GE Healthcare

Study Title: **A**ssessment of **D**iagnostic **A**ccuracy and **P**erformance of Digital Breast **T**omosynthesis Compared to Mammography **(ADAPT Trial)**

ADAPT-Enrich: Recruitment Plan for Initially Asymptomatic Women Referred for Breast Biopsy after Screening Digital Breast Tomosynthesis Exam

Study Number: 124.03-2015-GES-0001
Revision/Amendment: 4.0
Version Date: 23/May/2016

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Investigator's Signature Page

I hereby agree to:

(i) Conduct the investigation in accordance with the agreement, the investigational plan, applicable FDA or applicable government regulations, and conditions of approval imposed by the reviewing Ethics Committee, IRB or governing regulatory body;

(ii) Supervise all testing of the device involving human subjects; and

(iii) Ensure that the requirements for obtaining informed consent are met.

Investigator Signature _____ Date _____

Print Name _____

Site Name _____

Site Address _____

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Document and Version Control

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<tr><td>2.0</td><td>23/May/2016</td><td>Carrie Lauer</td><td>Clinical Writer – Updated protocol per amendments detailed in Appendix A: Study Site and Investigator List
The following investigator(s) at each study site will be responsible for the conduct of this study. In the event that changes are made to the investigator(s) and/or sites participating in this study, a revised and dated copy of this amended page may be submitted to the responsible EC, per their policy, and stored in the Sponsor's Clinical History File (CHF) as a supplement to the protocol.
<table>
<tr><td rowspan="2">Investigator(s):</td><td>Bruce Schroeder, MD, Investigator
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<tr><td>3.0</td><td>10/Mar/2016</td><td>Carrie Lauer</td><td>Clinical Writer – Updated protocol per amendments detailed in Appendix C: Amendment to Protocol Version 2.0 to 3.0</td></tr>
<tr><td>4.0</td><td>23/May/2016</td><td>Carrie</td><td>Clinical Writer – Updated protocol per amendments detailed in Appendix D:</td></tr>
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		Lauer	Amendment to Protocol Version 3.0 to 4.0

1. STUDY SYNOPSIS

Title of Study: Assessment of Diagnostic Accuracy and Performance of Digital Breast Tomosynthesis Compared to Mammography (ADAPT Trial)

ADAPT-Enrich: Recruitment Plan for Initially Asymptomatic Women Referred for Breast Biopsy after Screening Digital Breast Tomosynthesis Exam

Protocol Number (Study Number): 124.03-2015-GES-0001

Investigator(s) and Study Center(s): Up to two (2) centers in the United States (US)
Site and Investigator contact information are detailed in Appendix A: Study Site and Investigator List.

Objective: The aim of this recruitment plan (ADAPT-Enrich) is to collect image and technical data on both digital breast tomosynthesis (DBT) and full-field digital mammography (FFDM), along with other subject data including histology results from biopsy specimen examination and cancer classification data from initially asymptomatic women referred for biopsy after recall from screening DBT and diagnostic work-up. These data will be included in a subsequent and prospectively planned pooled analysis described in a separate protocol (ADAPT-BIE) examining superiority of DBT to FFDM for breast cancer diagnosis and other performance measures.

Study Design: An open-label, multi-center, accrual study collecting DBT and FFDM images from up to 200 initially asymptomatic women aged ≥30 years referred for clinically indicated breast biopsy based on suspicious DBT screening breast imaging results will be conducted. CC and MLO views from bilateral GE screening DBT and GE screening and/or diagnostic FFDM, with 2-view DBT and 2-view FFDM acquired within a 30 day window of each other, will be collected and assessed on-site by qualified radiologist(s) for clinical management purposes. Results of biopsies and histopathology, including lesion characteristics, will be recorded and considered as truth of cancer status if positive for breast cancer. Subjects with negative or benign histological breast findings will have their images and histopathology reviewed for concordance, per the site's standard procedures. Histologic concordance with imaging will be considered truth for non-cancer status.

DBT and FFDM data collected in this protocol will be pooled for evaluation by independent, blinded readers in a subsequent reader study. The detailed information on blinded image evaluation will be provided in a separate Independent Review Charter (IRC) detailed in the ADAPT-BIE (Blinded Image Evaluation) protocol.

This study's primary endpoint is collection of data to compare the diagnostic accuracy of two-view SenoClaire® - GE Breast Tomosynthesis and 2-view FFDM based on difference in receiver operating characteristic (ROC) area under the curve (AUC) detailed in the separate ADAPT-BIE protocol.

Device-related Adverse Events (AEs), serious adverse events (SAEs), and device malfunctions will be recorded and reported to Sponsor's medical monitor and applicable authorities. No other clinical safety assessments will be performed.

Selection of Subjects: The subject population consists of initially asymptomatic adult women (≥30 years of age) referred for breast biopsy.

Inclusion Criteria:

Subjects may be included that meet the following criteria:

1. Women aged 30 years or older (≥30 years old);
2. Initially asymptomatic women who underwent routine bilateral screening with Digital Breast Tomosynthesis (DBT), followed by diagnostic work-up showing one or more abnormalities and referred for breast biopsy[1,2];
3. Are able and willing to comply with study procedures;
4. Have signed and dated the informed consent form;
5. Documented as non-pregnant based on the investigator's medical judgment and in consideration of local clinical practice standards for evidence of non-pregnancy.

Exclusion Criteria:

Subjects must be excluded from participating in this study if they meet any of the following criteria:

1. Have been previously included in this study, ADAPT-SCR recruitment plan or ADAPT-BX recruitment plan;
2. Have undergone diagnostic or surgical intervention(s) or procedure(s) on either breast, including mastectomy and cytopunction, before study-related imaging;
3. Have breasts too large to be adequately positioned on 24 x 31 centimeter (cm) DBT or FFDM digital receptor without anatomical cut-off during a DBT or FFDM examination;
4. Have participated in (within the prior 30 days) another trial of an investigational product expected to interfere with study procedures or outcomes;
5. Have breast implant(s);
6. Have reconstructed breast(s).

Research Type:

Clinical (human)	☒ *Initially Asymptomatic Women Referred for Breast Biopsy after Screening DBT*
Pre-Clinical (animal)	☐
External Bench	☐

Brief Description of Study Purpose: This study is being conducted to accrue cancer cases detected by screening DBT for a subsequent blinded reader study comparing the diagnostic accuracy and performance of digital breast tomosynthesis (DBT) performed with the GE SenoClaire® GE Digital Breast Tomosynthesis compared to conventional GE full-field digital mammography (FFDM) in asymptomatic women. The study also provides for exploratory analysis of cancerous and non-cancerous lesion characteristics detected by DBT and FFDM systems. The statistically powered reader study is being conducted to support regulatory claims to expand the labeling of the DBT system.

[1] Subjects who had screening DBT or screening/diagnostic FFDM imaging on non-GE equipment may be enrolled if they agree to undergo repeat imaging on a GE system; If the prior screening and diagnostic DBT or mammographic examinations were not conducted at the recruiting site, review of those images by the investigator must confirm that breast biopsy recommendation is warranted and GE access to the images in DICOM digital format must be granted.

[2] Screening FFDM and DBT image acquisitions must be within 30 days of each other.

Sponsor Name: GE Healthcare (GEHC) **Sponsor contact:** Sara Lam, Senior Clinical Affairs Project Manager III	**Address:** 3000 N Grandview Blvd Waukesha, WI 53188-1696 US **Telephone:** +1 262-409-0828 **E-mail:** Sara.J.Lam@ge.com
Device/Product GEHC Modality: Detection and Guidance Solutions (DGS) **Device/Product GEHC Class:** SenoClaire® - GE Breast Tomosynthesis	
Device/Product Description: Commercially available SenoClaire® - GE Breast Tomosynthesis is a Digital Breast Tomosynthesis (DBT) device available for commercial full-field digital (FFDM) mammography systems (GE Senographe® Essential Full-Field Digital Mammography) and read on IDI MammoWorkstation with Volume-Preview Synthetic 2-D Mammography (V-Preview).	
Regulatory Status: Pre-Market ☐ Post-Market ☒ DBT, FFDM, and IDI MammoWorkstations used in this study are considered post-market in the US. V-Preview for DBT is a commercially available tool on the IDI MammoWorkstation not currently indicated for breast cancer diagnosis use.	
Primary endpoints: The primary endpoint will be the site's diagnosis for each subject of cancer status (positive or negative/benign) based on histopathology of biopsy/surgical findings and histologic concordance with imaging for benign lesions. **Secondary endpoints:** Secondary endpoints for all subjects will include histology findings and size, lesion type, and other lesion characteristics based on image appearance. Technical characteristics of electronic image data collected from subjects, such as information related to radiation dose, may be extracted and analyzed by the Sponsor for the purposes of this study. **Safety endpoints:** Device-related adverse events (AEs), serious adverse events (SAEs), and device malfunctions by overall occurrence and imaging modality (DBT and FFDM) that occur during the study will be collected. No other clinical safety assessments will be performed.	
Sample Size: Up to 200 subjects referred for breast biopsy (with an enrollment ceiling per site of 120 subjects) will be enrolled in this recruitment plan until approximately 70 histopathology-confirmed cancers have been accrued. Sample size is determined by the need to accrue at least 120 cancer cases and 250 non-cancer cases for the overall GE Healthcare (GEHC) DBT program (ADAPT-BIE). This protocol will enroll at least one-quarter of the required cancer cases from a DBT screening environment to enrich the other cancer cases enrolled from a FFDM screening environment, thus providing cases representative of a clinical screening population.	
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LIST OF ABBREVIATIONS

2-D	Two-dimensional
3-D	Three-dimensional
ACR	American College of Radiology
ACRIN	American College of Radiology Imaging Network
AE	Adverse Event
ALARP	As Low as Reasonably Practicable
ASF	Artifact Spread Function
AUC	Area Under the Curve
BIE	Blinded Image Evaluation
BI-RADS®	Breast Imaging Reporting and Data System
CC	Craniocaudal
CFR	Code of Federal Regulations
CHF	Clinical History File
CRF	Case Report Form
DBT	Digital Breast Tomosynthesis
DCF	Data Clarification Form
DGS	Detection and Guidance Solutions
DMP	Data Management Plan
EC	Ethics Committee
FDA	US Food and Drug Administration
FFDM	Full-field Digital Mammography
GCP	Good Clinical Practices
GE	General Electric Company
GEHC	General Electric Healthcare
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional/Independent Review Board
IRC	Independent Review Charter
MLO	Mediolateral Oblique
MQSA	Mammography Quality Standards Act
MRI	Magnetic Resonance Imaging
PI	Principal Investigator
Reader	Interpreting Physician, as defined under 21CFR §900.12(a)(1)(i)(B)(2)
ROC	Receiver Operating Characteristics
SAE	Serious Adverse Event

SFM	Screen-film Mammography
US	United States
V-Preview	Volume-Preview Synthetic 2-D Mammography

2. PRELIMINARY INVESTIGATIONS AND JUSTIFICATION

2.1. Literature Review

Introduction

Mammography screening is an important tool for reducing the rate of breast cancer mortality, reported to reduce mortality in women aged 39 to 69 years by 14-32%. [1] In the United States, women have a 12.3% (1 in 8 women) lifetime risk of developing breast cancer and 2.74% (1 in 36 women) lifetime risk of death due to breast cancer, according to the American Cancer Society (ACS) 2008-2010 US National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database. [2] The ACS Cancer Facts and Figures report (2013) [3] estimated that 232,340 new breast cancer diagnoses and 39,620 breast cancer deaths would occur in 2013. Progress in early detection and improved treatment have steadily decreased breast cancer mortality rates over the past three decades, with the most notable decreases in younger women. From 2005 to 2009, death rates decreased 3.0% per year in women younger than 50 and 2.0% per year in women 50 and older. [3] False-positive mammography results and additional imaging are, however, common and missed breast cancers still occur. [2] Thus, there remains a need for more effective tools for breast cancer screening and diagnosis to further improve breast cancer patient outcomes.

Screening with conventional screen-film mammography (SFM) became widely used by the 1980s [4, 5] and has been considered the gold standard for early detection of breast cancer since the 1980s. [6, 7, 8, 9] Numerous sizable randomized trials have demonstrated that regular mammographic screening reduces breast cancer mortality. [10, 11, 12, 13, 14] There remains controversy, however, as to the benefit of conventional mammography alone, owing to relatively high false-positive rates and risks associated with repeat ionizing radiation exposure. [7, 15, 16, 17] A ten-year study of the risk of false-positives in 9,762 screening mammograms conducted by Elmore *et al*. [16] estimated that the cumulative risk of a false-positive result was 49.1% (95% CI; 40.3-64.1%) after 10 mammograms, resulting in a $33 cost of evaluating false-positives for each $100 spent in breast cancer screening. Furthermore, overdiagnosis has been reported to occur in 1% to 10% of women that undergo screening mammography, and both overdiagnosis and overtreatment risks increase dramatically as women age, particularly above age 70. [2] Thus, there is currently an urgent need for improved breast cancer screening technology and care pathways that will enable early detection and minimize the risk of overdiagnosis and overtreatment, particularly in aging and high risk patient populations.

While age was previously considered the key determinant for false-positive risk in mammographic screening, recent evidence, including the AGE trial of 53,884 mammographic screening patients in the UK, has refuted the value of age as the sole determinant of abnormal

interpretation rate in mammographic screening for breast cancer. [19, 20, 21, 22] A study of 73,247 patients (46,340 mammograms) from the Washington State Mammography Tumor Registry further indicated that breast density rather than age, is the key factor in predicting the risk of false-positive screening mammograms, necessitating increased emphasis on breast density as a defining characteristics in clinical breast cancer screening strategies. [23] Analysis of data collected from 1994 to 2008 in a group of 11,474 women with breast cancer and 922,624 women without breast cancer who underwent mammography at facilities that contribute to the Breast Cancer Surveillance Consortium (BCSC) mammography registries indicated that the cumulative probability of false-positive mammography results was highest among women undergoing annual mammography with extremely dense breasts who were either aged 40 to 49 years (65.5%) or used estrogen plus progestogen (65.8%) and was lower among women aged 50 to 74 years with scattered fibroglandular densities (30.7% and 21.9%, respectively) or fatty breasts (17.4% and 12.1%, respectively). [22] Further work is still required to achieve optimal mammographic screening results, including reduction of false-positive rates, in women with dense breasts. The wide implementation of full-field digital mammography (FFDM) has incrementally improved mammographic breast cancer screening, as demonstrated by the significantly improved diagnostic accuracy of digital mammography compared to screen-film mammography in pre-menopausal women and women with dense breasts in the National Cancer Institute-sponsored American College of Radiology Imaging Network (ACRIN) Digital Mammographic Imaging Screening Trial (DMIST) [24, 25] and in other recent studies. [26, 27]

Digital breast tomosynthesis (DBT) has been reported to achieve superior accuracy in a variety of breast tissues types, potentially reducing false-positives and increasing cancer detection rates when applied as an adjuvant to mammography. [28, 29, 30, 31] Compared to conventional mammography, DBT also has been reported to reduce false-positives in non-calcified breast tissues by up to 10% and to provide superior information on mass lesions, focal asymmetries, and architecture distortions. [32, 33] Further evidence is required, however, to determine the most advantageous clinical pathways for DBT in clinical breast cancer screening and diagnosis.

This protocol is one of three GEHC protocols designed to collect data from asymptomatic women who have been referred to 1) screening mammography and 2) breast biopsy following diagnostic work-up. The data from these three protocols will be pooled for analysis to compare the diagnostic accuracy of DBT to FFDM for detecting breast cancers in asymptomatic women. This protocol will recruit initially asymptomatic women who have undergone screening digital breast tomosynthesis procedures and who have been recommended for breast biopsy because of one or more radiographically detected suspicious lesions.

2.2. Pre-Clinical (animal) Trials and Previous Clinical (human) Experience

There is previous clinical evidence that combined 3-D DBT images with 2-D synthetic images can improve diagnostic performance and confidence in cancer detection using DBT. The first combination 2-D synthetic and 3-D DBT system, Hologic C-View, was cleared by the US FDA in May 2013. [34] Using this device, the Oslo study revealed that DBT with 2-D synthetic and 3-D capabilities resulted in an approximately 30% improvement in breast cancer detection over 2-D FFDM alone. [34] The Sponsor previously tested the GE SenoClaire® DBT system in GE190-004 BIE

(Blinded Imaging Evaluation) study – US. A Multicenter Study to Test the Non-Inferiority of Digital Breast Tomosynthesis Compared to FFDM in Detecting Breast Cancer. [35]

2.3. Device Risk Analysis

2.3.1. Device Risk Analysis

DBT has not been reported to have additional side-effects or radiation exposure compared to conventional 2-D FFDM of similar views, and subjects that have DBT plus FFDM have been shown to have lower recall rates than those that have FFDM alone. [36] The Sponsor has completed a risk analysis (GEHC Breast Tomosynthesis Risk Analysis, GEHC internal document DOC0890254). Having both DBT and FFDM exams in a short time and possibly having repeat FFDM and/or DBT on GE equipment, as a result of participating in this study, can result in additional ionizing radiation exposure compared to having only routine mammography imaging. The additional radiation is not to exceed doses that are considered to be As Low as Reasonably Practicable (ALARP) for the purpose of this research and are not expected to exceed risks of routine clinical breast cancer screening and follow-up. No additional medications will be administered beyond those regularly required for the subject's medical care outside of this study, and regular medication should not be adversely impacted or delayed by study participation.

2.3.2. Benefits

Having both DBT and FFDM may benefit subjects by improving identification of suspicious findings. A benefit, however, cannot be guaranteed.

3. RESEARCH DEVICE/PRODUCT

3.1. SenoClaire® - GE Breast Tomosynthesis (DBT)

The SenoClaire® - GE Breast Tomosynthesis is a digital breast tomosynthesis (DBT) device capable of generating digital mammographic images for use in screening and diagnosis of breast cancer. The SenoClaire® - GE Breast Tomosynthesis is intended for the same clinical applications as traditional screen-film and digital mammography systems. GE Digital Breast Tomosynthesis is an add-on device for Senographe® Essential standard FFDM systems. SenoClaire® - GE Breast Tomosynthesis is a DBT hardware and software option available for new and existing Senographe Essential platforms.

DBT reconstructed three-dimensional (3-D) imaging technology uses multiple individual low-dose views acquired in a limited-angle, around a compressed breast in a step-and-shoot acquisition mode. The acquired projection images are processed electronically to reconstruct multiple in-focus planar views through the entire breast, with blurring of out-of-plane tissues. DBT is designed to reduce the structured noise of superimposed, out-of-plane tissues, which is a limiting factor in standard 2-D mammography.

To allow acquisition in a step-and-shoot mode using partial isocentric motion, the standard breast holder is replaced by a tomosynthesis module. Once the breast is compressed, the

system acquires a sequence of 9 projection views, each acquired with the X-ray tube located at a different angle along a linear arc. The reconstruction software and review workstation allows for reconstruction and display of a stack of planar DBT images through the breast, parallel to the breast support. Several refined processing algorithms used in FFDM are applicable to the DBT reconstruction process, including FineView processing. These processing algorithms, along with 100 micron pixel size, yield high spatial resolution DBT images through the entire breast that can be viewed by the radiologist with minimal manual image adjustment.

Information pertaining to the specific design differences between the SenoClaire® - GE Breast Tomosynthesis and conventional mammography were included in the Pre-Market Application (PMA), which has been approved by the US FDA (refer to PMA module 1) and European CE mark. Most notably, the tomosynthesis technique used by the DBT system employs improved artifact correction based on the artifact spread function (ASF). The ASF is the impulse response of the tomosynthesis system along the z-axis. It is sometimes used as a figure of merit for the assessment of out-of-plane artifacts, according to the theoretical approach described by Hu *et al*. [37]

3.2. Full-field digital mammography (FFDM)

GE Full-field digital mammography (FFDM) devices are integrated systems that include both the X-ray delivery system and integrated (non-removable) detector. These systems, such as the GE Senographe® Essential standard FFDM platform, are widely commercialized and routinely used for breast cancer screening and diagnosis.

3.3. IDI MammoWorkstation

The IDI MammoWorkstation system will be used in this study to enable readers to view FFDM images, as well as 3-D DBT and synthetic 2-D DBT images.

The IDI MammoWorkstation can be used to review FFDM, 3-D DBT images, and mammographic images from other modalities. IDI MammoWorkstation allows radiologists to smoothly navigate through the DBT dataset using dedicated 2-D/3-D hanging protocols and specific ergonomic features: [35]

- Straightforward visual identification of all series of tomosynthesis planes and slabs
- Dedicated tools to review tomosynthesis data sets: cine loop, bookmarks, breast localizer, breast height ruler
- V-Preview reconstructed images from tomosynthesis

3.3.1. Volume-Preview Synthetic 2-D Mammography (V-Preview)

Volume Preview Synthetic 2-D Mammography (V-Preview) is the algorithmic software developed by GE Healthcare for use on the IDI MammoWorkstation to reconstruct a synthetic 2-D view from tomosynthesis images, producing image quality designed to be similar to that of conventional full-field digital mammography (FFDM).

4. REGULATORY STATUS

The SenoClaire® - GE Breast Tomosynthesis (DBT) system, GE Senographe® Essential Full-Field Digital Mammography, and workstations (including software components) used in this study are commercially available as determined by the United States (US) Food and Drug Administration (FDA) and European CE mark. The IDI MammoWorkstation version 4.7.0, with the ability to interpret DBT images using V-Preview as a navigation tool is CE Marked and FDA cleared for use under US 510(k) K123575, however the V-Preview images are currently labeled not for diagnostic purposes and cannot be stored, printed or transmitted outside of the IDI MammoWorkstation.

4.1. Risk Category and Rationale (US Only)

The SenoClaire® - GE Breast Tomosynthesis (DBT) and mammography devices under investigation are considered non-significant risk devices per the 21 CFR 812. 3 definition:

1) it is not intended as an implant;

2) it is not purported or represented to be for a use in supporting or sustaining human life;

3) it is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health;

4) and it does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

This designation of non-significant risk is supported by the study design in which images collected for the purpose of the study will not be used as the sole measure of diagnosis without distinct confirmation from conventional methods, such as mammography or other standard of care procedures (e.g., breast ultrasound, breast magnetic resonance imaging (MRI), or biopsy) at the investigational site.

4.2. Device Classification and Rationale

In the United States (US), the SenoClaire® - GE Breast Tomosynthesis (DBT) is considered to be Class III, as defined by the US FDA CFR 1020.30-33. FFDM devices without tomosynthesis or computed tomography breast imaging devices are considered to be Class II and Class IIa (special controls), as defined by the US FDA 21 CFR 892.1715.

The IDI MammoWorkstation is a Class II medical device under 21 CFR 892.2050 Picture Archiving and Communications Systems (product Code LLZ) and Class IIa (special controls) in Europe.

4.3. Device Issuance and Replacement

SenoClaire® - GE Breast Tomosynthesis (DBT), FFDM, and IDI MammoWorkstation devices used in this study are commercially available. Unique identifying information (e.g. model, serial number, etc.) of each device used in this study will be recorded.

Ancillary equipment, including safety equipment such as protective vests, and surgical equipment necessary for biopsy(ies) procedure(s) will be used in this study according to the

standard of care at the investigational site. These devices will be owned and maintained by the investigational site.

Sites will be encouraged to use equipment owned by the site, if available. For sites that do not own required mammography equipment (DBT, FFDM, and/or IDI MammoWorkstation) or component software versions necessary to complete study procedures, the Sponsor may provide devices for study use.

4.3.1. Maintenance of Research Devices

Devices used in this study will be maintained, calibrated, and ensured to be functioning correctly during the study, in accordance with applicable site policy and state and federal requirements. The Site Principal Investigator (PI) should inform the Sponsor of any known or anticipated issues with device functionality or availability that could impact the conduct or outcomes of this research study.

4.3.2. Concurrent Use of Research Devices

The DBT and FFDM devices used in this study are commercially available, multiple-use devices. Devices owned by the site may be used concurrently in this research and for standard of care procedures outside of this study. Devices provided to the site by GE shall be limited to use for mutually agreed upon research projects. The site is responsible for completing routine care, such as prevention of cross-contamination, between procedures that could impact study subjects.

4.3.3. Device Software and Configuration Management

The most current commercial configuration and software version for SenoClaire® - GE Breast Tomosynthesis (DBT) will be used during this study, and the site(s) should use an IDI MammoWorkstation with software version 4.7 MR2 or higher (capable of viewing V-Preview images). In the event of commercial release of software versions or configuration changes that will be implemented on devices used in this study, changes shall not increase risk classification of the study. The site Principal Investigator (PI) is responsible for notifying the Sponsor of any current or planned software or configuration changes, including the date of implementation on a per-device basis. The Sponsor may, at its discretion or upon site request, require additional training or quality control procedures (e.g. calibration or other routine engineering maintenance activities) following software or configuration changes.

4.4. Disposition of the Device/Product

Devices and associated accessories provided to the site for the purposes of this clinical trial will be collected at the end of the study and returned to GE Healthcare as dictated by mutually agreed terms.

5. OBJECTIVES OF RESEARCH STUDY

5.1. Hypothesis

No statistical hypothesis is tested in this data collection study. The sample size for DBT-screened women who are ultimately referred for breast biopsy in this study is determined to provide sufficient accrual of cancer cases for a subsequent statistically powered analysis as part of a separate protocol (ADAPT-BIE).

5.2. Study Objectives

5.2.1. Primary Objective(s)

The aim of this recruitment plan (ADAPT-Enrich) is to collect image and technical data on both digital breast tomosynthesis (DBT) and full-field digital mammography (FFDM), along with other subject data including histology results from biopsy specimen examination and cancer classification data, from initially asymptomatic women referred for biopsy after recall from DBT screening and diagnostic work-up. These data will be included in a subsequent and prospectively planned pooled analysis to be described in a separate protocol (ADAPT-BIE) examining superiority of DBT to FFDM for breast cancer diagnosis and other clinical performance measures.

5.2.2. Secondary Objectives

An additional aim is to describe cancer and non-cancer cases identified in this accrual study based on histology findings and lesion type.

5.3. Study Endpoints

5.3.1. Primary endpoints

The primary endpoint will be the site's diagnosis for each subject of cancer status (positive or negative/benign) based on histopathology of biopsy/surgical findings and histologic concordance with imaging for benign lesions.

5.3.2. Secondary Endpoints

Secondary endpoints for all subjects will include histology findings and size, lesion type, and other lesion characteristics based on image appearance. Technical characteristics of electronic image data collected from subjects, such as information related to radiation dose, may be extracted and analyzed by the Sponsor for the purposes of this study.

5.3.3. Safety endpoints

Device-related adverse events (AEs), serious adverse events (SAEs), and device malfunctions by overall occurrence and imaging modality (DBT and FFDM) that occur during the study will be collected. No other clinical safety assessments will be performed.

6. DESIGN OF RESEARCH STUDY

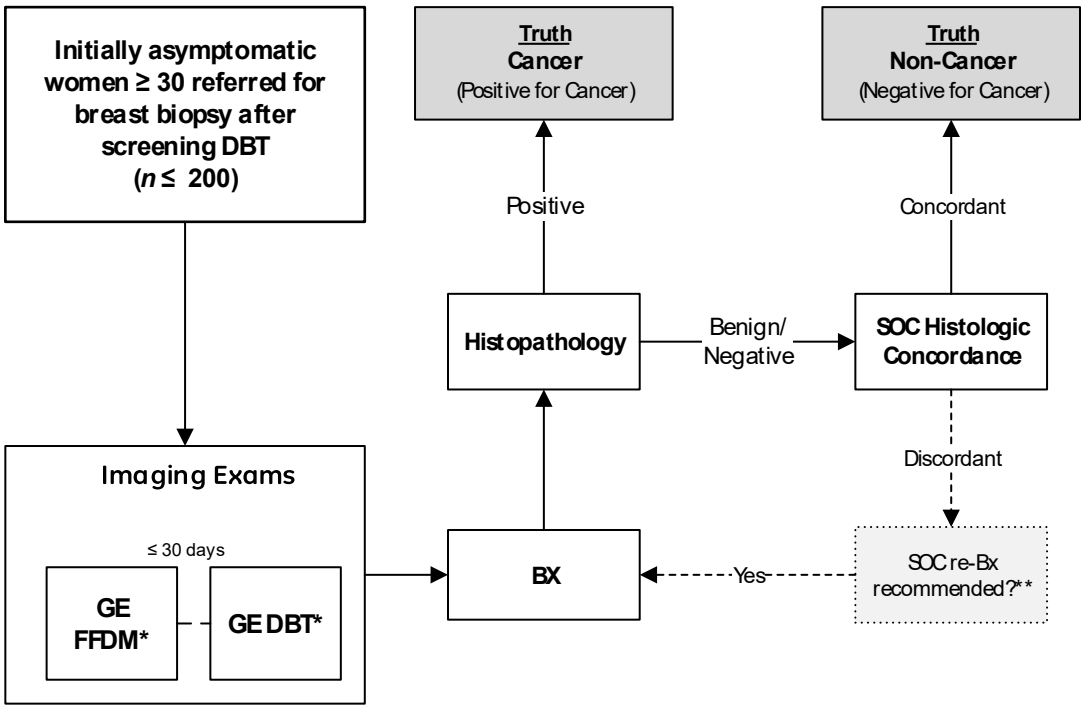
6.1. Type of Research Study

6.1.1. Study Type

This study (ADAPT-Enrich) is an open-label, multi-center, within-subject crossover, prospective, clinical research study, collecting images and associated data from bi-lateral two-view DBT and FFDM exams conducted with GE systems. Study subjects will be initially asymptomatic adult women ≥30 years of age presenting for breast biopsy based on screening DBT plus standard of care diagnostic work-up.

The data from this study will be pooled with data from other subjects who will have been recruited under other GEHC protocols (including ADAPT-SCR and ADAPT-BX), for analysis described in a separate protocol (ADAPT-BIE). Figure 1 depicts the study design and procedures.

Figure 1: Study Design and Procedures



*Images may be collected from FFDM and/or DBT performed on GE equipment prior to enrollment, if acquired within 30 days of each other.
** If rebiopsy is not recommended or if histopathology remains discordant with imaging findings after rebiopsy, the subject will be withdrawn from the study.

6.1.2. Study Design Details:

Open-Label	☒	*Interventions are known to researchers and subjects*
Blinded	☐	
Double-Blinded	☐	

Single-site	☐	
Multi-site	☒	*Data will be pooled from at least 3 studies (ADAPT-SCR, ADAPT-BX as well as this enrichment protocol) occurring at multiple sites.*
Randomization Procedure:	☐	
Not randomized:	☒	*Treatments occur as clinically indicated, not according to randomization*
Single arm	☐	
Comparator	☒	*Diagnostic accuracy of DBT vs FFDM will be assessed in a separate protocol (ADAPT-BIE)*
Crossover	☒	*This is a within-subject crossover study*
Prospective	☒	*Subjects are enrolled and then undergo study procedures*

6.2. Study Timeframe

The study is expected to begin in late 2015, and last for approximately two years (24 months), or until the target subject population is enrolled or the Sponsor otherwise indicates in writing that enrollment should be terminated. The end of the study shall be defined as the date when the last subject undergoes biopsy procedures and concordance is established, if applicable. Subject participation will be from the point of enrollment until truth determination of cancer status. The Investigator shall not begin the study until the applicable EC/IRB and necessary regulatory authority approvals, when required, have been obtained.

6.3. Controls and Minimization of Bias

The following bias control methods are being employed in this study:

a. Selection bias: In an effort to reduce the bias introduced by ADAPT-BX subjects who are expected to be referred for biopsy based primarily on FFDM screening, ADAPT-Enrich aims to enroll cancer cases reaching biopsy through a DBT screening program.

b. Spectrum bias will be limited by using a population expected to be representative of the general population at the investigational site, without regard for race or ethnicity.

7. STUDY SUBJECTS

7.1. Number of Subjects

Up to 200 subjects referred for breast biopsy (with an enrollment ceiling per site of 120 subjects) will be enrolled in this recruitment plan from up to two (2) centers located in the US until approximately 70 histopathology-confirmed cancers have been accrued. Sample size is determined by the need to accrue at least 120 cancer cases and 250 non-cancer cases for the overall GE Healthcare (GEHC) DBT program (ADAPT-BIE). This protocol will enroll at least one-quarter of the required cancer cases from a DBT screening environment to enrich the other cancer cases enrolled from a predominantly FFDM screening environment, thus providing cases

representative of a clinical screening population. Enrollment will be closed once the required number of cancers has been histologically identified. Data will be pooled with other sources to achieve the target number of positive and negative cancer cases, as described in Section 10.1.1 Sample Size Justification.

7.2. Subject Population

Study subjects will be adult women (≥30 years of age) clinically referred for breast biopsy due to abnormalities on routine screening Digital Breast Tomosynthesis (DBT); subjects must have been asymptomatic at the time of screening.

7.3. Protection of Vulnerable Subjects

This study does not intend to enroll vulnerable subject populations.

7.4. Procedures for Enrollment

All subjects must satisfy all the inclusion criteria and none of the exclusion criteria defined in the protocol. Subjects must sign and date the informed consent form prior to completing protocol specific procedures. The Investigator may discuss with the Sponsor any subject who does not strictly meet the inclusion/exclusion criteria but who is thought to be otherwise appropriate for the study; if the Sponsor and Investigator agree that inclusion of the subject would not affect the scientific or ethical aspects of the study, the Sponsor may provide a written exception for the subject. In this case, the details of the exception will be recorded on the Case Report Form (CRF). A subject will be considered enrolled when determined eligible and informed consent is signed, whether or not the subject undergoes study procedures.

7.5. Inclusion Criteria

Subjects may be included that meet the following criteria:

1. Women aged 30 years or older (≥30 years old);
2. Initially asymptomatic women who underwent routine bilateral screening with Digital Breast Tomosynthesis (DBT), followed by diagnostic work-up showing one or more abnormalities and referred for breast biopsy [1, 2];
3. Are able and willing to comply with study procedures;
4. Have signed and dated the informed consent form;
5. Documented as non-pregnant based on the investigator's medical judgment and in consideration of local clinical practice standards for evidence of non-pregnancy.

[1] Subjects who had screening DBT or screening/diagnostic FFDM imaging on non-GE equipment may be enrolled if they agree to undergo repeat imaging on a GE system; If the prior screening and diagnostic mammographic examinations were not conducted at the recruiting site, review of those images by the investigator must confirm that breast biopsy recommendation is warranted and GE access to the images in DICOM format must be granted.

[2] Screening FFDM and DBT image acquisitions must be within 30 days of each other.

7.6. Exclusion Criteria

Subjects must be excluded from participating in this study if they meet any of the following criteria:

1. Have been previously included in this study, ADAPT-SCR recruitment plan or ADAPT-BX recruitment plan;
2. Have undergone diagnostic or surgical intervention(s) or procedure(s) on either breast, including mastectomy and cytopunction, before study-related imaging;
3. Have breasts too large to be adequately positioned on 24 x 31 centimeter (cm) DBT or FFDM digital receptor without anatomical cut-off during a DBT or FFDM examination;
4. Have participated in (within the prior 30 days) another trial of an investigational product expected to interfere with study procedures or outcomes;
5. Have breast implant(s);
6. Have reconstructed breast(s).

7.7. Screening Subjects for Enrollment

Subjects will be screened for recruitment from initially asymptomatic populations referred for breast biopsy due to imaging findings at each site, in accordance with local EC/IRB recruitment policy. Enrollment decisions will be based upon the Investigator's judgment. Final subject screening will include confirmation that each subject meets all inclusion and no exclusion criteria. All screening will be conducted in compliance with applicable laws, regulations, and standard procedures at the investigational site.

8. PROCEDURES FOR RESEARCH STUDY

Table 1: Study Schedule of Events for Study Subjects

Variables	Pre – Study Imaging	Study Imaging	Post-Study imaging
Informed Consent	X		
Entry Criteria	X		
Demographic Information [a]	X		
Review relevant Medical/Surgical History	X		
DBT Imaging	X		
Collection of two-view FFDM Imaging [b]	X	X	
Repeat of DBT or FFDM Imaging [c]		X	
Safety Assessments (AE, SAE, device malfunctions) [d]		X	
Image assessment by site radiologist			X
Histopathology			X

DBT = Digital Breast Tomosynthesis; FFDM = Full field digital mammography; AE = adverse event; SAE = serious adverse event;
a: Including age, menopausal status. b: FFDM imaging may be acquired at either time point.
c: Only if prior two-view screening and/or diagnostic images are not available or were not obtained on a GE system. d: Device-related AEs and SAEs reported.

8.1. Pre-Study Imaging Procedures

All enrolled subjects will undergo the following procedures prior to receiving their additional study-specific DBT and/or FFDM imaging, as necessary:

- A notation will be made in the subject's medical chart that the subject is participating in the clinical trial. Additionally, the notation should indicate the subject had her questions answered , and that she has read, signed, dated and received a copy of the Informed Consent Form (ICF);
- Study entry criteria, demographic information (including age), relevant reproductive medical/surgical history such as oophorectomy, hysterectomy, or other reproductive surgeries and pregnancy/menopausal status will be reviewed;
- A subject number will be assigned.

There is no special subject preparation required to perform DBT or FFDM mammography.

8.2. Digital Breast Tomosynthesis (DBT) and Full Field Digital Mammography (FFDM) Examinations

Prior screening DBT and screening/diagnostic FFDM images will be collected from each subject's medical record. If prior screening and/or diagnostic images/views are not available or were not collected with GE equipment, a subject will undergo study-specific DBT and/or FFDM imaging, as needed. Study-specific imaging may include bilateral 2-view (CC/MLO) FFDM and/or DBT (as needed) performed using GE systems available at the site and according to the site's standard procedures.

Two-view DBT and two-view FFDM image acquisition (both CC and MLO views) on GE equipment shall be performed within 30 days of each other, regardless if FFDM or DBT was performed before or after the patient agreed to participate in the study. Subjects requiring study-specific imaging will undergo the following procedures:

- Enter a changing room to prepare for their mammogram;
- Each subject of child-bearing potential shall wear a lead apron or have equivalent shielding during the DBT and/or FFDM procedures;
- Undergo DBT and/or FFDM procedure(s);
- Will be monitored for AEs and SAEs from study-specific DBT and FFDM and will be recorded in the source document and CRF. Device malfunctions shall be sent to the Sponsor as per Section 12.5 Management of Device Complaints.

All scanning should be performed within the standard range of scan parameters, as per the manufacturer-provided operator's manual(s) for GE FFDM and DBT devices. The scan operator should conduct DBT and FFDM exams according to the standard clinical practice at the site with consideration for:

- Subjects with large breasts, because perspiration under the breast can cause the skin to soften, and become paper-thin;
- Any existing condition that may cause unusual discomfort or tearing of the skin, which could include telling the subject the importance of correct positioning. The subject should be positioned carefully to avoid any discomfort to abnormalities such as warts, scarring, or skin which is not intact;
- Warmth of the breast support surface, which can be warm to the touch, as it contains electronic components that generate heat;
- Positioning the breast properly in FFDM and DBT in the CC position, where it is essential that the breast is lifted away from the chest wall and gently pulled forward, in order to visualize the maximum amount of breast tissue.

8.3. Post-Study Imaging Procedures

The following assessments will be performed:

- DBT and FFDM images will be assessed at the study site by one or more MQSA-qualified radiologists, as per institutional standard practice;
- If clinically indicated based on imaging results, subjects will undergo biopsy or surgical intervention with breast tissue histopathological analysis, as per institutional standard practice;

The IDI MammoWorkstation permits 3-D-reconstruction and 2-D-reconstruction (V-Preview). The evaluating radiologist should use the image reconstruction views appropriate for diagnostic evaluation, per his or her medical judgment, and handle diagnostic evaluations in accordance with the standard of care at the investigational site.

8.3.1. On-Site Image Interpretation

DBT and FFDM images of all included subjects will be assessed at the study site by one or more MQSA-qualified radiologists on an IDI MammoWorkstation. The FFDM and/or DBT results may result in a recommendation that additional breast lesions be biopsied (in addition to that/those already planned when the patient entered the study). If so, biopsy plans may be changed accordingly.

The evaluating radiologist(s) at the site will record for each subject, the following parameters:

- Breast density (as defined by BI-RADS® density categories);
- Finding characteristics, to include breast laterality, lesion type, depth, quadrant and size. In the case of multiple findings, a maximum of three (3) most suspicious findings will be scored and localized;

8.3.2. Additional Diagnostic Imaging

If a subject is called back for further diagnostic assessment, the additional breast imaging that the subject undergoes will be recorded on the CRF.

8.4. Biopsy Procedures

Percutaneous and open surgical breast interventions will proceed as per standard of care at the recruiting site. The interpretation of the local pathologist will be recorded on the CRF.

If the subject does not complete the biopsy procedure as scheduled or if the biopsy procedure is not successful or produces indeterminate results that are not able to be resolved by clinically indicated procedures, such as repeat biopsy(ies), the subject will be withdrawn.

For benign/negative histopathology results, the site radiologist will review the subject's imaging and histopathology findings for concordance, per the site's standard of care, and results will be captured on a CRF. Histologic concordance with imaging for negative or benign lesions will be considered truth for non-cancer status. If surgical excision is recommended even after concordance between imaging and histopathology, the resulting histopathology from surgical excision may be collected as part of the study.

Subjects who have negative or benign histology findings that are discordant with imaging shall be followed-up per the site's standard of care. If rebiopsy is recommended, the histology findings and concordance assessment of the rebiopsy will be used to determine the subject's cancer status. If rebiopsy is not recommended or if histopathology remains discordant with imaging findings after rebiopsy, the subject will be withdrawn from the study.

8.5. Follow-up Procedures

Results from surgical intervention and/or any additional follow-up resulting from biopsy(ies) (e.g., breast ultrasound or breast MRI) will be considered in determining truth of cancer status. No additional follow-up appointments will be required for subjects that have completed biopsy/surgical intervention with positive findings or documented histologic concordance with imaging.

8.6. Incidental Findings

If any unexpected atypical or abnormal findings unrelated to the study aims (breast cancer identification) are identified during this study that may incidentally indicate other diseases or other unknown conditions, these cases will be reported to the Site Principal Investigator. If the Site Principal Investigator determines that these findings are medically significant in his or her medical judgment, he or she will notify the subject and refer her for further follow-up outside of this study according to the standard of care at the investigational site. Follow-up for incidental findings is not required by this study, but relevant images and data resulting from examinations related to incidental findings may be provided to the Sponsor, at the discretion of the Principal Investigator, if determined to be relevant to study conduct or integrity of study results.

8.7. Withdrawal and Discontinuation Criteria

8.7.1. Subject Withdrawal Rules

The subject's medical care shall take precedence over any research imaging or other procedures associated with the study. If it is discovered during the study (any time after consent has been signed or study procedures have begun) that any study procedure will negatively impact required clinical care, the subject shall be withdrawn from the study.

Each subject is free to withdraw from the study at any time. Investigator(s) also have the right to withdraw subjects from the study in the event of illness, AEs, SAEs, or other reasons concerning the health or well-being of the subject, or in the case of lack of cooperation.

If a subject withdraws (or is withdrawn), all efforts will be made to complete and report the observations up to the time of withdrawal. A complete final evaluation at the time of the subject's withdrawal should be made and an explanation given on the CRF given as to why the subject is withdrawing or being withdrawn from the study. If the reason for withdrawal is a clinical AE or SAE, monitoring will continue until the outcome is evident. The specific event or test result(s) must be recorded on the CRF.

In the event the subject experiences pain, undue discomfort, or destabilizing vital signs that is observed by visual inspection or via monitoring equipment, or requests to discontinue study procedures, the study procedures will be stopped immediately, and the appropriate response will be taken according to the standard of care at the investigational site.

A subject may withdraw from study participation at any time, for any reason without consequence. The study staff may withdraw a subject at any time for any reason. There shall be no negative repercussions to the subject. The reasons for withdrawal and discontinuation for any subject shall be recorded. These will be reported to the Sponsor. The EC/IRB should be notified per their notification of subject withdrawal policy.

As described in Section 8.4 Biopsy Procedures, subjects with initial benign/negative histopathology results that are discordant with imaging findings will be withdrawn from this study if rebiopsy is not recommended, or if histopathology remains discordant with imaging findings following rebiopsy.

Subjects withdrawn after consent is signed will be counted as enrolled subjects up until the time of withdrawal, and will be considered in reporting total enrolled subjects in this study per the populations defined in Section 10.1.2. - Study Populations.

9. TRAINING PLAN

9.1. Training Plan for Research Device/Product

Training will be provided to study staff on the use of device system(s), as needed. Study staff that will be operating the device(s) during subject procedures may be required to receive additional training above that is required by other study staff. The Sponsor will provide instructions for use of the device and, as necessary, subsequent training, at the Sponsor's discretion or upon request by the site.

9.2. Training Plan for Protocol

Study staff will be trained on the study protocol and study procedures, including completion of Informed Consent Forms (ICFs), Case Report Forms (CRFs), and other study documentation.

Training will also be provided to ensure appropriate storage and handling of images and data. All study staff will be required to be trained on Good Clinical Practice (GCP) guidelines per ISO 14155: 2011.

A record of all formal training attendance and date conducted will be stored in the Site Regulatory Binder and provided to the Sponsor for inclusion in the Sponsor's Clinical History File (CHF).

9.3. Reader Training

All study staff assessing images for this study will be qualified radiologists at the investigational site(s), and reads will be performed according to the standard of care at the investigational site. All readers will be trained on the study protocol and on recording of data on CRFs prior to reading images. Determinations made by site radiologists based on DBT and FFDM images collected in this study may be included in the subject's regular medical record.

10. DATA ANALYSIS AND STATISTICS

10.1. Statistical Analysis Methods

10.1.1. Sample Size Justification

The projected sample size is determined by the need to accrue at least 120 cancer cases and 250 non-cancer cases for the overall GE Healthcare SenoClaire® - GE Breast Tomosynthesis (DBT) development program. To achieve these overall accrual targets, the data from this study will be pooled with data from other studies (e.g. ADAPT-SCR and ADAPT-BX).

In this study, for an enrollment of 200 subjects recommended for breast biopsy, it is assumed, based on the GE-190-003 experience, approximately 33% are expected to have a proven cancer

and approximately 33% will have a benign lesion. So, at least 66 cancer cases and 66 non-cancer cases are expected to be accrued in this study. Up to 200 subjects referred for breast biopsy (enrollment ceiling per site will be 120 subjects) will be enrolled from up to two (2) centers located in the US until approximately 70 histopathology-confirmed cancers have been accrued. Enrollment will be managed to ensure equitable accrual of subjects across sites, if applicable.

Based on the GE-190-001 experience, for an enrollment of 250 subjects having screening mammography, about 185 (75%) will complete the study with a normal 1-year follow-up. Approximately 2% are expected to have a proven cancer either at screening or during follow-up, which will provide an estimated 6 cancer cases; expected to be accrued in the ADAPT-SCR protocol.

In the ADAPT-BX study, for a target enrollment of 275 subjects recommended for breast biopsy, it is assumed that, based on the GE-190-003 experience, approximately 33% are expected to have a proven cancer and approximately 33% will have a benign lesion. So, at least 90 cancer cases and 90 non-cancer cases are expected from the ADAPT-BX accrual.

Thus, in the combined ADAPT-SCR and ADAPT-BX protocols, it is expected that about 90 cancer cases and 250 non-cancer cases will be accrued, in which cancer cases were predominantly flagged using FFDM. To reduce the bias from the FFDM screening exam, cancer cases initially flagged using DBT will be accrued from this protocol, until at least 120 eligible cancer cases are accrued between the three protocols.

The data from this study will be pooled with data from the ADAPT-SCR and ADAPT-BX protocols. If necessary, data from other sources also may be included to achieve the required number of cancer and non-cancer cases. The accrued DBT and FFDM images will be used in a blinded image evaluation to analyze the diagnostic performance of SenoClaire® - GE Breast Tomosynthesis (DBT) compared to FFDM through receiver operating characteristic (ROC) analysis, sensitivity, specificity, recall rate, and other analyses.

No statistical analyses are included as part of this study. A descriptive summary will be provided for data collected in this study.

10.1.2. Study Populations

The *Efficacy Population* will consist of those subjects meeting the study inclusion/exclusion criteria with no protocol violations judged to affect the ability to evaluate the subject whose DBT and FFDM images are diagnostically evaluable, and whose mammography images are available for the independent blinded evaluation regardless of the image quality. Non-available images will include:

- those lost due to corrupted media or inability of site to transport to image review center;
- subjects where no images are acquired.

The Sponsor will make any decisions regarding whether any subjects or any individual values belonging to a subject will be excluded from the evaluations when a protocol violation is

considered to have a negative impact on the scientific aspects and interpretation of the study results. The reason(s) for any exclusion(s) will be documented in the study report.

The *Safety Population* will include all subjects enrolled into the study.

10.1.3. Subject Disposition and Characteristics

Subjects enrolled, imaged, and withdrawn will be summarized overall and by site and imaging modality. Descriptive statistics and summaries will be provided for demographics, medical histories, image acquisition, lesions and findings.

Specific subgroups of interest include stratification by the following variables:

- Age;
- Menopausal status; and
- Breast density.

10.1.4. Adverse Events

Adverse events will be reported from the time the subject enters the imaging suite for study procedures until the time the subject leaves the imaging suite after the study procedure. Device-related AEs and SAEs reported by subjects within 30 days of imaging (only those reported by subjects will be considered, and no separate 30-day follow-up is planned), and device malfunctions occurring in the safety population will be summarized with subject counts overall and by modality (DBT and FFDM). Additionally, individual subject listings will be provided to detail all AE/SAE information collected.

10.1.5. Methods

All descriptive analyses will be performed using SAS V9 (SAS Institute, Inc. Cary, North Carolina, USA).

Any deviations, changes, or additions to the statistical analysis outlined in the protocol will be described with reasons for the deviations in the final Clinical Study Report.

10.2. Interim Analysis

No interim analysis is prospectively planned. The Sponsor may, however, review and monitor data collected to date at any point during the study for purposes of monitoring study conduct and completion.

10.3. Handling of Missing Data

There will be no imputation of missing data and collected data will be analyzed as is.

10.4. Pass/Fail Criteria of the Study

No statistical criteria for success are defined for this accrual study, which will be considered successful if subject number and truth accrual targets are met, without consideration for subsequent analysis results.

11.DEVIATIONS

11.1. Management of Protocol Deviations

Deviations to the protocol may occur when necessary to protect the life or physical well-being of a subject. Except in an emergency, prior approval by the Sponsor is required for changes in, or planned deviations from this protocol. If these changes affect the scientific soundness or the safety and welfare of the subject, prior ethics committee/institutional review board (EC/IRB) approval is also required. Planned Protocol Deviation documentation must be filed in the Site Study Regulatory Binder. There are two types of unplanned protocol deviations, critical deviations and non-critical deviations. All deviations must be documented and reported, the criticality of the deviation will determine the reporting path.

Critical Deviations:

Critical protocol deviations are those that significantly affect the safety, efficacy, integrity or conduct of the study. These deviations must be reported to the Sponsor no later than 5 working days from awareness of occurrence and reported to the EC per the deviation reporting policy.

If an Investigator uses a device without obtaining informed consent, per Section 14.4 Informed Consent and Privacy Requirements, the Investigator shall consider this a critical deviation and report the event to the Sponsor and the EC/IRB within 5 working days of the occurrence.

Non-critical Deviations:

Non-critical protocol deviations are those that DO NOT significantly affect the safety, efficacy, integrity or conduct of the trial. These deviations must be documented on the Case Report Form Protocol Deviation page and will be reviewed by the study monitor.

12.COMPLAINT HANDLING AND ADVERSE EVENT REPORTING

12.1. Foreseeable Adverse Events and Device Effects

There are no known additional medical risks or side effects from DBT beyond those of conventional mammography. Expected AEs that apply to mammography and are also applicable to digital mammography using the Senographe Essential system may include but are not limited to:

- bruising;
- discomfort;
- skin irritation, abrasions, bruising or tears.

There is also the risk that imaging studies will falsely indicate an abnormality that could cause extra procedures to be done, and cause unnecessary anxiety for subjects.

The breast radiation dose from a two-view DBT acquisition is approximately the same as from conventional two-view FFDM mammography. In this study, subjects must have undergone

FFDM and DBT on GE equipment. If they have not, they must have FFDM CC and MLO views as well as DBT CC and MLO repeated on GE equipment, as applicable.

Patients will thus get up to four-times (if repeat DBT and FFDM imaging is required) the radiation dose that they normally would if they underwent mammography outside of the clinical trial, a dose within expected limits for routine mammography procedures and considered ALARP to complete this study.

It is generally agreed that the risk to a fetus due to radiation from screening mammography is extremely low; however, clinical practice is to try to determine pregnancy status of women referred for mammography and to not allow women known or suspected to be pregnant to undergo screening mammography or other elective radiologic procedures.

12.2. Adverse Event Definitions

Adverse Event (AE): As defined by EN ISO 14155-2011: any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

Serious Adverse Event (SAE): As defined by EN ISO 14155 – 2011: an adverse event that

(a) led to death;

(b) led to a serious deterioration in the health of the subject, that either resulted in:

(1) a life-threatening illness or injury, or

(2) a permanent impairment of a body structure or a body function, or

(3) in-patient or prolonged hospitalization, or

(4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function;

(c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

Anticipated: Any adverse event and/or reaction, the specificity or severity of which is consistent with the EC/IRB approved informed consent, protocol, investigator brochure, or product labeling.

Unanticipated Adverse Device Effect (UADE) : As defined by 21 CFR 812. 3: means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

12.3. Management of Adverse Event Reporting

Any adverse events will be recorded in the subjects study record and the Adverse Event Case Report Form. The following information should be obtained:

- Description of Event

- Date of onset and resolution
- Intensity (mild, moderate, severe)
  - **Mild**: Symptom(s) barely noticeable to the subject or does not make the subject uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).
  - **Moderate**: Symptom(s) of a sufficient severity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) may be needed.
  - **Severe**: Symptom(s) of a sufficient severity to cause the subject severe discomfort. Treatment for symptom(s) may be given.
- Serious (yes/no)
- Relationship to device (unrelated, possibly related, probably related)
  - **Unrelated**: The adverse event is reasonably expected to be related to (or caused by) a concurrent illness, effect of another device/drug or other cause, and is unlikely related to the investigational product
  - **Possibly related**: The adverse event is reasonably expected to be related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product
  - **Probably related**: There is a strong relationship to investigational product, or recurs on re-challenge, and another etiology is unlikely, or there is no other reasonable medical explanation for the event.
- Treatment given and/or action taken (procedure stopped, withdrawn from study, no action)
- Anticipated (yes/no)

Adverse events will be reported to the local EC/IRB per their policy.

12.4. Management of Serious Adverse Event and Unanticipated Adverse Device Effect Reporting

All SAEs and or UADEs will be documented as above and reported in writing to the Sponsor within 72 hours of knowledge of the event The Investigator shall submit the Adverse Event Case Report Form and GEHC_GQP_10. 07. 005_F002 Site Notification and Assessment of Serious and Unexpected Adverse Events (DOC0910335) with redacted supporting documentation to SAE mailbox.

If the event resulted in the death of a subject, the event shall also be reported via telephone to the Sponsor within 24 hours of knowledge of the event. SAEs will be reported to the local EC/IRB per their policy.

Sponsor contact for SAEs and/or UADEs:

Ron von Jako, MD, PhD
Fax: 800-888-3983
E-mail: SAE@ge.com

If additional information (i.e. outcome of event, date event resolved, additional treatments) is required to submit a follow-up report, the Investigator shall update the AE CRF and resubmit to GE Healthcare.

The Investigator shall submit the follow-up SAE and/or UADE report to the local EC/IRB per their policy.

12.5. Management of Device Complaints

Any complaints regarding the operation of the device or software or any malfunctions are to be reported to the Clinical Affair Project Manager.

Sponsor Contact for Device Complaints:

Sara Lam, Senior Clinical Affairs Project Manager III
Phone: +1-262-409-0828
Email: Sara.J.Lam@ge.com

13.EARLY TERMINATION OR SUSPENSION

13.1. Criteria for Early Termination or Suspension

There are no formal termination criteria for this study. The Sponsor reserves the right to terminate the study at any time. Investigators have the responsibility to comply with International Conference on Harmonisation (ICH) E6-Good Clinical Practice (GCP) guidance. The Sponsor, the Institutional/Independent Review Board (IRB) or Ethics Committee (EC), or the health authorities may terminate a center for the following (but not limited to) reasons:

1. If any SAEs or other technical safety issues occur;
2. Failure of the investigator to comply with pertinent ICH E6-GCP guidelines and regulations;
3. If serious protocol violations occur;
4. Submission of knowingly false information from the research facility to the Sponsor, clinical monitor, or other party involved in the study;
5. Failure of the investigator to enroll subjects into the study at an acceptable rate as agreed to with the Sponsor;
6. Repeated failure to have imaging data transferred or CRF completed and ready for submission to the Sponsor in the agreed time frame.
7. If the Sponsor determines that unanticipated adverse event(s) presents an unreasonable risk to subjects or for any other reason as Sponsor determines to be appropriate.

The Sponsor will promptly notify the Investigators of any determination to terminate the study outside of the protocol timeframe.

Termination shall occur no later than 5 working days after the Sponsor makes the determination and no later than 15 working days after Sponsor first received notice of the effect.

The Sponsor will provide each Investigator with written guidelines/instructions on termination processes and timelines.

The Investigator is responsible for reporting the early termination to their local EC/IRB.

13.2. Withdrawal of EC/IRB Approval

The Investigator will notify the Sponsor of any withdrawal of EC/IRB approval within 5 working days of such occurrence.

If the EC/IRB terminates or suspends its approval of the Study, the Investigator will promptly notify Sponsor and provide a detailed written explanation of the termination or suspension.

Upon receipt, the Sponsor will provide written guidelines/instructions on subject withdrawal/termination processes and timelines.

14.ETHICS COMMITTEE (EC) AND REGULATORY FILINGS

14.1. Regulatory Authority Approval Requirements (Global)

All regulations for the local country at the investigational site will be followed.

14.2. Ethics Committee Approval Requirements

This study is to be submitted to the EC/IRB for review and approval prior to enrolling subjects.

The Investigator is responsible for keeping approval current and maintaining appropriate correspondence and reports.

Copies of all EC/IRB applications, approval letters, ICFs and other correspondence are to be sent to the Sponsor, with originals kept in the Site Study Regulatory Binder.

14.3. Management of Protocol Revisions/Amendments

All protocol amendments will be approved and released by the Sponsor and receive approval from applicable local and, if necessary, central EC/IRB prior to implementation at the investigational site(s).

14.4. Informed Consent and Privacy Requirements

In accordance with US FDA, informed consent will be obtained from all subjects prior to participation in the study, per the determination of the local EC/IRB.

Informed consent will be documented in the source record of each subject. The Investigator or designee will consent the subject per regulatory guidelines which include the subject has ample time to review the ICF and have all questions answered to their satisfaction; the subject may take the ICF home to review with family members or others prior to agreeing to participate in

the study; upon agreeing to participate in the study, the subject signs and dates the document, and the person who consented the subject signs and dates the document.

The subject will be given a copy of the signed informed consent form and the original will be retained with Subject Files at the investigational site(s).

15.DATA AND QUALITY MANAGEMENT

15.1. Management of Data

Images acquired during imaging (DBT and FFDM) examinations will be stored on an internal or external disk system for preliminary assessment, before permanent archiving.

The digital technology used by the devices in this study provides the ability to transfer acquired images between workstations, and to store them on hard disk. However, the hospital should utilize devices that are intended or approved as archiving devices for permanent storage of images.

Electronic image data (scan files) and associated data will be collected from subjects enrolled in this study and labeled with de-identified subject identification designation (SID) that will not contain any identifiable personal information. Images acquired by device procedures in this study will be handled by approved third-party contract research organizations (CROs).

FFDM and DBT images in this study will be collected from participating subjects in electronic format, which contains information about technical characteristics of the scan session. The Sponsor may extract and analyze electronic image data to determine technical information about the subject's scan session, including radiation dose information and other factors determined by the Sponsor. Applicable data extracted from electronic image files and calculated values based on such image data may be extracted and summarized by the Sponsor at an authorized engineering facility separate from the clinical site for the purposes of this study.

During this study, data and images from clinically indicated mammography (DBT and FFDM) occurring prior to the beginning of the subject's participation (date of consent) in this study period may be collected and provided to the Sponsor for research purposes. In the event of AE or SAE occurrence or appearance of incidental findings that initiate clinical follow-up, information about other interventions, including any diagnostic imaging results, will be recorded in the CRF and source images and/or other associated data may be provided to the Sponsor as part of this research study.

GEHC may use image data for regulatory claims, future technology development, marketing purposes, publications or any other possible use. Specifically, the image data obtained in this study is intended for use as part of a regulatory submission supplementing the approval of SenoClaire® - GE Breast Tomosynthesis in the United States. These data and images collected as part of this research study may also be transported to countries outside of the United States for purposes of future research, engineering development, and global regulatory submissions in other countries.

The approved Data Management Plan (DMP) will be located in the study's CHF maintained by the Sponsor.

15.2. Subject De-identification

Each enrolled subject will be assigned a unique Subject Identification number which is used to provide a means for subject de-identification. The Site Principal Investigator (PI) or authorized delegate will capture the subject information in the Enrollment Log and assign a corresponding Subject Identification number. These numbers will be assigned in consecutive order of enrollment with numbering format provided by the Sponsor.

15.3. Completion of Case Report Forms (CRFs)

Data will be collected using paper CRFs. To ensure the quality and integrity of the data, it is the responsibility of the Principal Investigator or designee to complete CRFs in a timely manner for each subject who is enrolled in this study. The Sponsor will provide CRFs and any applicable the instructions for their completion, if necessary.

CRFs shall be completed as information becomes available. If errors or omissions are found in the course of monitoring, a query will be raised and the site shall make the correction per GCP on the CRFs. In the event of a CRF audit, or data review once the CRFs have been pulled from the site, a Data Clarification Form (DCF) will be generated and the error, omissions, or clarifications will be corrected on these forms.

The Sponsor may additionally request copies of any clinical imaging datasets (including FFDM and/or DBT scan datasets and other clinically indicated imaging examinations) or biopsy results that are conducted during the study period.

15.4. Record Retention at the Site

All records pertaining to the conduct of the study, including CRFs, ICFs, EC/IRB correspondence, and other study documentation must be retained at the investigational site for inspection at any time by the GEHC Study Monitor or authorized Sponsor agent. These records will be maintained according to GEHC Retention Policies. Elements should include the following:

- Subject Files – containing the completed subject CRFs and possibly signed ICFs
- Regulatory Binder – containing the protocol and amendments, EC/IRB submissions and approvals, blank and possibly signed/dated ICF(s), and Site study logs
- Reference Manuals – containing the resource list, responsibilities of the Investigator, Sponsor, adverse event and informed consent guidelines, study aids (training material, device screen shots), and central supplier instructions.

No records will be destroyed without first notifying and receiving approval from the Sponsor.

16.MONITORING PLAN

16.1. Brief Description

In collaboration with the investigational site, the Sponsor will ensure proper monitoring of the study to confirm that all the clinical requirements are met. Monitoring visits will ensure adherence to the protocol, completion of ICFs, EC/IRB review of the study, maintenance of records, primary outcomes review, and review of CRFs and source documentation for accuracy and completeness.

16.2. Reference to Approved Monitoring Plan

The approved monitoring plan will be located in the study's CHF maintained by the Sponsor.

17.PUBLICATION POLICY

The Sponsor will reach consensus with each investigational site regarding publication of work relating to the study that will allow both parties and their authorized representatives to promote publication of such material as appropriate through journals, meetings, and symposia. To ensure adequate patent protection for any inventions or discoveries and to protect any other commercial interests of both parties, specific guidelines for submission and review of publications will be determined in a separate contractual agreement between the Sponsor and the Site, which governs publications of this work by the Investigators and any persons at the investigational site with knowledge of this study.

18.ADDITIONAL COUNTRY-SPECIFIC REGULATORY REQUIREMENTS

Applicable reporting processes for AEs and device issues will be followed at each site, in compliance with applicable local laws and regulations and with local and (if applicable) central EC/IRB policies. The clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

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APPENDIX A: STUDY SITE AND INVESTIGATOR LIST

The following investigator(s) at each study site will be responsible for the conduct of this study. In the event that changes are made to the investigator(s) and/or sites participating in this study, a revised and dated copy of this amended page may be submitted to the responsible EC, per their policy, and stored in the Sponsor's Clinical History File (CHF) as a supplement to the protocol.

Investigator(s):	**Bruce Schroeder, MD, Investigator** *Telephone*: 1-252-414-9348 *E-mail*: Schroeder@cbispecialists.com	*Site:* **Carolina Breast Imaging Specialists** *Address:* 990 Johns Hopkins Greenville, NC 27834, USA
	Patrick Nelson, MD, Investigator *Telephone*: 1-605-322-7465 *E-mail*: Patrick.Nelson@avera.org	*Site:* **Avera Breast Center** *Address:* 1000 East 23rd Street Sioux Falls, SD 57105, USA

APPENDIX B: AMENDMENT TO PROTOCOL VERSION 1.0 TO 2.0

Purpose: This amendment document describes the changes from protocol version 1.0 to 2.0, including:

- Updates to the sites that may participate in this study;
- Clarification to inclusion and exclusion criteria; and
- Updates to enrollment and accrual targets.

The following amendments were made to version 1.0 to produce version 2.0. Point-by-point revisions in this amendment are shown with additions in double-underline (double-underline) and deletions in strikethrough (~~strikethrough~~).

Item	Section	Revision or Clarification	Justification
1.	Section 1. Study Synopsis – Investigators and Study Center(s)	Up to ~~T~~two (2) centers in the United States (US) Site and Investigator contact information are detailed in Appendix A: Study Site and Investigator List.	Clarified the number of centers that may be included.
2.	Section 1. Study Synopsis – Investigators and Study Center(s)	~~Kathy Schilling, M.D. Boca Raton Regional Hospital Christine E. Lynn Women's Health and Wellness Institute~~ ~~**Address**: 690 Meadows Road Boca Raton, Florida 33486 **Telephone**: 561-955-5000 **E-mail**: kschilling@brrh.com~~ ~~Bruce Schroeder, M.D. Carolina Breast Imaging Specialists~~ ~~**Address**: 990 Johns Hopkins Greenville, NC 27834 **Telephone**: 1-252-414-9348 **E-mail**: Schroeder@cbispecialists.com~~	Removed the non-participating site (Boca Raton Regional Hospital). Moved contact information for the participating site (Carolina Breast Imaging Specialists) to Appendix A: Study Site and Investigator List.
3.	Section 1. Study Synopsis – Study Design	An open-label, multi-center, accrual study collecting DBT and FFDM images from up to ~~200~~90 initially asymptomatic women aged ≥30 years referred for clinically indicated breast biopsy based on suspicious breast imaging results will be conducted.	Enrollment target adjusted to accommodate accrual redistribution of cancer cases based upon the capacities of sites participating in this study and the ADAPT-BX study.
4.	Section 1. Study Synopsis and Section 7.5. Inclusion Criteria	2. Initially asymptomatic women who underwent routine bilateral screening with Digital Breast Tomosynthesis (DBT), followed by diagnostic work-up showing one or more abnormalities and referred for breast biopsy ~~within 30 days before study entry~~[1,2]; 5. Documented as non-pregnant based on the investigator's medical judgment and in consideration of local clinical practice standards for evidence of non-pregnancy. ~~Are either surgically sterile or postmenopausal[3] or, if of childbearing potential, the possibility of~~	Clarified that the screening must be bilateral and removed 30-day requirement prior to study entry. Clarified criterion to ensure the site's

Item	Section	Revision or Clarification	Justification
		~~pregnancy is remote based on a documented negative patient history and, optionally, has a negative urine pregnancy test (if subject requests one).~~ *Footnotes:* [2] ~~30 day window requirement is between the~~ Screening FFDM and DBT image acquisitions must be within 30 days of each other. [3]~~Post-menopausal is defined as documented 12 months of spontaneous amenorrhea.~~	standard practice and investigator's judgement are utilized when determining pregnancy status. Clarified in footnote that FFDM and DBT image acquisitions have a 30-day window requirement. Removed inessential footnote.
5.	Section 1. Study Synopsis and Section 7.6. Exclusion Criteria	2. Have undergone diagnostic or surgical intervention(s) or procedure(s) on either breast, including mastectomy and cytopunction, before study-related imaging; ~~Have a history of any symptoms and/or physical signs of breast cancer in either breast (or if she has had a mastectomy, have signs or symptoms of breast cancer in the remaining breast)~~	Revised to clarify intent of criterion, which is to reduce bias in subsequent BIE study.
6.	Section 1. Study Synopsis – Device/Product Description	Commercially available SenoClaire® - GE Breast Tomosynthesis is a Digital Breast Tomosynthesis (DBT) device available for commercial full-field digital (FFDM) mammography systems (GE Senographe® Essential Full-Field Digital Mammography~~ or equivalent GE FFDM~~) and read on IDI MammoWorkstation with Volume-Preview Synthetic 2-D Mammography (V-Preview).	Removed equivalent option to ensure that GE Senographe® Essential Full-Field Digital Mammography systems are used.
7.	Section 1. Study Synopsis – Primary endpoints and Section 5.3.1. Primary Endpoints	The primary endpoint will be the site's diagnosis for each subject of cancer status (positive or negative/benign) based on histopathology of biopsy/surgical findings~~, and in the case histopathology is negative,~~ or 10-16 month imaging (if applicable). ~~BI-RADS® scores on both DBT and FFDM and~~ Lesion appearance and characteristics on imaging will also ~~will~~ be collected.	Clarified primary endpoint and removed screening BI-RADS scoring.
8.	Section 1. Study Synopsis – Sample Size	Up to ~~200~~ 90 subjects referred for breast biopsy (with an enrollment ceiling per site of ~~120~~ 54 subjects) will be enrolled in this recruitment plan until ~~70~~ 30 (max. ~~75~~35) histopathology-confirmed cancers have been accrued. Sample size is determined by the need to accrue at least 120 cancer cases and 250 non-cancer cases for the overall GE Healthcare (GEHC) DBT program (ADAPT-BIE). This protocol will enroll approximately ~~half~~ one-quarter of the required cancer cases from a DBT screening environment to ~~balance~~ enrich the other ~~half of~~ cancer cases enrolled from a FFDM screening environment, thus providing cases representative of a clinical screening population .	Revised enrollment and accrual targets to accommodate accrual redistribution between ADAPT-BX and ADAPT-Enrich protocols. Clarified purpose of enriching subject population from a DBT screening environment.

Item	Section	Revision or Clarification	Justification
9.	Section 4. Regulatory Status	The SenoClaire® - GE Breast Tomosynthesis (DBT) system, GE Senographe® Essential Full-Field Digital Mammography ~~or equivalent GE FFDM system~~, and workstations (including software components) used in this study are commercially available as determined by the United States (US) Food and Drug Administration (FDA) and European CE mark.	Removed mention of equivalent system.
10.	Section 6.1.1. Study Type – Figure 1.	**Initially asymptomatic women ≥ 30 referred for breast biopsy after screening DBT (*n* = ~~200~~ 90)**	Updated "n" to reflect change in enrollment target.
11.	Section 6.1.2. Study Design Details	Comparator: *Diagnostic accuracy of DBT vs FFDM ~~is~~ will be assessed in a separate protocol (ADAPT-BIE)*	Clarified that ADAPT-BIE will be conducted subsequently.
12.	Section 6.3. Controls and Minimization of Bias	a. Selection bias: In an effort to ~~eliminate~~ reduce the bias introduced by subjects in ADAPT-BX and expected to be referred for biopsy based on FFDM screening, ADAPT-Enrich aims to enroll ~~an equal number of~~ cancer cases reaching biopsy through a DBT screening program.	Clarified purpose of reducing rather than eliminating bias with cancer cases from this study.
13.	Section 7.1. Number of Subjects	Up to ~~200~~ 90 subjects referred for breast biopsy (with an enrollment ceiling per site of ~~120~~ 54 subjects) will be enrolled in this recruitment plan from up to two (2) centers located in the US until ~~70~~ 30 (max. ~~75~~35) histopathology-confirmed cancers have been accrued. Sample size is determined by the need to accrue at least 120 cancer cases and 250 non-cancer cases for the overall GE Healthcare (GEHC) DBT program (ADAPT-BIE). This protocol will enroll approximately ~~half~~ one-quarter of the required cancer cases from a DBT screening environment to ~~balance~~ enrich the ~~other half of~~ cancer cases enrolled from a FFDM screening environment, thus providing cases representative of a clinical screening population.	Updated enrollment and accrual targets.
14.	Section 8. Procedures for Research Study – Table 1	*Amendment to footnote* – a: Including age, menopausal status ~~and history of surgical breast intervention~~.	Revised due to change in exclusion criterion #2.
15.	Section 8.1. Pre-Mammography Procedures	~~An area also will be allowed on the CRFs for additional notes or comments relevant to the subject's study procedures, to be completed by the Investigator .~~ There is no special subject preparation required to perform DBT or FFDM mammography.	Deleted to reflect approved format of case report forms.

Item	Section	Revision or Clarification	Justification
16.	Section 8.3.1. On-Site Image Interpretation	The evaluating radiologist(s) at the site will record for each subject, the following parameters: • Breast density (as defined by BI-RADS® density categories) • Finding characteristics, to include breast location, lesion type, depth, quadrant and size. In the case of multiple findings, a maximum of three (3) most suspicious findings will be scored and localized. • ~~Screening BI-RADS® score (BI-RADS 1, 2, 3, 4, 5), scores of 0 (indeterminate) should be approximated to the closest definition score of 1 to 5 for each breast based on DBT and FFDM separately.~~	Omitted screening BI-RADS score per change to primary endpoint data collection.
17.	Section 10.1.1. Sample Size Justification	The projected sample size is determined by the need to accrue at least 120 cancer cases and 250 non-cancer cases for the overall GE Healthcare SenoClaire® - GE Breast Tomosynthesis (DBT) development program. To achieve these overall accrual targets, the data from this study will be pooled with data from other studies (e.g. ADAPT-SCR and ADAPT-BX). In this study, for an enrollment of ~~200~~ 90 subjects recommended for breast biopsy, it is assumed, based on the GE-190-003 experience, approximately 33% are expected to have a proven cancer and approximately 33% will have a benign lesion with normal 1-year follow-up. So, at least ~~66~~ 30 cancer cases and ~~66~~ 30 non-cancer cases with normal 1-year follow-up are expected to be accrued in this study. Up to ~~200~~ 90 subjects referred for breast biopsy (enrollment ceiling per site will be ~~120~~ 54 subjects) will be enrolled from up to two (2) centers located in the US until ~~70~~ 30 (max. ~~75~~ 35) histopathology-confirmed cancers have been accrued. Enrollment will be managed to ensure equitable accrual of subjects across sites, if applicable. In the ADAPT-BX study, for a target enrollment of 275 subjects recommended for breast biopsy, it is assumed that, based on the GE-190-003 experience, approximately 33% are expected to have a proven cancer and approximately 33% will have a benign lesion with normal 1-year follow-up. So, at least 90 cancer cases and 90 non-cancer cases with normal 1-year follow-up are expected from the ADAPT-BX accrual. Thus, in the combined ADAPT-SCR and ADAPT-BX protocols, it is expected that about ~~70~~ 90 cancer cases and 250 non-cancer cases will be accrued, in which cancer cases were initially flagged using FFDM. ~~In an effort to balance~~ To reduce the bias ~~for~~ from the FFDM screening exam, ~~an approximately equal number of 70~~30 cancer cases initially flagged using DBT will be accrued from this protocol, thus totaling at least 120 cancer cases between the three protocols.	Updated enrollment and accrual targets. Clarified the total accrual targets for the overall GEHC DBT program and the strategy for combining cancer and non-cancer cases from different sources to achieve the program targets.
18.	Section 10.1.3. Subject Disposition and Characteristics	Subjects enrolled, imaged, and withdrawn will be summarized overall and by site and imaging modality. Descriptive statistics and summaries will be provided for demographics, medical histories, image acquisition, lesions and findings ~~and BI-RADS® assessments~~.	Removed screening BI-RADS assessment per change to primary endpoint data

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<tr><th>Item</th><th>Section</th><th>Revision or Clarification</th><th>Justification</th></tr>
<tr><td></td><td></td><td></td><td>collection.</td></tr>
<tr><td>19.</td><td>Section 11.1. Management of Protocol Deviations</td><td>Critical Deviations:
If an Investigator uses a device without obtaining informed consent, per Section 14.4 Informed Consent and Privacy Requirements, the Investigator shall consider this a critical deviation and report the event to the Sponsor and the EC/IRB within 5 working days of the occurrence.</td><td>Specified section that defines requirements for obtaining informed consent.</td></tr>
<tr><td>20.</td><td>APPENDIX A: STUDY SITE AND INVESTIGATOR LIST</td><td>The following investigator(s) at each study site will be responsible for the conduct of this study. In the event that changes are made to the investigator(s) and/or sites participating in this study, a revised and dated copy of this amended page may be submitted to the responsible EC, per their policy, and stored in the Sponsor’s Clinical History File (CHF) as a supplement to the protocol.
<table>
<tr><td>Investigator(s):</td><td>Bruce Schroeder, MD, Investigator
Telephone: 1-252-414-9348
E-mail: Schroeder@cbispecialists.com</td><td>Site: Carolina Breast Imaging Specialists
Address: 990 Johns Hopkins, Greenville, NC 27834, USA</td></tr>
</table></td><td>Included process permitting site and investigator updates without requiring a protocol amendment.
Moved site and investigator contact information from Synopsis to Appendix.</td></tr>
</table>

APPENDIX C: AMENDMENT TO PROTOCOL VERSION 2.0 TO 3.0

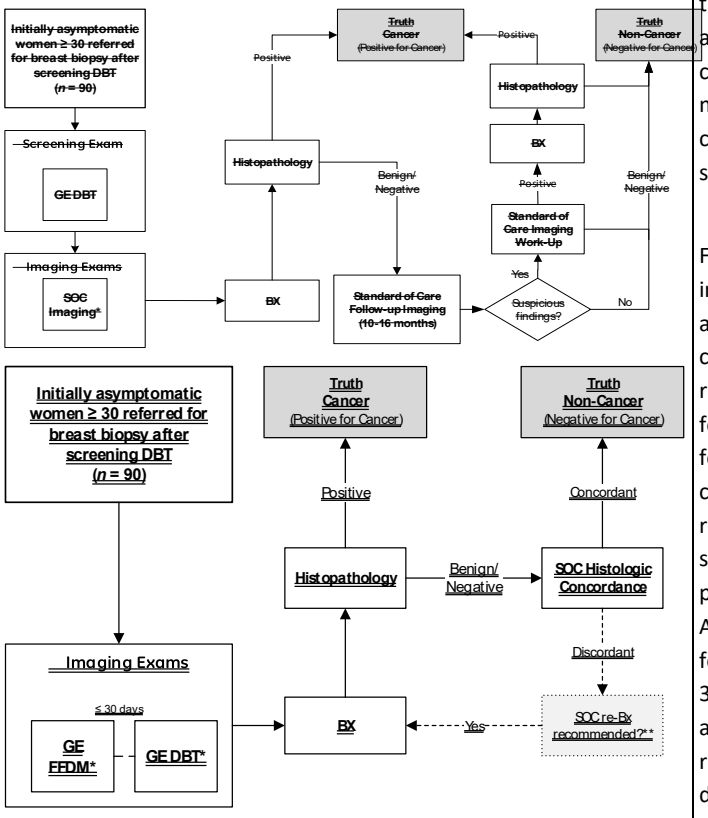
Purpose: This amendment document describes the changes from protocol version 2.0 to 3.0, including:

- Updates to the participating study centers;
- Addition of documented concordance assessments for non-cancer truth status of negative/benign cases; and
- Clarification to the type of study-specific imaging that may be required.

The following amendments were made to version 2.0 to produce version 3.0. Point-by-point revisions in this amendment are shown with additions in double-underline (double-underline) and deletions in strikethrough (~~strikethrough~~).

Item	Section	Revision or Clarification	Justification
21.	Section 1. Study Synopsis – Study Design	An open-label, multi-center, accrual study collecting DBT and FFDM images from up to 90 initially asymptomatic women aged ≥30 years referred for clinically indicated breast biopsy based on suspicious DBT screening breast imaging results will be conducted. CC and MLO views from bilateral GE screening DBT and GE screening and/or diagnostic FFDM, with 2-view DBT and 2-view FFDM acquired within a 30 day window of each other, will be collected and assessed on-site by qualified radiologist(s) for clinical management purposes ~~and BI-RADS® scores will be recorded~~. Results of biopsies and histopathology, including lesion characteristics, will be recorded and considered as truth of cancer status if positive for breast cancer. Subjects with negative or benign histological breast findings will ~~be followed for~~ have their images and histopathology reviewed for concordance, per the site's standard procedures. Histologic concordance with imaging will be considered truth for non-cancer status. ~~approximately one year (10-16 months) by standard of care imaging.~~	Clarified language regarding the 30-day window. Removed inconsequential BI-RADS data collection. Added assessment of image and histopathology concordance for non-cancer truth status of negative/benign cases. Removed one-year follow-up for non-cancer truth determination.
22.	Section 1. Study Synopsis – Brief Description of Study Purpose	The study also provides for exploratory analysis of cancerous and non-cancerous lesion characteristics detected by DBT and FFDM systems. The statistically powered reader study is being conducted to support regulatory claims to expand the labeling of the DBT system.	Updated to include non-cancerous lesion characteristics.
23.	Section 1. Study Synopsis and Section 5.3.1 – Primary endpoints	The primary endpoint will be the site's diagnosis for each subject of cancer status (positive or negative/benign) based on histopathology of biopsy/surgical findings and histologic concordance with imaging for benign lesions ~~or 10-16 month imaging (if applicable)~~. ~~Lesion appearance and characteristics on imaging will also be collected.~~	Revised to include histologic concordance with imaging rather than one-year follow-up for truth of non-cancer status. Removed lesion characterization from primary endpoint

Item	Section	Revision or Clarification	Justification
			because data are included in secondary endpoints.
24.	Section 1. Study Synopsis and Section 5.3.2 – Secondary endpoints	Secondary endpoints for all subjects ~~with positive cancer status~~ will include ~~invasive/non-invasive characteristics and~~ histology findings and size, lesion type, and other lesion characteristics based on image appearance ~~and other lesion characteristics~~. Technical characteristics of electronic image data collected from subjects, such as information related to radiation dose, may be extracted and analyzed by the Sponsor for the purposes of this study.	Revised to include non-cancerous findings and to clarify lesion data being collected based on image appearance.
25.	Section 1. Study Synopsis and Section 5.3.3 Safety endpoints	Device-related adverse events (AEs), serious adverse events (SAEs), and device malfunctions by overall occurrence and imaging modality (~~repeated~~ DBT and FFDM) that occur during the study will be collected. No other clinical safety assessments will be performed.	Removed unnecessary term (“repeated”). Reporting period defined for safety endpoint.
26.	Section 1. Study Synopsis – Sample Size	Up to 90 subjects referred for breast biopsy (with an enrollment ceiling per site of 54 subjects) will be enrolled in this recruitment plan until at least 30 ~~(max. 35)~~ histopathology-confirmed cancers have been accrued.	Clarified the minimum accrual target for histopathology-confirmed cancers and removed the maximum limit to allow for meeting the target.
27.	Section 1. Study Synopsis – Research Manager	Address: 3562 Lookout Court #478 ~~3200 N Grandview Blvd~~ Oceanside, CA 92056-5259, US ~~Waukesha, WI 53188-1678~~	Updated contact information.
28.	Section 1. Study Synopsis – Medical Monitor	Address: 1100 Technology Park Drive Billerica, ~~3200 N Grandview Blvd~~ MA 01821-4111, US ~~Waukesha, WI 53188-1678~~ Telephone: +1-617-669-3200 ~~781-262-5579~~	Updated contact information.
29.	Section 2.3.1. Device Risk Analysis	Having both DBT and FFDM exams in a short time and possibly having repeat FFDM and/or DBT on GE equipment, as a results of participating in this study, can result in additional ionizing radiation exposure compared to having only routine mammography imaging.	Clarified that both repeat FFDM and DBT may be required for the study, if the subject’s screening/ diagnostic FFDM and/or DBT mammography do not fulfill the study criteria outlined in the

Item	Section	Revision or Clarification	Justification
			protocol.
30.	Section 5.2.2. Secondary Objectives	An additional aim is to describe cancer and non-cancer cases identified in this accrual study based on ~~cancer characteristics~~ histology findings and lesion type.	Clarified to include non-cancerous lesion characteristics.
31.	Section 6.1.1. Study Type	This study (ADAPT-Enrich) is an open-label, multi-center, within-subject crossover, prospective, clinical research study, collecting images and associated data from bi-lateral two-view DBT and FFDM exams conducted with GE systems ~~comparing DBT and FFDM in the detection of breast cancer~~. Figure 1. Study Design and Procedures  *Images may be collected from FFDM and/or DBT performed on GE equipment prior to enrollment, if acquired within 30 days of each other. ~~If Standard of Care (SOC) imaging does not include GE 2D FFDM, one must be performed within 30 days of DBT and prior to biopsy.~~ ** If rebiopsy is not recommended or if histopathology remains discordant with imaging findings after rebiopsy, the subject will be withdrawn from the study.	Revised to represent this study's objective and to clarify that the comparison of the two modalities will be conducted under a separate protocol. Figure 1 updated to include assessment and documentation of concordance and to remove one-year follow-up procedures for negative/benign cases. Imaging exams revised to represent study-specific procedures only. Added language to footnotes clarifying the 30-day image acquisition requirement and describing the process for discordance.

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32.	Section 6.1.2. Study Design Details	Multi-site: Data will be pooled from at least 3 studies (ADAPT-SCR, ADAPT-BX as well as this enrichment protocol) occurring at multiple sites.	Clarified that other sources may be pooled with these data.
33.	Section 6.2. Study Timeframe	The study is expected to begin in late 2015, and last for approximately two years (24 months), or until the target subject population is enrolled or the Sponsor otherwise indicates in writing that enrollment should be terminated. The end of the study shall be defined as the date ~~of~~ when the last subject undergoes biopsy procedures and concordance is established~~, if applicable is imaged in the one-year follow-up~~. ~~Total~~ Subject participation will be from the point of enrollment until truth determination of cancer status ~~for each subject is expected to be 10-16 months, unless completed early due to positive cancer diagnosis~~. The Investigator shall not begin the study until the applicable EC/IRB and necessary regulatory authority approvals, when required, have been obtained.	Updated to reflect the revised non-cancer truth determination.
34.	Section 6.3. Controls and Minimization of Bias	a. Selection bias: In an effort to reduce the bias introduced by ADAPT-BX subjects in ~~ADAPT-BX and~~ who are expected to be referred for biopsy based primarily on FFDM screening, ADAPT-Enrich aims to enroll cancer cases reaching biopsy through a DBT screening program.	Revised to clarify ADAPT-BX screening population.
35.	Section 7.1. Number of Subjects	Up to 90 subjects referred for breast biopsy (with an enrollment ceiling per site of 54 subjects) will be enrolled in this recruitment plan from up to two (2) centers located in the US until at least 30 ~~(max. 35)~~ histopathology-confirmed cancers have been accrued. Sample size is determined by the need to accrue at least 120 cancer cases and 250 non-cancer cases for the overall GE Healthcare (GEHC) DBT program (ADAPT-BIE). This protocol will enroll approximately one-quarter of the required cancer cases from a DBT screening environment to enrich the other cancer cases enrolled from a predominantly FFDM screening environment, thus providing cases representative of a clinical screening population. Enrollment will be closed once the required number of cancers has been histologically identified. ~~Subjects awaiting one-year follow-up will continue to be followed for truth.~~ Data will be pooled with other sources to achieve the target number of positive and negative cancer cases, as described in Section 10.1.1 Sample Size Justification.	Clarified the minimum accrual target for histopathology-confirmed cancers and removed the maximum limit to allow for meeting the target. Clarified screening population. Removed one-year follow-up language.
36.	Section 7.5. Inclusion Criteria	*Footnote:* [1] Subjects who had screening DBT ~~and~~ or screening/diagnostic FFDM imaging on non-GE equipment may be enrolled if they agree to undergo repeat imaging on a GE ~~FFDM~~ system; If the prior screening and diagnostic mammographic examinations were not conducted at the recruiting site, review of those images by the investigator must confirm that breast biopsy recommendation is warranted and GE access to the images in DICOM format must be granted.	Revised to match footnote presented with Inclusion Criteria in Study Synopsis.

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37.	Section 8. Procedures for Research Study	Table 1: Study Schedule of Events for Study Subjects Histopathology ~~(if applicable)~~ | | | X	Removed unnecessary language.
38.	Section 8.1 Pre-Study Imaging Procedures	8.1. Pre-~~Mammography~~ Study Imaging Procedures All enrolled subjects will undergo the following procedures prior to receiving their additional study-specific DBT and/or FFDM imaging, as necessary: • A notation will be made in the subject's medical chart that the subject is participating in the clinical trial. Additionally, the notation should indicate the subject had her questions answered , and that she has read, signed, dated and received a copy of the Informed Consent Form (ICF); • Study entry criteria, demographic information (including age), relevant reproductive medical/surgical history such as oophorectomy, hysterectomy, or other reproductive ~~or breast~~ surgeries ~~(e.g. aspiration, core biopsy, breast reduction, implant removal surgery, or other surgery)~~ and pregnancy/menopausal status will be reviewed; • A subject number will be assigned.	Revised section title for consistency with Table 1 headings. Clarified "study-specific" imaging. Removed documentation of breast surgeries due to exclusion criterion #2.
39.	Section 8.2. Digital Breast Tomosynthesis (DBT) and Full Field Digital Mammography (FFDM) Examinations	8.2. ~~Baseline (Month 0)~~ Digital Breast Tomosynthesis (DBT) and Full Field Digital Mammography (FFDM) Examinations Prior screening DBT and screening/diagnostic FFDM images will be collected from each subject's medical record. If prior screening and/or diagnostic images/views are not available or were not collected with GE equipment, a subject will undergo ~~repeat~~ study-specific DBT and/or FFDM imaging, as needed. Study-specific imaging ~~will~~ may include bilateral ~~be performed on a GE system available at the site to ensure availability of~~ 2-view (CC/MLO) FFDM and/or ~~2-view (CC/MLO)~~ DBT (as needed) performed using GE systems available at the site and according to the site's standard procedures. ~~on GE equipment for each enrolled subject.~~ Two-view DBT and two-view FFDM image acquisition (both CC and MLO views) on GE equipment shall be performed within 30 days of each other, regardless if FFDM or DBT was performed before or after the patient agreed to participate in the study. ~~Each subject~~ Subjects requiring study-specific imaging will undergo the following procedures: • Enter a changing room to prepare for their mammogram; • Each subject of child-bearing potential shall wear a lead apron or have equivalent shielding during the DBT and/or FFDM procedures; • Undergo DBT and/or FFDM procedure(s); • Will be monitored for AEs and SAEs from ~~repeated~~ study-specific DBT and FFDM and will ~~to~~ be recorded in the source document and	Revised section title to reflect omission of one-year follow-up. Clarified that subjects will undergo study-specific DBT and FFDM imaging only if required, per the defined criteria. Corrected typographical errors. Removed SenoClaire-specific check, as the equipment checks are appropriately described for both FFDM and DBT systems.

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		CRF. Device malfunctions shall be sent to the Sponsor as per Section 12.5 Management of Device Complaints. ~~Proper equipment checks as noted in the SenoClaire® - GE Breast Tomosynthesis Operators Manual will be performed prior to treating any subject.~~ All scanning should be performed within the standard range of scan parameters, as per the manufacturer-provided operator's manual(s) for GE FFDM and DBT devices. The scan operator should conduct DBT and FFDM exams according to the standard clinical practice at the site with consideration for:	
40.	Section 8.3. Post-Study Imaging Procedures	8.3. Post-~~Mammography~~ Study Imaging Procedures	Revised section title for consistency with Table 1 headings.
41.	Section 8.3.1. On-Site Image Interpretation	DBT and FFDM images of all included subjects will be assessed at the study site by one or more MQSA-qualified radiologists on an IDI MammoWorkstation. . The FFDM and/or DBT results may result in a recommendation that additional breast lesions be biopsied (in addition to that/those already planned when the patient entered the study). If so, biopsy plans may be changed accordingly. The evaluating radiologist(s) at the site will record for each subject, the following parameters: • Breast density (as defined by BI-RADS® density categories); • Finding characteristics, to include breast ~~location~~ laterality, lesion type, depth, quadrant and size. In the case of multiple findings, a maximum of three (3) most suspicious findings will be scored and localized;	Clarified that both modalities will be assessed at the study site. Specified that breast laterality will be recorded.
42.	Section 8.3.2. Additional Diagnostic Imaging	If a subject is called back for further diagnostic assessment, the additional ~~FFDM~~ breast imaging ~~views~~ that the subject undergoes will be recorded on the CRF. ~~In addition, any other imaging that the subject undergoes will be recorded (e.g., breast ultrasound or breast MRI).~~	Generalized statement to include any additional breast imaging during the study.
43.	Section 8.4. Biopsy Procedures	Percutaneous and open surgical breast interventions will proceed as per standard of care at the recruiting site. ~~A record of breast lesion characteristics, including the type of lesion and approximate size based upon histology and surgical findings, and location of the lesion by left or right breast and within a breast quadrant will be recorded on the CRF for all subjects.~~ The interpretation of the local pathologist will be recorded on the CRF. ~~Subjects who undergo biopsy(ies) may feel apprehensive because of the pending diagnosis. Consequently, a simple but precise explanation of all study procedures should be provided to reassure the subject.~~ If the subject does not complete the biopsy procedure as scheduled or if the biopsy procedure is not successful or produces indeterminate	Modified to accurately represent data being collected. Deleted inconsequential language for the study protocol; appropriate language presented in the informed consent form. Added procedure for histologic concordance with imaging for

Item	Section	Revision or Clarification	Justification
		results that are not able to be resolved by clinically indicated procedures, such as repeat biopsy(ies), the subject will be withdrawn. For benign/negative histopathology results, the site radiologist will review the subject's imaging and histopathology findings for concordance, per the site's standard of care, and results will be captured on a CRF. Histologic concordance with imaging for negative or benign lesions will be considered truth for non-cancer status. If surgical excision is recommended even after concordance between imaging and histopathology, the resulting histopathology from surgical excision may be collected as part of the study. Subjects who have negative or benign histology findings that are discordant with imaging shall be followed-up per the site's standard of care. If rebiopsy is recommended, the histology findings and concordance assessment of the rebiopsy will be used to determine the subject's cancer status. If rebiopsy is not recommended or if histopathology remains discordant with imaging findings after rebiopsy, the subject will be withdrawn from the study.	negative/benign cases.
44.	Section 8.5. Follow-up Procedures	8.5. Follow-up ~~(Month 10-16)~~ Procedures Results from surgical intervention and/or any additional follow-up resulting from biopsy(ies) (e.g., breast ultrasound or breast MRI) will be considered in determining truth of ~~positive~~ cancer status. No additional follow-up appointments will be required for subjects that have completed biopsy/surgical intervention with positive findings or documented histologic concordance with imaging. ~~Subjects with negative or benign histology findings will be followed at approximately one year (10-16 months) by standard of care imaging.~~ ~~Subjects should be scheduled to complete one year follow-up by month 15, allowing for one month (until month 16) to reschedule subjects unable to attend or to collect previously completed one-year follow-up imaging completed at another clinical site. If no suspicious findings are observed at one-year follow-up, this will be considered truth of non-cancer status. If suspicious findings are observed, the subject will undergo standard of care diagnostic work-up, and results will be considered truth for non-cancer, benign, or cancer status.~~	Revised section title to reflect omission of one-year follow-up. Clarified follow-up procedures to account for revised truth determination of negative/benign cases. Removed one-year follow-up language.
45.	Section 8.7.1. Subject Withdrawal Rules	As described in Section 8.4 Biopsy Procedures, subjects with initial benign/negative histopathology results that are discordant with imaging findings will be withdrawn from this study if rebiopsy is not recommended, or if histopathology remains discordant with imaging findings following rebiopsy.	Added withdrawal rules for discordance.
46.	Section 10.1.1. Sample Size Justification	In this study, for an enrollment of 90 subjects recommended for breast biopsy, it is assumed, based on the GE-190-003 experience, approximately 33% are expected to have a proven cancer and approximately 33% will have a benign lesion ~~with normal 1-year follow-up~~. So, at least 30 cancer cases and 30 non-cancer cases ~~with~~	Removed one-year follow-up language. Clarified the minimum accrual target for histopathology-

Item	Section	Revision or Clarification	Justification
		~~normal 1-year follow-up~~ are expected to be accrued in this study. Up to 90 subjects referred for breast biopsy (enrollment ceiling per site will be 54 subjects) will be enrolled from up to two (2) centers located in the US until at least 30 ~~(max. 35)~~ histopathology-confirmed cancers have been accrued. Enrollment will be managed to ensure equitable accrual of subjects across sites, if applicable. Based on the GE-190-001 experience, for an enrollment of 250 subjects having screening mammography, about 185 (75%) will complete the study with a normal 1-year follow-up. Approximately 2% are expected to have a proven cancer either at screening or during follow-up, which will provide an estimated 6 cancer cases; expected to be accrued in the ADAPT-SCR protocol. In the ADAPT-BX study, for a target enrollment of 275 subjects recommended for breast biopsy, it is assumed that, based on the GE-190-003 experience, approximately 33% are expected to have a proven cancer and approximately 33% will have a benign lesion ~~with normal 1-year follow-up~~. So, at least 90 cancer cases and 90 non-cancer cases ~~with normal 1-year follow-up~~ are expected from the ADAPT-BX accrual.	confirmed cancers and removed the maximum limit to allow for meeting the target.
47.	Section 12.1. Foreseeable Adverse Events and Device Effects	Patients will thus get up to ~~three~~ four-times (if repeat DBT and FFDM imaging is required) the radiation dose that they normally would if they underwent mammography outside of the clinical trial, a dose within expected limits for routine mammography procedures and considered ALARP to complete this study.	Updated to reflect the potential for repeated mammography with both modalities.
48.	Appendix A: Study Site and Investigator List	**Investigator(s):** **Bruce Schroeder, MD, Investigator** *Telephone*: 1-252-414-9348 *E-mail*: Schroeder@cbispecialists.com *Site:* **Carolina Breast Imaging Specialists** *Address:* 990 Johns Hopkins Greenville, NC 27834, USA **Patrick Nelson, MD, Investigator** *Telephone*: 1-605-322-7465 *E-mail*: Patrick.Nelson@avera.org *Site:* Avera Breast Center *Address:* 1000 East 23rd Street Sioux Falls, SD 57105, USA	Added new site and investigator information.

APPENDIX D: AMENDMENT TO PROTOCOL VERSION 3.0 TO 4.0

Purpose: This amendment document describes the changes from protocol version 3.0 to 4.0, including updates to enrollment and accrual targets.

The following amendments were made to version 3.0 to produce version 4.0. Point-by-point revisions in this amendment are shown with additions in double-underline (double-underline) and deletions in strikethrough (~~strikethrough~~).

Item	Section	Revision or Clarification	Justification
49.	Section 1. Study Synopsis – Study Design	An open-label, multi-center, accrual study collecting DBT and FFDM images from up to ~~90~~ 200 initially asymptomatic women aged ≥30 years referred for clinically indicated breast biopsy based on suspicious DBT screening breast imaging results will be conducted.	A sample size reassessment was implemented to ensure sufficient case collection and power for the subsequent BIE study, and to ensure adequate representation of cancer cases from a DBT screening population. The increase in sample size is not expected impact the safety profile or scientific integrity of this open-label, non-randomized data collection study, which is not designed to test a statistical hypothesis. The adjusted enrollment target is based on the original intent of version 1.0 of this protocol.
50.	Section 1. Study Synopsis – Sample Size	Up to ~~90~~ 200 subjects referred for breast biopsy (with an enrollment ceiling per site of ~~54~~ 120 subjects) will be enrolled in this recruitment plan until ~~at least~~ approximately ~~30~~ 70 histopathology-confirmed cancers have been accrued. Sample size is determined by the need to accrue at least 120 cancer cases and 250 non-cancer cases for the overall GE Healthcare (GEHC) DBT program (ADAPT-BIE). This protocol will enroll ~~approximately~~ at least one-quarter of the required cancer cases from a DBT screening environment to enrich the other cancer cases enrolled from a FFDM screening environment, thus providing cases representative of a clinical screening population.	Revised based on sample size reassessment.

Item	Section	Revision or Clarification	Justification
51.	Section 6.1.1. Study Type	Figure 1: Study Design and Procedures **Initially asymptomatic women ≥ 30 referred for breast biopsy after screening DBT (*n* ≤ 200 ~~= 90~~)**	Revised "n" based on sample size reassessment.
52.	Section 7.1. Number of Subjects	Up to ~~90~~ 200 subjects referred for breast biopsy (with an enrollment ceiling per site of ~~54~~ 120 subjects) will be enrolled in this recruitment plan from up to two (2) centers located in the US until approximately ~~at least 30~~ 70 histopathology-confirmed cancers have been accrued. Sample size is determined by the need to accrue at least 120 cancer cases and 250 non-cancer cases for the overall GE Healthcare (GEHC) DBT program (ADAPT-BIE). This protocol will enroll ~~approximately~~ at least one-quarter of the required cancer cases from a DBT screening environment to enrich the other cancer cases enrolled from a predominantly FFDM screening environment, thus providing cases representative of a clinical screening population. Enrollment will be closed once the required number of cancers has been histologically identified. Data will be pooled with other sources to achieve the target number of positive and negative cancer cases, as described in Section 10.1.1 Sample Size Justification.	Revised based on sample size reassessment.
53.	Section 10.1.1. Sample Size Justification	… In this study, for an enrollment of ~~90~~ 200 subjects recommended for breast biopsy, it is assumed, based on the GE-190-003 experience, approximately 33% are expected to have a proven cancer and approximately 33% will have a benign lesion. So, at least ~~30~~ 66 cancer cases and ~~30~~ 66 non-cancer cases are expected to be accrued in this study. Up to ~~90~~ 200 subjects referred for breast biopsy (enrollment ceiling per site will be ~~54~~ 120 subjects) will be enrolled from up to two (2) centers located in the US until approximately ~~at least 30~~ 70 histopathology-confirmed cancers have been accrued. Enrollment will be managed to ensure equitable accrual of subjects across sites, if applicable. … Thus, in the combined ADAPT-SCR and ADAPT-BX protocols, it is expected that about 90 cancer cases and 250 non-cancer cases will be accrued, in which cancer cases were ~~initially~~ predominantly flagged using FFDM. To reduce the bias from the FFDM screening exam, ~~30~~ cancer cases initially flagged using DBT will be accrued from this protocol, ~~thus totaling~~ until at least 120 eligible cancer cases are accrued between the three protocols.	Revised based on sample size reassessment. Clarified that cases from ADAPT-BX were primarily screened with FFDM. Revised to ensure the combination of all accrual sources provide sufficient cancer cases to adequately power the subsequent BIE study. Combined accrual targets are over-estimated in reference to the statistically powered target of 120 cancer cases to

Item	Section	Revision or Clarification	Justification
			account for attrition and slow enrollment rates across sites in the ADAPT-BX study. Clarified that only eligible cases will count toward the accrual targets.

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