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-BX: Recruitment Plan for Initially Asymptomatic Women Referred for Breast Biopsy

Study Number: 124.03-2014-GES-0010
Revision/Amendment: 4.0
Version Date: 08/Mar/2016

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

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Investigator's Signature Page

I have read this protocol and study related documents and agree to conduct this study in full accordance with the stipulations of the protocol described herein, and any subsequent amendments.

Investigator Signature _____ Date _____

Print Name _____

Site Name _____

Site Address _____

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This document contains the following sections:

Document and Version Control

This section records all changes made to the protocol for a specific study. In the table below, record each and every relevant change by indicating what changes were made.

Revision	Date *(DD/Mmm/YYYY)*	Revision Author	Comments/Changes
1.0	17/Sep/2014	Sara Lam	Initial Version
2.0	08/Mar/2016	Carrie Lauer	Clinical Writer – Updated protocol per amendments detailed in **APPENDIX** A: Amendment to Protocol Version 1.0 to 2.0
3.0	08/Mar/2016	Carrie Lauer	Clinical Writer – Updated protocol per amendments detailed in Appendix B: Amendment to Protocol Version 2.0 to 3.0
4.0	08/Mar/2016	Carrie Lauer	Clinical Writer – Updated protocol per amendments detailed in Appendix C: 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-BX. Recruitment Plan for Initially Asymptomatic Women Referred for Breast Biopsy (ADAPT-BX)

Protocol Number (Study Number): 124.03-2014-GES-0010

Investigators and Study Center(s): Up to 3 centers in the United States (US) and France (FR)

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Objective: The aim of this recruitment plan (ADAPT-BX) 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 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 clinical performance measures.

Study Design: An open-label, multi-center, accrual study collecting DBT and FFDM images from up to 275 initially asymptomatic women aged ≥30 years referred for clinically indicated breast biopsy based on suspicious breast imaging results will be conducted. CC and MLO views from bilateral GE DBT and GE screening and/or diagnostic FFDM taken 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 biopsy(ies) and histopathology, including lesion characteristics, will be recorded and considered as truth if positive for cancer status. Subjects with negative or benign histological 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.
Accrual DBT and FFDM data will be pooled for evaluation by independent blinded readers in a subsequent reader study. The detailed information for the blinded image evaluation will be provided in a separate Independent Review Charter (IRC) detailed in the ADAPT-BIE (Blinded Image Evaluation) study. This study's

primary endpoint is collection of data to compare the diagnostic accuracy of two-view SenoClaire® - GE Breast Tomosynthesis and two-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 FFDM, breast ultrasound (U/S), breast magnetic resonance imaging (MRI), and/or 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;
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) 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*
Pre-Clinical (animal)	☐
External Bench	☐

[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.

Brief Description of Study Purpose: This study is being conducted to accrue cancer cases 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. This statistically powered study is being conducted to support regulatory claims to expand the labeling of the DBT system.	
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 and Europe. 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 respective site's diagnosis for each subject of cancer status (positive or negative/benign) based on histology of biopsy/surgical findings and histologic concordance with imaging for benign lesions. **Characteristic Endpoints:** Characteristic 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 endpoint:** 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 275 subjects referred for breast biopsy (Enrollment ceiling per site will be 165 subjects) will be enrolled in this recruitment plan until at least 90 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).	
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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 In 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 up to 14-32%. [1] In the United States, women have a 12.29% lifetime risk (1 in 8 women) of developing breast cancer and 2.74% lifetime risk (1 in 36 women) 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] predicts that 232,340 new diagnoses and 39,620 deaths occur each year due to breast cancer, though progress in early breast cancer detection, improved treatment, and decreased use of menopausal hormone therapy 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. [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 results 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 determinate characteristic 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 determinate 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 paramount factor in prediction of false positive screening mammograms, necessitating increased emphasis on breast density as a defining characteristics in clinical breast cancer screening strategies and patient education for

patients with dense breasts.[23] Analysis of data collected from 1994 to 2008 in a group of 11,474 women with breast cancer and 922,624 without breast cancer that 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 and American College of Radiology Imaging Network (ACRIN) Digital Mammographic Imaging Screening Trial (DMIST) (335 mammograms)[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 has also been reported to reduce false positives in noncalcified 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 multiple 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 protocols will be pooled for analysis to compare diagnostic accuracy of DBT to FFDM for detecting breast cancers in asymptomatic women. This protocol will recruit initially asymptomatic women who have undergone clinically recommended mammography 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 approximately 30% improvements 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 can result in additional ionizing radiation exposure, 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. As a result of participating in this study, the subject may be exposed to additional radiation compared to having only routine mammography on FFDM or DBT only. 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, and providing access to DBT imaging otherwise unavailable to some subjects. 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 image through the breast, parallel to the breast support. Several refined processing algorithms used in FFDM are applicable in 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 approved 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 are intended to be used on existing X-ray systems where the removable detector, such as a computed radiography cassette, replaces the film/screen detector. [39] 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 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. 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 DBT data 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) and France, the SenoClaire® - GE Breast Tomosynthesis (DBT) is considered to be Class III, as defined by the US FDA CFR 1020.30-33 and French National Agency for the Safety of Medicine and Health Products regulations in accordance with the European Medical Directive 93/42/EEC. 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 and French National Agency for the Safety of Medicine and Health Products regulations in accordance with the European Medical Directive 93/42/EEC.

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 will be 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 only for this protocol. 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.

5. OBJECTIVES OF RESEARCH STUDY

5.1. Hypothesis

No statistical hypothesis is tested in this data collection study. The sample size for breast biopsy subjects 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-BX) 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 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 clinical performance measures.

5.2.2. Characteristic Objectives

An exploratory 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 respective site's diagnosis for each subject of cancer status (positive or negative/benign) based on histology of biopsy/surgical findings and histologic concordance with imaging for benign lesions.

5.3.2. Characteristic Endpoints

Characteristic 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 endpoint

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

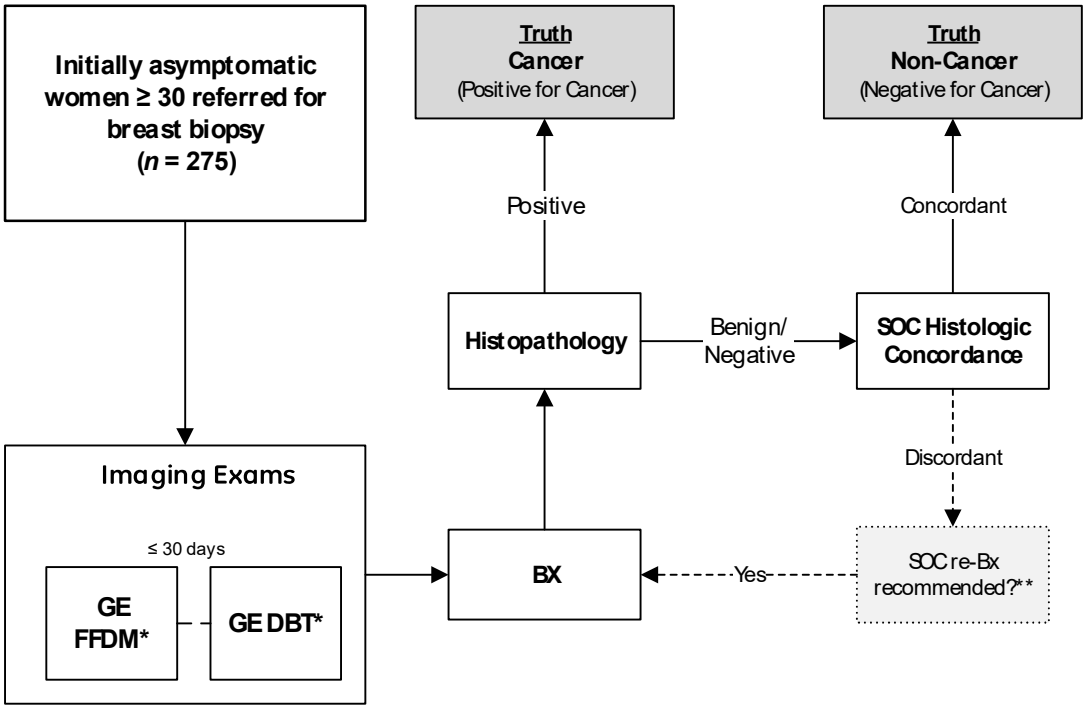
6.1. Type of Research Study

6.1.1. Study Type

This study (ADAPT-BX) 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 prior breast imaging.

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-ENRICH), 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 conducted 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 multiple studies (e.g. ADAPT-SCR, ADAPT-BX, & ADAPT-ENRICH) 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)*
Parallel	☐	
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 the fourth quarter of 2014, 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 (when required) approval 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 allocating subjects to interventional groups will be limited by attempting to enroll consecutively eligible subjects. To reduce bias introduced from this study by subjects who are expected to be referred for biopsy primarily based on FFDM screening, other sources (e.g. ADAPT-ENRICH) may be pooled to include 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 275 subjects referred for breast biopsy (Enrollment ceiling per site will be 165 subjects) will be enrolled from three (3) centers located in the US and Europe (France) until at least 90 histopathology-confirmed cancers have been accrued. 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 Mammography, breast ultrasound (U/S), breast Magnetic Resonance Imaging (MRI) or 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 FFDM, breast ultrasound (U/S), breast magnetic resonance imaging (MRI), and/or 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;
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) 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 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

All enrolled subjects will undergo the following procedures prior to receiving study-specific imaging (if required) and/or undergoing their clinically indicated biopsy procedure:

- 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 that the subject had her questions answered, and that she read, signed and dated, and had been given 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.

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

Prior screening and/or diagnostic FFDM and/or DBT images will be collected from each subject's medical record. If necessary (e.g. because prior screening and/or diagnostic FFDM and/or DBT

mammography images/views are not available or were not collected with GE equipment), a subject may undergo study-specific FFDM and/or DBT imaging. Study-specific imaging will include a bilateral two-view (both CC and MLO views) FFDM and/or DBT performed using the GE FFDM and/or DBT system available at the site and according to the hospital's standard procedure.

Two-view DBT and FFDM image acquisition (both CC and MLO views) 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 will wear a lead apron or have equivalent shielding during the FFDM and/or DBT procedures;
- Undergo FFDM and/or DBT procedure(s);
- Will be monitored for AEs and SAEs from study-specific DBT and FFDM and will be recorded in the source documents 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 exam 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 condition that exists which 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 front part of the breast support, 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.

8.2. Post-Mammography 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 and 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.

8.2.1. 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 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 results of DBT alone, however, will not be used as a basis to cancel plans for biopsy of any lesion.

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.

8.2.2. 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.

8.3. 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.

8.4. Follow-up Procedures

Results from surgical intervention and/or any additional follow-up resulting from biopsy(ies) (e.g., breast ultrasound or magnetic resonance imaging [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.

8.5. 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.

8.6. Withdrawal and Discontinuation Criteria

8.6.1. 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 8.3 Biopsy Procedures, subjects with initial benign/negative histopathology results that are discordant with imaging findings will be withdrawn from this study if no rebiopsy or histopathology occurs, 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-ENRICH).

In this study, for an enrollment of 275 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 90 cancer cases and 90 non-cancer cases are expected to be accrued in this study. Up to 275 subjects referred for breast biopsy (Enrollment ceiling per site will be 165 subjects) will be enrolled from three (3) centers located in the US and Europe (France) until at least 90 histopathology-confirmed cancers have been accrued.

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 that are expected to be accrued in the ADAPT-SCR study.

In the ADAPT-ENRICH study, for a target 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. Thus, at least 30 cancer cases are expected from the ADAPT-ENRICH study.

With the combination of these studies (ADAPT-SCR, ADAPT-BX, and ADAPT-ENRICH), it is expected that at least 120 cancer cases and 250 non-cancer cases will be accrued for the overall GEHC DBT development program. If necessary, data from other sources may also 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 adverse events (AEs) and serious adverse events (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 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:

Deviations 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:

Protocol deviations 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 digital breast tomosynthesis (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 radiation dose for a two-view DBT acquisition is approximately the same as for conventional two-view FFDM mammography. In this study, subjects must have previously undergone FFDM and/or DBT on GE equipment. If they have not, they must have FFDM and/or DBT (CC and MLO views) repeated on GE equipment.

Patients will thus get approximately twice (four-times if repeat FFDM and DBT 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 of radiation from a screening mammography is extremely low; however, clinical practice is to try to determine pregnancy status of women referred for mammography and 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 and the French National Agency for the Safety of Medicine and Health Products regulations in accordance with the European Medical Directive 93/42/EEC regulations, 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 may provide 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 2-D and/or 3-D mammography 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 adverse event (AE) and serious adverse event (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.

GE Healthcare (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 (DBT) in the United States and in Europe. This data and images collected as part of this research study may also be transported to countries outside of the United States and France 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 Clinical History File (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 Good Clinical Practice (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 Clinical History File (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.

In France, applicable study documents will be submitted and, as necessary, approved by the Comité de Protection des Personnes (CPP) and Health Authorities, including Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM). Sites in France will comply with Privacy law (Loi "informatique et libertés").

REFERENCES

1. Nelson H, Tyne K, Naik A, et al. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2009;151(10):727-37.
2. American Cancer Society. Lifetime Risk of Developing or Dying From Cancer: US National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Database. *Learn About Cancer: Cancer Basics*. Sep 5, 2013. Available at: http://www.cancer.org/cancer/cancerbasics/lifetime-probability-of-developing-or-dying-from-cancer. Accessed Sep 25, 2013.
3. American Cancer Society. *Cancer Facts and Figures 2013*. United States: American Cancer Society; 2013.
4. Lerner B. *The Breast Cancer Wars: Hope, Fear and the Pursuit of a Cure of Twentieth-Century America*. New York: Oxford; 2001.
5. Shimkin M. X-ray Mammography And Thermography In Breast Cancer. *Calif Med*. 1970;113(1):55–56.
6. Gordenne W. Mammography: the gold standard of breast mass screening. *J Belge Radiol*. Oct 1990;73(5):335-8.
7. Cuomo M. *Mammography: A Limited Tool for Early Detection of Breast Cancer*: Huffington Post; 2013.
8. Onega T, Anderson M, Miglioretti D, et al. Establishing a gold standard for test sets: variation in interpretive agreement of expert mammographers. *Acad Radiol*. 2013;20(6):731-9.
9. Randal J. ter 40 Years, Mammography Remains as Much Emotion as Science. *JNCI J Natl Cancer Inst*. 2000;92(20):1630-1632.
10. Shapiro S, Strax P, Venet L. Periodic breast cancer screening in reducing mortality from breast cancer. *JAMA*. 1971;215(11):1777-1785.
11. Thurfjell E, Lendgren J. Breast cancer survival rates with mammographic screening: similar favorable survival rates for women younger and those older than 50 years. *Radiology*. 1996;201(2).
12. Hendrick R, Smith R, Rutledge J, Smart C. Benefit of screening mammography in women aged 40-49: a new meta-analysis of randomized controlled trials. *J Natl Cancer Inst Monogr*. 1997;22:87-92.
13. Tabar L, Vitak B, Chen H, Yen M, Duffy S, Smith R. Beyond randomized controlled trials: organized mammographic screening substantially reduces breast carcinoma mortality. *Cancer*. 2001;91(9):1724-1731.
14. The Swedish Organized Service Screening Evaluation Group. Reduction in breast cancer mortality from organized service screening with mammography: 1. Further confirmation with extended data. *Cancer Epidemiol*. 2006;15(1):45-51.
15. Stewart K, Neumann P, Fletcher S, Barton M. The Effect of Immediate Reading of Screening Mammograms on Medical Care Utilization and Costs after False-Positive Mammograms. *Health Serv Res*. 2007;42(4):1464–1482.

16. Elmore J, Barton M, Moceri V, Polk S, Arena P, Fletcher S. Ten-year risk of false positive screening mammograms and clinical breast examinations. *N Engl J Med*. Apr 1998;338(16):89-96.
17. Heywang-Köbrunner S, Hacker A, Sedlacek S. Advantages and Disadvantages of Mammography Screening. *Breast Care (Basel)*. 2011;6(3):199-207.
18. Gøtzsche PC, Nielsen M. Screening for breast cancer with mammography. *Cochrane Database Syst Rev*. 2011;19(1):CD001877.
19. Johns L, Moss S, Group ATM. False-positive results in the randomized controlled trial of mammographic screening from age 40 ("Age" trial). *Cancer Epidemiol Biomarkers Prev*. Nov 2010;19(11):2758-64.
20. Boyd N, Rommens J, Vogt K, et al. Mammographic breast density as an intermediate phenotype for breast cancer. *Lancet Oncol*. 2005;6(10):798-808.
21. Checka C, Chun J, Schnabel F, Lee J, Toth H. The relationship of mammographic density and age: implications for breast cancer screening. *AJR Am J Roentgenol*. 2012;198(3):W292-5.
22. Kerlikowske K, Zhu W, Hubbard R, et al. Outcomes of screening mammography by frequency, breast density, and postmenopausal hormone therapy. *JAMA Intern Med*. May 2013;173(9):807-16.
23. Lehman C, White E, Peacock S, Drucker M, Urban N. Effect of age and breast density on screening mammograms with false-positive findings. *AJR Am J Roentgenol*. Dec 1999;173(6):1651-5.
24. Pisano E, Acharyya S, Cole E, et al. Cancer cases from ACRIN digital mammographic imaging screening trial: radiologist analysis with use of a logistic regression model. *Radiology*. 2009;252(2):348-57.
25. Pisano ED, Hendrick RE, Yaffe MJ, et al. Diagnostic accuracy of digital versus film mammography: exploratory analysis of selected population subgroups in DMIST. *Radiology*. 2008;246(2):376-83.
26. Lewin J, Hendrick E, D'Orsi C, et al. Comparison of Full-Field Digital Mammography with Screen-Film Mammography for Cancer Detection: Results of 4,945 Paired Examinations. *Radiology*. 2001;218:873-880.
27. Skaane P, Skejennald A. Screen-Film Mammography versus Full-Field Digital Mammography with Soft-Copy Reading: Randomized Trial in a Population-based Screening Program—The Oslo II Study1. *Radiology*. 2004;232:197-204.
28. Houssami N, Skaane P. Overview of the evidence on digital breast tomosynthesis in breast cancer detection. *Breast*. 2013;22(2):101-8.
29. Bernardi D, Ciatto S, Pellegrini M, et al. Prospective study of breast tomosynthesis as a triage to assessment in screening. *Breast Cancer Res Treat*. 2012;133(1):267-71.
30. Houssami N, Skaane P. Overview of the evidence on digital breast tomosynthesis in breast cancer detection. *Breast*. Apr 2013;22(2):101-8.
31. Gur D, Abrams G, Chough D, et al. Digital breast tomosynthesis: observer performance study. *AJR Am J Roentgenol*. Aug 2009;193(2):586-91.
32. Zuley ML, Bandos AI, Ganott MA, et al. Digital breast tomosynthesis versus supplemental diagnostic mammographic views for evaluation of noncalcified breast lesions. *Radiology*. 2013;266(1).

33. Yang T, Liang H, Chou C, Huang J, Pan H. The Adjunctive Digital Breast Tomosynthesis in Diagnosis of Breast Cancer. *Biomed Res Int*. 2013:597253.
34. Brosky J. JFR 2013: Challengers emerge as Hologic advances tomo for screening. *Medical Device Daily*. October 2013.
35. GEHC. *SenoClaire*. Waukesha, WI: GE Healthcare; 2013.
36. Destounis S, Arieno A, Morgan R. Initial Experience with Combination Digital Breast Tomosynthesis Plus Full Field Digital Mammography or Full Field Digital Mammography Alone in the Screening Environment. *J Clin Imaging Sci*. 2014;4(9).
37. Yue-Houng H, Bo Z, Wei Z. Image artifacts in digital breast tomosynthesis: Investigation of the effects of system geometry and reconstruction parameters using a linear system approach. *Med Phys*. 2008;35(12):5242.
38. Suryanarayanan S, Karellas A, Vedantham S, Waldrop SM, D'Orsi CJ. Detection of Simulated Lesions on Data-compressed Digital Mammograms. *Radiology*. 2005;236:31-36.
39. FDA. Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Full Field Digital Mammography System. *Medical Devices*. April 2012, 2012. Available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm107552.htm. Accessed August 9, 2013.
40. Padilla F, Roubidoux MA, Paramagul C, Sinha SP. Breast mass characterization using 3-dimensional automated ultrasound as an adjunct to digital breast tomosynthesis: a pilot study. *J Ultrasound Med*. 2013;32(1):93-104.
41. Dorfman D, Berbaum K, Metz C. Receiver operating characteristic rating analysis: generalization to the population of readers and patients with the jackknife method. *Investigative Radiology*. 1997;27:723-731.

APPENDIX A: 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:

- Discussion of additional cancer case collection study (ADAPT-ENRICH);
- 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 – Study Design	An open-label, multi-center, accrual study collecting DBT and FFDM images from up to ~~200~~ 275 initially asymptomatic women aged ≥30 years referred for clinically indicated breast biopsy based on suspicious breast imaging results will be conducted. Accrual DBT and FFDM data will be pooled for evaluation by independent blinded readers in a subsequent reader study. The detailed information for ~~on~~ the blinded image evaluation will be provided in a separate Independent Review Charter (IRC) detailed in the ADAPT-BIE (Blinded Image Evaluation) ~~protocol~~ study. This study's primary endpoint is collection of data to compare the ~~of~~ diagnostic accuracy of two-view SenoClaire® - GE Breast Tomosynthesis and two ~~2~~-view FFDM based on difference in receiver operating characteristic (ROC) area under the curve (AUC) detailed in the separate ADAPT-BIE protocol.	Enrollment target adjusted to accommodate accrual redistribution based on the capacities of sites participating in this study and other studies contributing to the overall GEHC DBT program. Revised for clarification.
2.	Section 1. Study Synopsis and Section 7.5. Inclusion Criteria	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 pregnancy is remote based on a documented negative patient history and, optionally, has a negative urine pregnancy test (if subject requests one).~~ ~~[3]Post-menopausal is defined as documented 12 months of spontaneous amenorrhea.~~	Clarified criterion to ensure the sites' standard practices and investigators' judgements are utilized when determining pregnancy status. Removed inessential footnote.
3.	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.

Item	Section	Revision or Clarification	Justification
4.	Section 1. Study Synopsis – Brief Description of Study Purpose	This study is being conducted to accrue cancer cases for a subsequent blinded reader study comparing the diagnostic accuracy and~~,~~ performance~~, and reading time~~ 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 lesion characteristics detected by DBT and FFDM systems. This statistically powered study is being conducted to support regulatory claims to expand the labeling of the DBT system.	Clarified purpose of subsequent BIE study.
5.	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.
6.	Section 1. Study Synopsis and Section 5.3.1. Primary endpoints	The primary endpoint will be the respective site's diagnosis for each subject of cancer status (positive or negative/benign) based on histology and surgical findings or 10-16 month imaging (if applicable). ~~for both DBT and FFDM, and l~~Lesion appearance and characteristics on imaging will also be collected.	Clarified for this multi-site study. Omitted BI-RADS score from primary endpoint data collection.
7.	Section 1. Study Synopsis – Sample Size	Up to ~~200~~ 275 subjects referred for breast biopsy (Enrollment ceiling per site will be ~~120~~ 165 subjects) will be enrolled in this recruitment plan until ~~70~~ 90 (max. ~~75~~ 95) histopathology-confirmed cancers have been accrued. Sample size is determined by the need to accrue at least ~~70~~120 cancer cases and 250 non-cancer cases for the overall GE Healthcare (GEHC) DBT program (ADAPT-BIE).	Revised enrollment and accrual targets based on power analysis for the overall GEHC DBT program.
8.	Section 2.1. Literature Review – Introduction	This protocol is one of multiple ~~two~~ 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 ~~two~~ protocols will be pooled for analysis to compare diagnostic accuracy of DBT to FFDM for detecting breast cancers in asymptomatic women.	Updated to clarify that other sources may be pooled for subsequent BIE study.
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.

Item	Section	Revision or Clarification	Justification
10.	Section 6.1.1. Study Type	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-ENRICH), for analysis described in a separate protocol (ADAPT-BIE). Figure 1 depicts the study design and procedures.	Included a third case collection study, ADAPT-ENRICH, which was developed to provide additional cancer cases for the overall GEHC DBT program. Similar language added throughout version 2.0 of this protocol to clarify this update.
11.	Section 6.1.1. Study Type – Figure 1.	**Initially asymptomatic women ≥ 30 referred for breast biopsy (*n* = ~~200~~ 275)**	Updated "n" to reflect change in enrollment target.
12.	Section 6.1.2. Study Design Details	Multi-site: *Data will be pooled from ~~2~~ multiple studies (e.g. ADAPT-SCR, ~~&~~ ADAPT-BX, & ADAPT-ENRICH) at multiple sites* Comparator: *Diagnostic accuracy of DBT vs FFDM ~~is~~ will be assessed in a separate protocol (ADAPT-BIE)*	Clarified that more than two (2) studies may be pooled for analyses. Clarified that ADAPT-BIE will be conducted subsequently.
13.	Section 6.3. Controls and Minimization of Bias	a. Selection bias in allocating subjects to interventional groups will be limited by attempting to enroll~~ing~~ consecutively eligible subjects~~, however despite inclusion of subjects referred from DBT, US or MRI screening, as most subjects in this study are expected to be biopsy referrals based on FFDM, a selection bias in favor of FFDM is possible~~. To reduce bias introduced from this study by subjects who are expected to be referred for biopsy based on FFDM screening, other sources (e.g. ADAPT-ENRICH) may be pooled to include cancer cases reaching biopsy through a DBT screening program.	Revised with efforts to reduce FFDM screening bias.
14.	Section 7.1. Number of Subjects	Up to ~~200~~ 275 subjects referred for breast biopsy (Enrollment ceiling per site will be ~~120~~ 165 subjects) will be enrolled from two (2) centers located in the US and Europe (France) until ~~70~~ 90 (max. ~~75~~95) histopathology-confirmed cancers have been accrued. Enrollment	Updated enrollment and accrual targets.

Item	Section	Revision or Clarification	Justification
		will be closed once the required number of cancers has been histologically identified.	
15.	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.
16.	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.
17.	Section 8.2. Baseline (Month 0) Digital Breast Tomosynthesis (DBT) and Full Field Digital Mammography (FFDM) Examinations	Study subjects will undergo two-view DBT (both CC and MLO view) of both breasts ~~or of one breast if they have had prior mastectomy~~. Prior screening and/or diagnostic FFDM images will be collected from each subject's medical record or, if necessary (because prior screening and/or diagnostic mammography images are not available or were not collected with GE FFDM equipment), a subject may also need to undergo repeat FFDM; if so, this will be a bilateral two-view FFDM (both CC and MLO views) performed on the GE FFDM system available at the site and according to the hospital's standard procedure. DBT and two-view FFDM image acquisition (both CC and MLO views) shall be performed within 30 days of each other, regardless if FFDM was performed before or after the patient agreed to participate in the study. Each subject will undergo the following procedures: • Enter a changing room to prepare for their mammogram; • Each subject of child-bearing potential will wear a lead apron or have equivalent shielding during the DBT (and, if necessary, FFDM) procedures; • Undergo DBT (and, if necessary, FFDM) procedure(s); • Will be monitored for AEs, SAEs from DBT and ~~repeated~~ FFDM (if required) and will ~~to~~ be recorded in the source documents and CRF. Device malfunctions shall be sent to the Sponsor as per Section 12.5 Management of Device Complaints.	Revised due to change in exclusion criterion #2. Clarified that FFDM may be repeated, if necessary.
18.	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	Omitted screening BI-RADS score per change to primary endpoint data collection.

Item	Section	Revision or Clarification	Justification
		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.~~	
19.	Section 8.4. Biopsy Procedures	~~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 results that are not able to be resolved by clinically indicated procedures, such as repeat biopsy(ies) the subject will be withdrawn.	Deleted inconsequential language for the study protocol. Appropriate language presented in the informed consent form.
20.	Section 10.1.1. Sample Size Justification	The projected sample size is determined by the need to accrue at least ~~70~~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-ENRICH). In this study, for an enrollment of ~~200~~ 275 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~~ 90 cancer cases and ~~66~~ 90 non-cancer cases with normal 1-year follow-up are expected to be accrued in this study. Up to ~~200~~ 275 subjects referred for breast biopsy (Enrollment ceiling per site will be ~~120~~ 165 subjects) will be enrolled from two (2) centers located in the US and Europe (France) until ~~70~~ 90 (max. 95) ~~75)~~ histopathology-confirmed cancers have been accrued. 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~~;~~ that are expected to be accrued in the ADAPT-SCR ~~protocol~~ study. In the ADAPT-ENRICH study, for a target 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	Updated enrollment and accrual targets. Clarified total accrual targets for the overall GEHC DBT program. Revised to include ADAPT-ENRICH and to clarify strategy for combing cancer and non-cancer cases from different sources to achieve the overall program targets.

Item	Section	Revision or Clarification	Justification
		cancer. Thus, at least 30 cancer cases are expected from the ADAPT-ENRICH study. ~~Thus, in the combined protocols (ADAPT-SCR and ADAPT-BX), it is expected that at least 70 cancer cases and 250 non-cancer cases will be accrued.~~ ~~The data from this study will be pooled with data from other subjects who will be recruited from other sources, such as the separate protocols (ADAPT-SCR). If necessary, data from other sources may also be included to achieve the required number of cancer and non-cancer cases.~~ With the combination of the protocols (ADAPT-SCR and ADAPT-BX) and other sources, it is expected that at least 120 cancer cases and 250 non-cancer cases will be accrued for the overall GE Healthcare SenoClaire® - GE Breast Tomosynthesis (DBT) development program. If necessary, data from other sources may also be included to achieve the required number of cancer and non-cancer cases.	
21.	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 score per change to primary endpoint data collection.
22.	Section 11.1. Management of Protocol Deviations	**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.	Specified section that defines requirements for obtaining informed consent.
23.	Section 12.1. Foreseeable Adverse Events and Device Effects	The radiation dose for a two-view DBT acquisition is approximately the same as for conventional two-view FFDM mammography. In this study, subjects must have previously undergone FFDM on GE equipment. If they have not, they must have FFDM CC and MLO views repeated on GE equipment. ~~They will then undergo DBT, which has radiation dose similar to FFDM.~~ Patients will thus get approximately twice (three-times if ~~screening~~ repeat FFDM 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.	Deleted redundant statement. Clarified that FFDM may be repeated, if necessary.

APPENDIX B: AMENDMENT TO PROTOCOL VERSION 2.0 TO 3.0

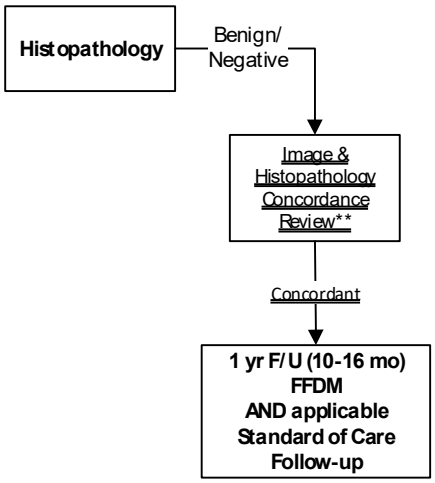
Purpose: This amendment document describes the changes from protocol version 2.0 to 3.0, including:

- Updates to the participating study centers;
- Clarification to inclusion and exclusion criteria;
- Addition of documented concordance assessments for 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
24.	Section 1. Study Synopsis – Investigators and Study Center(s)	Up to 3 ~~2~~ centers in the United States (US) and France (FR) Kathy Schilling, MD Boca Raton Regional Hospital Christine E. Lynn Women's Health and Wellness Institute **Address**: 690 Meadows Road Boca Raton, FL, 33486 US **Telephone**: +1-561-955-5000 **E-mail**: kschilling@brrh.com	Updated the number of participating centers and added new site's contact information.
25.	Section 1. Study Synopsis – Study Design	An open-label, multi-center, accrual study collecting DBT and FFDM images from up to 275 initially asymptomatic women aged ≥30 years referred for clinically indicated breast biopsy based on suspicious breast imaging results will be conducted. CC and MLO views from bilateral GE DBT and GE screening and/or diagnostic FFDM ~~(conducted before or after enrollment)~~ taken 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 biopsy(ies) and histopathology, including lesion characteristics, will be recorded and considered as truth if positive for cancer status. Subjects with negative or benign histological findings will have their images and histopathology reviewed for concordance and will be followed at ~~for~~ approximately one year (10-16 months) by FFDM and any additional standard of care practice.	Clarified language regarding the 30-day window. Added assessment of image and histopathology concordance for negative/benign cases.
26.	Section 1. Study Synopsis and Section 7.5. Inclusion Criteria	2. Initially asymptomatic women who ~~that~~ underwent routine bilateral screening FFDM, breast ultrasound (U/S), breast magnetic resonance imaging (MRI), and/or DBT, followed by diagnostic work-up showing one or ~~of~~ more abnormalities and referred for breast biopsy [1,2] ~~within of 30 days before study entry~~; *Footnote:* [2] ~~30 day window requirement is between the~~ Screening FFDM and DBT image acquisitions must be within 30 days of each other.	Clarified that the screening must be bilateral and removed 30-day requirement prior to study entry. Corrected minor typographical errors. Clarified in footnote that FFDM and DBT image acquisitions

Item	Section	Revision or Clarification	Justification
			have a 30-day window requirement.
27.	Section 1. Study Synopsis and Section 7.6. Exclusion Criteria	3. Have breasts too large to be adequately positioned on 24 x 31 centimeter (cm) FFDM digital receptor without anatomical cut off during a DBT or FFDM examination ~~(or FFDM, if required)~~;	Clarified that the criterion applies to both DBT and FFDM.
28.	Section 1. Study Synopsis – Primary endpoints	The primary endpoint will be the respective site's diagnosis for each subject of cancer status (~~cancer~~ positive or negative/benign) based on histology and surgical findings or 10-16 month imaging (if applicable) ~~/or follow-up of suspicious findings~~. Lesion appearance and characteristics on imaging will also be collected	Revised to mirror language in Section 5.3.1 Primary endpoints.
29.	Section 1. Study Synopsis and Section 5.3.3 Safety endpoint	Device-related adverse events (AEs), serious adverse events (SAEs), and device malfunctions by overall occurrence and imaging modality (DBT and ~~repeated~~ 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.
30.	Section 1. Study Synopsis – Research Manager	Address: 3562 Lookout Court #478 ~~3200 N Grandview Blvd~~ Oceanside, CA 92056-5259, US ~~Waukesha, WI 53188-1678~~ Telephone: +1-414-379-4201 ~~721-4393~~	Updated contact information.
31.	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.
32.	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 can result in additional ionizing radiation exposure, 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. As a result of participating in this study, the subject may be exposed to additional radiation compared to having only routine mammography on FFDM or DBT only.	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 protocol. Similar language was amended throughout revision 3.0 to clarify this point.

Item	Section	Revision or Clarification	Justification
33.	Section 6.1.1. Study Type	This study (ADAPT-BX) 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  *** In the event of discordant histopathology and imaging findings, rebiopsy and resulting histopathology results will be acquired to establish concordance. If no rebiopsy or histopathology occurs, or if histopathology remains discordant with imaging findings, 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 for negative/benign cases. Added language describing the process for discordance.
34.	Section 6.3. Controls and Minimization of Bias	a. Selection bias in allocating subjects to interventional groups will be limited by attempting to enroll consecutively eligible subjects. To reduce bias introduced from this study by subjects who are expected to be referred for biopsy primarily based on FFDM screening, other sources (e.g. ADAPT-ENRICH) may be pooled to include cancer cases reaching biopsy through a DBT screening program.	Clarified that the majority of subjects are expected to be referred from an FFDM screening population.
35.	Section 7.1. Number of Subjects	Up to 275 subjects referred for breast biopsy (Enrollment ceiling per site will be 165 subjects) will be enrolled from three ~~two~~ (3 ~~2~~) centers located in the US and Europe (France) until at least 90 ~~(max. 95)~~ histopathology-confirmed cancers have been accrued.	Updated number of participating sites. Clarified the minimum accrual target for histopathology-confirmed cancers and removed the maximum limit to allow for meeting the target.

<table>
<tr><th>Item</th><th>Section</th><th>Revision or Clarification</th><th>Justification</th></tr>
<tr><td>36.</td><td>Section 7.5. Inclusion Criteria</td><td>[1] Subjects who had screening DBT and 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</td><td>Revised to mirror footnote in Section 1. Study Synopsis, Inclusion Criteria</td></tr>
<tr><td>37.</td><td>Section 8. Procedures for Research Study</td><td>~~**Table 1: Study Schedule of Events for Study Subjects**~~
<table>
<tr><th>~~Variables~~</th><th>~~Pre – Mammography~~</th><th>~~Mammography~~</th><th>~~Post-Mammography~~</th></tr>
<tr><td>~~Informed Consent~~</td><td>~~X~~</td><td></td><td></td></tr>
<tr><td>~~Entry Criteria~~</td><td>~~X~~</td><td></td><td></td></tr>
<tr><td>~~Demographic Information [a]~~</td><td>~~X~~</td><td></td><td></td></tr>
<tr><td>~~Review relevant~~</td><td>~~X~~</td><td></td><td></td></tr>
<tr><td>~~DBT Imaging~~</td><td></td><td>~~X~~</td><td></td></tr>
<tr><td>~~Collection of Prior two-view~~</td><td>~~X~~</td><td></td><td></td></tr>
<tr><td>~~Repeat of FFDM Imaging [b]~~</td><td></td><td>~~X~~</td><td></td></tr>
<tr><td>~~Safety Assessments (AE, SAE, device malfunctions) [c]~~</td><td></td><td>~~X~~</td><td></td></tr>
<tr><td>~~Image assessment by site~~</td><td></td><td></td><td>~~X~~</td></tr>
<tr><td>~~Histopathology (if~~</td><td></td><td></td><td>~~X~~</td></tr>
</table>
~~DBT = Digital Breast Tomosynthesis; FFDM = Full field digital mammography; AE = adverse event; SAE = serious adverse event;~~
~~a: Including age, menopausal status. b: Only if prior two-view screening and/or diagnostic images are not available or were not obtained on a GE FFDM system~~
~~Device-related AEs and SAEs reported.~~
~~8.1. Pre-Mammography Procedures~~

All enrolled subjects will undergo the following procedures prior to receiving study-specific imaging (if required) and/or undergoing their clinically indicated biopsy procedure ~~their DBT (and, if necessary, FFDM) mammogram(s)~~:

- 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 that the subject had her questions answered, and that she read, signed and dated, and ~~has~~ had been given 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 ~~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.

There is no special subject preparation required to perform DBT or FFDM mammography.</td><td>Removed Table 1 to clarify study procedures and pre-study versus study-specific image acquisition.

Clarified the procedures that will be conducted prior to study-specific imaging and biopsy.

Modified typographical errors.

Removed documentation of breast surgeries due to exclusion criterion #2.</td></tr>
</table>

Item	Section	Revision or Clarification	Justification
38.	Section.8.1. Baseline (Month 0) Digital Breast Tomosynthesis (DBT) and Full Field Digital Mammography (FFDM) Examinations	~~Study subjects will undergo two-view DBT (both CC and MLO view) of both breasts.~~ Prior screening and/or diagnostic FFDM and/or DBT images will be collected from each subject's medical record. ~~or, i~~ If necessary (e.g. because prior screening and/or diagnostic FFDM and/or DBT mammography images/views are not available or were not collected with GE ~~FFDM~~ equipment), a subject may ~~also need to~~ undergo study-specific ~~repeat~~ FFDM and/or DBT imaging. Study-specific imaging ~~; if so, this~~ will ~~be a~~ include a bilateral two-view (both CC and MLO views) FFDM and/or DBT ~~(both CC and MLO views)~~ performed ~~on~~ using the GE FFDM and/or DBT system available at the site and according to the hospital's standard procedure. Two-view DBT and ~~two-view~~ FFDM image acquisition (both CC and MLO views) 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 ~~Each subject~~ will undergo the following procedures: • Enter a changing room to prepare for their mammogram; • Each subject of child-bearing potential will wear a lead apron or have equivalent shielding during the FFDM and/or DBT ~~(and, if necessary, FFDM)~~ procedures; • Undergo ~~DBT (and, if necessary,~~ FFDM~~)~~ and/or DBT procedure(s); • Will be monitored for AEs and ~~,~~SAEs from study-specific DBT and FFDM ~~(if required)~~ and will be recorded in the source documents and 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 exam 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 condition that exists which 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 front part of the breast support, 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	Clarified criteria for use of images acquired prior to enrollment. 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.

Item	Section	Revision or Clarification	Justification
		chest wall and gently pulled forward, in order to visualize the maximum amount of breast tissue.	
39.	Section 8.2.2. Additional Diagnostic Imaging	If a subject is called back for further diagnostic assessment, the additional ~~FFDM views~~ breast imaging that the subject undergoes will be recorded on the CRF. ~~In addition, any other imaging which the subject undergoes will be recorded (e.g., breast ultrasound or magnetic resonance imaging [MRI]).~~	Generalized statement to include any additional breast imaging during the study.
40.	Section 8.3 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. For benign/negative histopathology results, the site radiologist will review the subject's imaging and histopathology findings for concordance and document the assessment on a CRF. If the findings are concordant, then the subject will continue with the 1-year follow-up procedure in approximately 10-16 months. If surgical excision is recommended even after concordance between imaging and histopathology, the resulting histopathology from surgical excision will be collected and used to establish the subject's cancer status. If breast cancer status is negative, 1-year follow-up will be used to establish final cancer status. If the imaging and histopathology findings are discordant, rebiopsy and resulting histopathology will be required to establish concordance, per the site's standard of care. Once concordance is achieved and histopathology continues to be negative for cancer, the subject will continue with the 1-year follow-up procedure in approximately 10-16 months from initial study imaging. If no rebiopsy or histopathology occurs, or if histopathology remains discordant with imaging findings following rebiopsy, the subject will be withdrawn from the study.	Modified to accurately represent data being collected. Added procedure and documentation for assessing concordance of negative/benign cases.
41.	Section 8.4. Follow-up (Month 10-16) Procedures	No additional follow-up appointments will be required for subjects that have completed biopsy with positive findings. Subjects with negative or benign histology findings will be followed at approximately one year (10-16 months) by ~~FFDM in addition to any additional imaging as required 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 ~~FFDM images~~ imaging completed at another clinical site. If no suspicious findings are observed at one-year ~~FFDM~~ follow-up, this will be considered truth of non-cancer status. If suspicious findings are observed, the subject will undergo standard of care	Modified to allow for standard of care imaging without requiring FFDM.

Item	Section	Revision or Clarification	Justification
		diagnostic work-up, and results will be considered truth for non-cancer, ~~benign,~~ or cancer status.	
42.	Section 8.6.1. Subject Withdrawal Rules	As described in Section 8.3 Biopsy Procedures, subjects with initial benign/negative histopathology results that are discordant with imaging findings will be withdrawn from this study if no rebiopsy or histopathology occurs, or if histopathology remains discordant with imaging findings following rebiopsy.	Added withdrawal rules for discordance.
43.	Section 10.1.1 Sample Size Justification	In this study, for an enrollment of 275 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 90 cancer cases and 90 non-cancer cases with normal 1-year follow-up are expected to be accrued in this study. Up to 275 subjects referred for breast biopsy (Enrollment ceiling per site will be 165 subjects) will be enrolled from three ~~two~~ (3 ~~2~~) centers located in the US and Europe (France) until at least 90 ~~(max. 95)~~ histopathology-confirmed cancers have been accrued.	Updated number of participating sites. Clarified the minimum accrual target for histopathology-confirmed cancers and removed the maximum limit to allow for meeting the target.
44.	Section 12.1. Foreseeable Adverse Events and Device Effects	The radiation dose for a two-view DBT acquisition is approximately the same as for conventional two-view FFDM mammography. In this study, subjects must have previously undergone FFDM and/or DBT on GE equipment. If they have not, they must have FFDM and/or DBT (CC and MLO views) repeated on GE equipment. Patients will thus get approximately twice (~~three~~ four-times if repeat FFDM and DBT 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.
45.	Section 15.1. Management of Data	During this study, data and images from clinically indicated 2-D and/or 3-D mammography 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.	Clarified that both FFDM and DBT image may be collected.

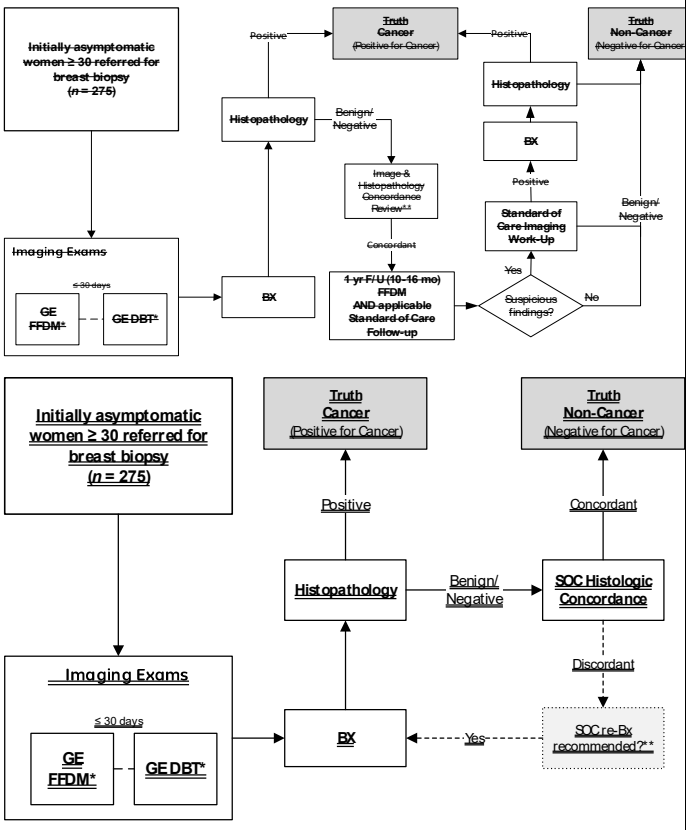
APPENDIX C: AMENDMENT TO PROTOCOL VERSION 3.0 TO 4.0

Purpose: This amendment document describes the changes from protocol version 3.0 to 4.0, including:

- Replacement of one-year follow-up with histologic concordance for truth determination of non-cancer status of negative/benign cases; and
- Inclusion of data collection for non-cancerous lesions.

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
46.	Section 1. Study Synopsis – Study Design	Subjects with negative or benign histological 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. ~~and will be followed at approximately one year (10-16 months) by FFDM and any additional standard of care practice~~.	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.
47.	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. This statistically powered study is being conducted to support regulatory claims to expand the labeling of the DBT system.	Updated to include non-cancerous lesion characteristics.
48.	Section 1. Study Synopsis and Section 5.3.1 – Primary endpoints	The primary endpoint will be the respective site's diagnosis for each subject of cancer status (positive or negative/benign) based on histology ~~and~~ 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 because data are included in characteristic endpoints.

Item	Section	Revision or Clarification	Justification
49.	Section 1. Study Synopsis and Section 5.3.2 – Characteristic endpoints	Characteristic 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.
50.	Section 5.2.2. Characteristic Objectives	An exploratory 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.
51.	Section 6.1.1. Study Type	Figure 1. Study Design and Procedures  **Images may be collected from FFDM and/or DBT performed on GE equipment prior to enrollment, if conducted within 30 days of each other.* *** ~~In the event of discordant histopathology and imaging findings, rebiopsy and resulting histopathology results will be acquired to establish concordance~~ If rebiopsy is not recommended or if histopathology remains discordant with imaging findings after rebiopsy, the subject will be withdrawn from the study.*	Figure 1 updated to represent histologic concordance as truth for non-cancer and to remove one-year follow-up procedures for negative/benign cases. Updated language in footnotes, clarifying the 30-day image acquisition requirement and describing the process for discordance.

Item	Section	Revision or Clarification	Justification
52.	Section 6.2. Study Timeframe	The study is expected to begin in the fourth quarter of 2014, 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 (when required) approval have been obtained.	Updated to reflect the revised non-cancer truth determination.
53.	Section 7.1. Number of Subjects	Up to 275 subjects referred for breast biopsy (Enrollment ceiling per site will be 165 subjects) will be enrolled from three (3) centers located in the US and Europe (France) until at least 90 histopathology-confirmed cancers have been accrued. 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.	Removed one-year follow-up language.
54.	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 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.
55.	Section 8.1. Digital Breast Tomosynthesis (DBT) and Full Field Digital Mammography (FFDM) Examinations	8.1. ~~Baseline (Month 0)~~ Digital Breast Tomosynthesis (DBT) and Full Field Digital Mammography (FFDM) Examinations	Revised section title to reflect omission of one-year follow-up.
56.	Section 8.2 Post-Mammography Procedures	• If clinically indicated based on imaging results, subjects will undergo biopsy or surgical intervention and breast tissue histopathological analysis, as per institutional standard practice.	Clarified types of procedures.
57.	Section 8.2.1. 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 DBT results may result in a recommendation that additional breast lesions be biopsied (in	Clarified that both modalities will be assessed at the study site.

Item	Section	Revision or Clarification	Justification
		addition to that/those already planned when the patient entered the study). If so, biopsy plans may be changed accordingly. The results of DBT alone, however, will not be used as a basis to cancel plans for biopsy of any lesion. 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.	Specified that breast laterality will be recorded.
58.	Section 8.3. 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 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. 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 ~~and document the assessment on a CRF. If the findings are concordant, then the subject will continue with the 1-year follow-up procedure in approximately 10-16 months~~, 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. ~~will be collected and used to establish the subject's cancer status. If breast cancer status is negative, 1-year follow-up will be used to establish final cancer status.~~ Subjects who have negative or benign histology ~~If the imaging and histopathology~~ findings that are discordant~~, rebiopsy and resulting histopathology will be required to establish concordance,~~ with imaging shall be followed-up per the site's standard of care. ~~Once concordance is achieved and histopathology continues to be negative for cancer, the subject will continue with the 1-year follow-up procedure in approximately 10-16 months from initial study imaging.~~ If rebiopsy is recommended, the histology findings and concordance assessment of the rebiopsy will be used to determine the subject's cancer status. If ~~no~~ rebiopsy is not recommended ~~or~~	Modified to accurately represent data being collected. Clarified procedure for histologic concordance with imaging for negative/benign cases. Removed one-year follow-up language.

Item	Section	Revision or Clarification	Justification
		~~histopathology occurs,~~ or if histopathology remains discordant with imaging findings ~~following~~ after rebiopsy, the subject will be withdrawn from the study.	
59.	Section 8.4. Follow-up Procedures	8.4 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 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. Clarified types of procedures. Removed one-year follow-up language.
60.	Section 10.1.1. Sample Size Justification	In this study, for an enrollment of 275 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 90 cancer cases and 90 non-cancer cases ~~with normal 1-year follow-up~~ are expected to be accrued in this study. Up to 275 subjects referred for breast biopsy (Enrollment ceiling per site will be 165 subjects) will be enrolled from three (3) centers located in the US and Europe (France) until at least 90 histopathology-confirmed cancers have been accrued.	Removed one-year follow-up language.
61.	Section 18. Additional Country-Specific Regulatory Requirements	The clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki ~~could be added~~.	Deleted inessential language.

End of Document