked to sign and date this form.

You are being invited to participate in this research study because it is time for your routine breast cancer screening or you have recently been screened and are returning for diagnosis of suspicious findings.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to learn the safest way to use an imaging technology called tomosynthesis (called "study imaging" in this document) while getting images that will benefit you by showing potential breast cancers. Researchers will compare your study imaging with standard care using digital mammography, and other images taken to determine your breast health. They hope to determine the best way to obtain study images, which provide good information about your breast health while exposing you to no more radiation than routine x-ray mammography. Doctors are also trying to learn whether the study imaging can be used alone or should be used with digital mammography.

About Tomosynthesis (Study Imaging)

Mammograms provide two-dimensional (2-D), flat images. Tomosynthesis can be used to create three-dimensional (3-D) images of the breast. The 3-D images may allow doctors to "scroll through" images of your breast to better see the layers of normal breast tissue that can sometimes appear to be concerning on regular 2-D mammography. This technique may see cancers that were hidden by normal tissue that overlaps on 2-D mammography. The study imaging will be completed after your standard imaging. If a separate machine is needed for the study imaging, then your breasts will be compressed again. Once you

are positioned in the machine, the study imaging will take about as much time as a routine mammography of both breasts.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 550 women with no history of breast cancer will take part in this trial. This study will be conducted at approximately two (2) breast cancer screening institutions located in Pennsylvania.

HOW LONG WILL I BE IN THE STUDY?

You will be in the study up to 18 months from your initial breast screening. For the study, you are being asked to undergo study imaging immediately after routine imaging either for screening or for diagnosis. Your treating doctors will decide your treatment (for example, biopsy). Your study doctor and other research staff will contact you, a proxy if you are unavailable, and/or your treating doctor to learn about your health up to 18 months after your screening.

This trial is expected to end after all study participants have completed the study-related visits and all follow-up information has been collected. This trial may be stopped at any time by your study doctor or by ACRIN without your consent for the following reasons:

- Your health or safety may be at risk;
- You have not been following study instruction;
- An administrative decision has been made by ACRIN or the study doctor.

These actions do not require your consent, but you will be informed of any of these decisions.

You can stop participating at any time. Your decision to stop participating in the study will not interfere with your future medical care. However, if you decide to stop participating in the trial, we encourage you to talk to the study doctor and your treating doctor first.

WHAT AM I BEING ASKED TO DO IN THE STUDY?

If you agree to take part in this study and are determined to be eligible by research staff, you will be asked to read and sign this consent form before you are enrolled to participate in this trial and before any study procedures are performed. See the Schemas and Study Chart at the end of this section for a visit-by-visit outline of what will be expected of you if you decide to participate in this trial. When you are enrolled into the study, you will have the following tests and procedures.

Standard medical procedures that are part of regular standard of care and would probably be done even if you do not join the study:

- A review of your medical history;
- Digital mammography;
- Diagnostic procedures.

Medical procedures that are being done specifically because you are in this study (these may or may not be done if you do not join the study):

- Study imaging (tomosynthesis) on both breasts;

- Follow up for as along as 18 months—the research staff will want to access your medical records from your treating doctor. If you change treating doctor during this time, research staff may call you or a proxy to ask for contact information for your new treating doctor and perhaps ask about your breast health over the phone.

If you agree to participate in this study, you will be assigned to one of two different study groups, depending on whether you are being screened for breast cancer (Group A: Screening) or are returning for further evaluation after screening (Group B: Diagnosis).

For Group A: Screening

If you are enrolled in Group A, you are going for your routine breast-cancer screening using digital mammography. You will receive the standard of care for this screening as determined by your study and treating doctors. You will also have study imaging called tomosynthesis. Your treating and study doctors may determine that no additional testing is needed after reviewing your image results; or, they may find it necessary to ask you to return for more imaging to diagnose suspicious findings that may be breast cancer. You will be asked to return for diagnosis if something suspicious is found on either digital mammography or study imaging. The study team will want to collect all of your images and results from screening and diagnostic studies.

For Group B: Diagnosis

If you are enrolled in Group B, you have already had your routine breast-cancer screening using digital mammography, and are returning to your treating doctor because of findings on the screening mammogram that were concerning and could possibly be due to a cancer. You will receive standard-of-care imaging and will have additional study imaging called tomosynthesis. The study team will want to collect all of your images and results from screening and diagnostic studies.

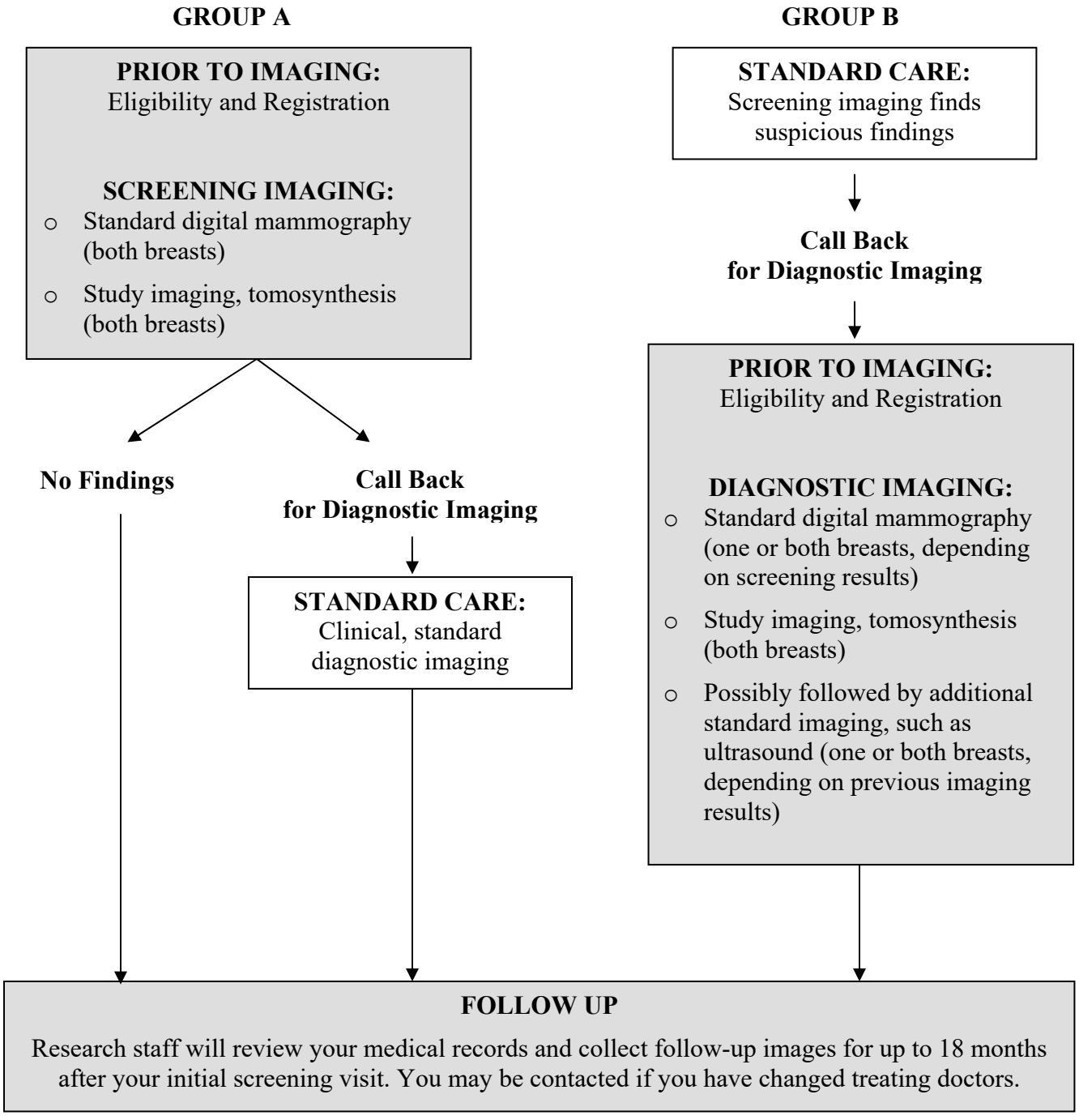
Most likely, you are returning for diagnosis of findings in only one breast. If you agree to join the trial, study imaging will take images of both breasts. If something concerning is found on study imaging, you may be asked to undergo more diagnostic procedures in either breast. Your treating doctor will then determine what additional steps may be needed, such as biopsy. Your treating doctor may make this decision based on findings from either standard diagnostic imaging or study imaging.

Follow Up for Both Groups A and B

The study doctor and research staff want to collect information on your breast health from your medical records up to 18 months after your screening visit. If you switch doctors during this time, it is important to let the study team know. Otherwise, they may need to contact you or, if necessary, a proxy (family member or someone who will know about your health) to learn how to contact your new treating doctor. At the very least, the research staff would like to know whether you are cancer free. If we cannot contact you or your treating doctor, the research staff may check national registries to learn about your health status.

STUDY SCHEMAS BY GROUP

(Shaded boxes contain study-related procedures.)



STUDY CHART

PRIOR TO IMAGING: Group A and Group B Eligibility and Registration	• Read and sign the informed consent form; • Provide medical history and demographic information; • Undergo pregnancy test if you are a woman of childbearing potential; • Provide telephone contact information for yourself and a proxy (someone who will be able to report on your health status).
GROUP A IMAGING: Imaging for Screening	• Confirm contact information; • Undergo imaging: - Standard-of-care screening imaging (both breasts); and - Study imaging (both breasts); • Answer questions about how you feel after the imaging.*
GROUP B IMAGING: Imaging for Diagnosis	• Confirm contact information; • Undergo imaging: - Standard-of-care diagnostic imaging (on one or both breasts, depending on your screening results); - Study imaging (on both breasts), and - Possibly other diagnostic assessment (such as ultrasound, again on one or both breasts, depending on imaging results); • Answer questions about how you feel after the imaging.*
FOLLOW UP: Group A and Group B (Up to 18 Months After Screening)	• Provide additional information related to your breast health up to 18 months after screening. Research staff may need to review your medical records and/or contact you, a proxy, and/or your treating physician to obtain this information.

* If at any time within 30 days after study-related imaging, you have adverse effects you think may be related to the study, contact your study doctor and let him or her know.

WHAT ARE THE POSSIBLE RISKS OR DISCOMFORTS OF THE STUDY?

While on the study, you may be at risk for these side effects from the following procedures. You should discuss these with your study and/or treating doctor(s). There also may be other side effects that we cannot predict. Many side effects go away shortly after the imaging scan is stopped, but in some cases side effects can be serious, long lasting, or permanent.

Risks Associated With Study Imaging (Tomosynthesis)

Likely

- Discomfort from breast compression that is similar to routine mammography;
- Bruising similar to routine mammography.

If you are in Group A, study imaging during screening may lead to additional findings compared with standard screening imaging alone. Suspicious findings on either set of images will mean you will be

asked to return for diagnosis. If you do not join the trial, your treating doctor will use standard screening imaging to determine whether you need to return or not.

If you are in Group B, study imaging included for diagnosis may lead to additional findings and procedures compared with standard diagnostic imaging alone. You are agreeing for both of your breasts to undergo study imaging even though you may have been called back for diagnostic imaging on only one breast. This may lead to findings with study imaging that were not found during your initial screening visit. Therefore you may need to have additional diagnostic imaging of that breast. If you do not join the trial, your treating doctor will use standard imaging for diagnosis to determine whether you need further testing or not.

Radiation Risks

This research study involves exposure to radiation from the study imaging called tomosynthesis. In addition to the radiation you receive for your regular mammogram, you will be receiving a similar, second dose of radiation from the study imaging. The amount of radiation exposure will be largely dependent on your breast size. Your study doctor can explain how the dose might be higher for denser and larger breasts. Part of this study will look at radiation dose in hopes of obtaining quality images while optimizing radiation exposure to people in the future.

This radiation dose is not necessary for your standard medical care and will occur only as a result of being in this study and undergoing study imaging. The dose that you will receive will very likely have no effects at all. Radiation doses much higher than what you will receive are known to increase the risk of developing cancer after many years.

Reproductive Risks

Because possible exposure to radiation can damage an unborn baby, you will need to inform your study doctor if you are pregnant or suspect that you may be pregnant. If you are pregnant, you will not be able to participate in this study. If you are unsure, you will need to have a negative pregnancy result per usual care prior to enrolling in this trial and throughout the trial prior to imaging if you are unsure of your pregnancy status.

For more information about risks and side effects, ask your study doctor.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART IN THE STUDY?

Taking part in this study may or may not benefit you. The results of the study imaging will be shared with your treating doctor. The study imaging for screening or diagnosis in this trial may improve your health by finding cancers not seen on standard imaging. On the other hand, study-related findings may lead to additional imaging or unnecessary treatment, such as biopsy. These risks are common in breast-cancer screening and diagnostic imaging currently available. The hope is to reduce these risks in the future with better imaging through tomosynthesis. We hope the information learned from this study will benefit other women during breast cancer screening and diagnosis in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO PARTICIPATE?

You may choose not to take part in this study. If you choose not to participate, there will be no penalty or loss of benefits to which you are otherwise entitled. Please talk with your study and/or treating doctor(s) about this and other options.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

We will do our best to make sure that your personal information will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. Records of your participation on this study, your progress, and images submitted while you are on the study will be kept in a confidential form at *<<Institution>>* and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN) in Philadelphia. All data sent to ACRIN over the Internet will be coded so that other people cannot read it. All personal identifiers are removed and replaced with a unique identifying number.

You further understand and agree that authorized representatives of ACRIN, the Pennsylvania Dept. of Health, the Institutional Review Board (IRB) of *<<Institution>>*, and other groups or organizations that have a role in this study may, without obtaining additional consent from you, have access to and copy both your medical and research records, including the results of your participation in this study. This access is necessary to ensure the accuracy of the findings, the completion of the study, and your safety and welfare. If any publication or presentations result from this study, you will not be identified by name. Results will be reported in a summarized manner in which you cannot be identified.

Your research records and images will be kept permanently on file at ACRIN and may be used for future research. All personal identifiers are removed and replaced with a unique identifying number. The studies that may be done with the information will not specifically help you. But, it might help people in the future who have or are at risk for breast cancer.

WILL I HAVE TO PAY FOR ANYTHING?

Taking part in this study may or may not lead to added costs to you or your insurance company. Please ask your study doctor about any expected added costs or insurance problems.

You and/or your health insurance will be charged for any portion of your care that is considered standard care. You and/or your insurance company will be charged for continuing medical care and/or hospitalization. You may be responsible for any co-payments and deductibles that are standard for your insurance coverage.

You or your insurance company will not be charged for the following part of this research study:

- Study imaging with tomosynthesis.

You will receive no payment for taking part in this study.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, *<<insert name>>*, if you feel that you have been injured because of taking part in this study or if any medical emergency, injury, or illness occurs during this study. You can tell the study doctor in person or call him/her at *<<insert telephone number>>*.

In the case of medical emergency, injury, or illness during this study, emergency medical treatment is available but will be provided at the usual charge. You and/or your insurance will be responsible for the

cost of the medical care of that illness or injury. There is no financial compensation that has been set aside to compensate you in the event of injury.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is your choice. You may choose to or not to take part in the study. If you decided to participate, you are free to leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your decision whether or not to participate in this study will not interfere with your future care. You can still get your medical care from our institution.

During the study, we may find out more information that could be important to you. A Data and Safety Monitoring Board (an independent group of experts) may be reviewing the data from this research throughout the study. This includes information that might cause you to change your mind about being in the study. If information becomes available from this or other studies that may affect your health, welfare, or willingness to stay in this study, we will tell you about it as soon as possible.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

(This section must be completed)

You can talk with your study doctor(s) about any questions or concerns you have about this study. Contact your study doctor *<<insert name>>* at *<<insert telephone number>>*.

This document explains your rights as a study participant. It you have any questions regarding your participation in this research study or you have any questions regarding your rights as a research participant, do not hesitate to speak with your study doctor or anyone listed below.

For additional information about your health or in case of a medical emergency, you may contact: *Usually the name of the local hospital information is provided and with instructions to study participants to inform the ER doctor of their participation in a clinical trial.*

_____	_____
Name	Telephone Number

For information about your rights as a research subject, you may contact *<<Institution Name>>* Institutional Review Board (a group of people who review the research to protect your rights):
(Provide the name of local IRB contact person)

_____	_____
Name	Telephone Number

WHERE CAN I GET MORE INFORMATION?

For more information, you may also visit the American College of Radiology Imaging Network web site, **www.acrin.org**. For more information about Tomosynthesis, you can go to the Patients section of the ACRIN web site.

ACKNOWLEDGEMENT

When you sign this document, you are agreeing to take part in this study. This means you have read all the above information, asked questions regarding your participation, and received answers that you understand to all your questions. You have also had the opportunity to take this consent form home for review or discussion if you want to.

You willingly give your consent to participate in this study. A copy of this signed informed consent form will be given to you.

Printed Name of Study Participant/ Legal Representative	Signature	Date

<Insert other signature and date lines as appropriate per local IRB policies and procedures>

APPENDIX II

ACRIN PA 4006

SUPPLEMENTAL MATERIALS AVAILABLE ONLINE

Supplemental materials that support the conduct of the trial are available on the ACRIN web site at the ACRIN PA 4006 protocol web page (www.acrin.org/4006_protocol.aspx). Types of materials posted include:

- Application and protocol activation documents (General Qualifying and Protocol Specific Applications, protocol activation checklist, etc.);
- Data forms;
- Imaging materials (Image Transmittal Worksheet), available directly via www.acrin.org/4006_imagingmaterials.aspx;
- Recruitment and education materials;
- Regulatory resources, available directly via www.acrin.org/pdrc.aspx;
- Participating site list.

For more information related to the trial, contact the ACRIN PA 4006 Contact Personnel link on the above-mentioned web page for a list of protocol team members at ACRIN Headquarters and their roles.