

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

**Study Number:** 124.03-2014-GES-0010

**Protocol:** 2.0

GE Healthcare



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

***ADAPT-SCR: Recruitment Plan for Asymptomatic Women Undergoing Screening Mammography***

**Study Number:** 124.03-2014-GES-0010

**Revision/Amendment:** 2.0

**Version Date:** 15/Jun/2016

#### **Confidentiality Statement**

This protocol is provided for conducting a research study. The information contained in this document is confidential and, except to the extent necessary to obtain informed consent or EC/IRB approval, cannot be disclosed unless required by governmental regulation. Persons to whom any portion of the contents of this document is disclosed must be informed that the information is confidential and may not further be disclosed by them.

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Compared to Mammography (ADAPT Trial)**

***ADAPT-SCR: Recruitment Plan for Asymptomatic Women Undergoing Screening  
Mammography***

GEHC Study Number: 124.03-2014-GES-0010

Revision/Amendment: 2.0

Version Date: 15/Jun/2016

**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

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Site Name

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Site Address



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## 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	10/Sep/2014	Sara Lam	Initial Protocol
2.0	15/Jun/2016	Carrie Lauer	Clinical Writer – Updated protocol per amendments detailed in Appendix A: Amendment to Protocol Version 1.0 to 2.0



## 1. STUDY SYNOPSIS

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

*ADAPT-SCR: Recruitment Plan for Asymptomatic Women Undergoing Screening Mammography*

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

**Investigators and Study Center(s):** Two (2) centers in the United States (US) will collect cases as part of this study protocol.

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**Objective:** The aim of this recruitment plan (ADAPT-SCR) is to collect image and other data on both digital breast tomosynthesis (DBT) and full-field digital mammography (FFDM) from asymptomatic women undergoing screening mammography. 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 screening images from up to 250 asymptomatic women aged  $\geq 30$  years undergoing routine breast cancer screening will be conducted. CC and MLO views from bilateral GE DBT and GE FFDM (conducted before or after enrollment) within a 30 day window will be collected and assessed on-site by qualified radiologist(s) for clinical management purposes. BI-RADS® scores will be recorded. Results of biopsy(ies) and histopathology, including lesion characteristics, will be recorded.

Subjects with negative or benign imaging findings will be followed for approximately one year (10-16 months) by standard of care imaging to determine 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 or evidence of negative one-year follow-up will be considered truth for non-cancer status. A positive histology result will be considered truth for cancer.

Accrual DBT and FFDM data will be pooled for evaluation by independent blinded readers in a subsequent reader study. The detailed information on the blinded image evaluation will be provided in a separate Independent Review Charter (IRC) detailed in the ADAPT-BIE (Blinded Image Evaluation) protocol. This study's primary endpoint is collection of data to compare the diagnostic accuracy of two-view SenoClaire® - GE Breast Tomosynthesis (DBT) verses 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 asymptomatic adult women ( $\geq 30$  years of age) scheduled for routine screening mammography.

**Inclusion Criteria:**

Subjects may be included that meet the following criteria:

1. Women aged 30 years or older ( $\geq 30$  years old);
2. Asymptomatic women scheduled for screening mammography or have completed a screening mammogram within the past 30 days;
3. Mammography completed on a GE FFDM system (with CC and MLO views) at the site or another clinical facility<sup>1 2</sup>;
4. Are able and willing to comply with study procedures;
5. Have signed and dated the informed consent form;
6. Are either surgically sterile or postmenopausal<sup>3</sup> or, if of childbearing potential, the possibility of pregnancy is remote based on a documented negative patient history and, optionally, a negative urine pregnancy test (if subject requests one).

**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 a history of breast cancer and are in active treatment. However, subjects with a prior lumpectomy ( $\geq 5$  years prior) who receive only routine screening mammography views can be included;
3. Have breasts too large to be adequately positioned on 24 x 31 centimeter (cm) FFDM digital receptor without anatomical cut off during either FFDM or DBT 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)      | <input checked="" type="checkbox"/> <i>Asymptomatic Women Scheduled for Screening Mammography</i> |
| Pre-Clinical (animal) | <input type="checkbox"/>  |
| External Bench        | <input type="checkbox"/>  |

<sup>1</sup> If prior mammographic examinations were not conducted at the recruiting site, review of those images by the Investigator must confirm that the subject is qualified for this study (CC and MLO views present) and access to the images in DICOM digital format by GE must be granted.

<sup>2</sup>Subjects who had prior imaging on non-GE equipment may be enrolled if they agree to undergo repeat imaging on a GE FFDM system.

<sup>3</sup>Post-Menopausal is defined as documented 12 months of spontaneous amenorrhea.





**Brief Description of Study Purpose:** This study is being conducted to accrue breast cancer screening cases of asymptomatic women for a subsequent blinded reader study comparing the diagnostic accuracy and performance of digital breast tomosynthesis (DBT) performed with the GE SenoClaire® - GE Breast Tomosynthesis (DBT) compared to conventional GE full-field digital mammography (FFDM) in asymptomatic women. The study also provides data 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.

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**Device/Product GEHC Modality:** Detection and Guidance Solutions (DGS)

**Device/Product GEHC Class:** SenoClaire® - GE Breast Tomosynthesis (DBT)

**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).

**Regulatory Status:**

Pre-Market ☐

Post-Market ☒ DBT, FFDM, and IDI MammoWorkstations used in this study are considered post-market in the US. V-Preview for DBT is a commercially available tool on the IDI MammoWorkstation not currently indicated for breast cancer diagnosis use.

**Primary endpoints:** The primary endpoint will be the site's diagnosis of cancer status (positive or negative/benign) for each subject based on DBT and FFDM at baseline (0 months) and 10-16 months, and/or (if clinically indicated) histology and surgical findings. Histologic concordance with imaging will be assessed for benign lesions, when applicable, and DBT and FFDM image sets will be assessed using BI-RADS® scores.

**Characteristic Endpoints:** Characteristic endpoints for all subjects will include histology findings and size, lesion type, and other lesion characteristics based on image appearance. Technical factors of 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 as needed, repeat FFDM) that occur during the study will be collected. No other clinical safety assessments will be performed.

**Sample Size:** 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), for which accrual of 200 biopsy cases (ADAPT-BX and other sources) and 250 screening mammography cases (ADAPT-SCR and other sources) are required.

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

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**Protocol:** 2.0

GE Healthcare



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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

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

**Study Number:** 124.03-2014-GES-0010

**Protocol:** 2.0

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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%.<sup>1</sup> 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.<sup>2</sup> The ACS Cancer Facts and Figures report (2013)<sup>3</sup> 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.<sup>3</sup> False-positive mammography results and additional imaging are, however, common.<sup>2</sup> 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<sup>4, 5</sup> and has been considered the gold standard for early detection of breast cancer since the 1980s.<sup>6, 7, 8, 9</sup> Numerous sizable randomized trials have demonstrated that regular mammographic screening reduces breast cancer mortality.<sup>10, 11, 12, 13, 14</sup> 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.<sup>7, 15, 16, 17</sup> A ten-year study of the risk of false positives in 9,762 screening mammograms conducted by Elmore *et al.*<sup>16</sup> 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.<sup>2</sup> 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.<sup>19, 20, 21, 22</sup> 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.<sup>23</sup> 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).<sup>22</sup> 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)<sup>24, 25</sup> and in other recent studies.<sup>26, 27</sup>

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.<sup>28, 29, 30, 31</sup> 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.<sup>32, 33</sup> 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 some 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.<sup>34</sup> 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.<sup>34</sup> 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.<sup>35</sup>



## **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.<sup>36</sup> 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 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 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.*<sup>37</sup>

### **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.<sup>39</sup> 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:<sup>35</sup>

- 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 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. 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), the SenoClaire® - GE Breast Tomosynthesis (DBT) is considered to be Class III, as defined by the US FDA CFR 1020.30-33. FFDM devices without tomosynthesis or computed tomography breast imaging devices are considered to be Class II, as defined by the US FDA 21 CFR 892.1715. In Europe, the SenoClaire® - GE Breast Tomosynthesis (DBT) is considered to be Class IIb as defined by the 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 are commercially available. Unique identifying information (e.g. model, serial number, etc.) of each device used in this study will be recorded.



Ancillary equipment, including safety equipment such as protective vests, and surgical equipment necessary for biopsy(ies) procedure(s) will be used in this study according to the standard of care at the investigational site. These devices will be owned and maintained by the investigational site.

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

#### **4.3.1. Maintenance of Research Devices**

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

#### **4.3.2. Concurrent Use of Research Devices**

The DBT and FFDM devices used in this study are commercially available, multiple-use devices. Devices owned by the site may be used concurrently in this research and for standard of care procedures outside of this study. Devices provided to the site by GE shall be limited to use 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 screening mammography subjects in this study is determined to provide sufficient accrual of non-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-SCR) is to collect image and other data on both digital breast tomosynthesis (DBT) and full-field digital mammography (FFDM) from asymptomatic women undergoing screening mammography. 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 site's diagnosis of cancer status (positive or negative/benign) for each subject based on DBT and FFDM at baseline (0 months) and 10-16 months, and/or (if clinically indicated) histology and surgical findings. Histologic concordance with imaging will be assessed for benign lesions, when applicable, and DBT and FFDM image sets will be assessed using BI-RADS® scores.

#### **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 factors of 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 as needed, repeat FFDM) that occur during the study will be collected. No other clinical safety assessments will be performed.



## 6. DESIGN OF RESEARCH STUDY

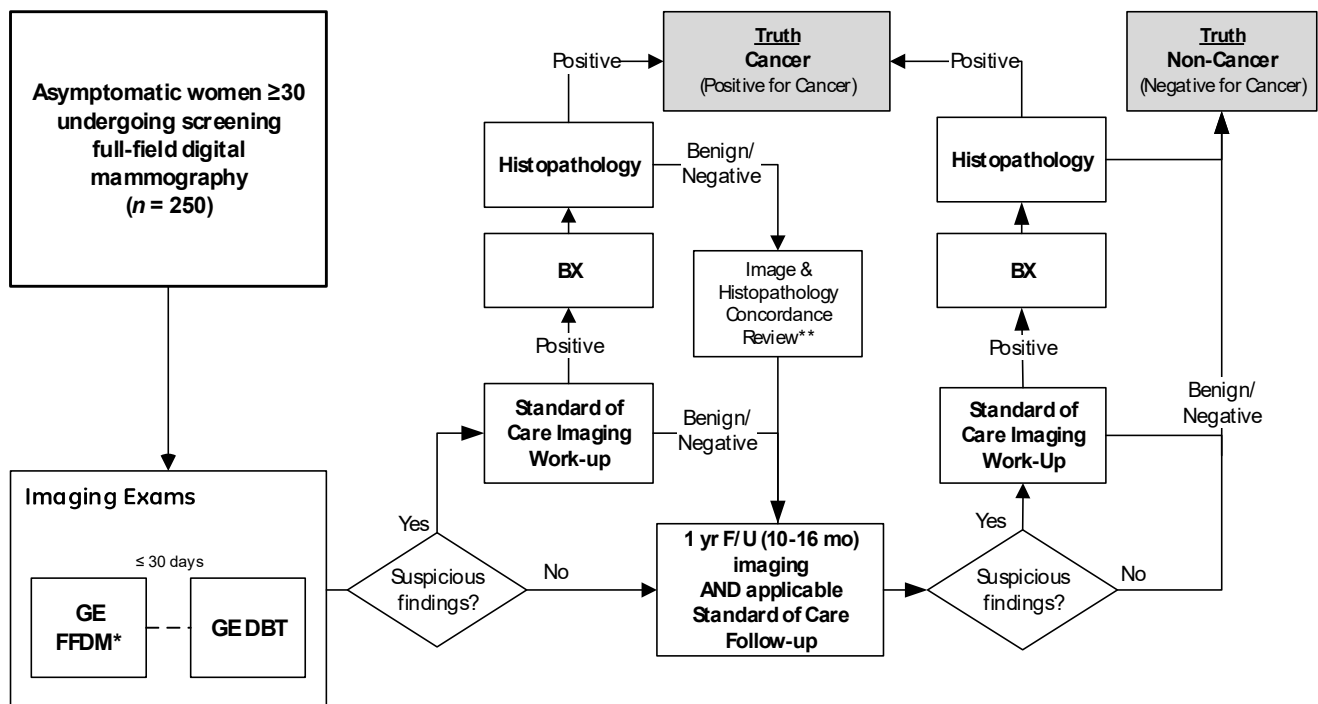
### 6.1. Type of Research Study

#### 6.1.1. Study Type

This study (ADAPT-SCR) is an open-label, multi-center, within-subject crossover, randomized, 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 asymptomatic adult women aged  $\geq 30$  years undergoing routine screening mammography.

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

**Figure 1: Study Design and Procedures**



\*FFDM may be collected prior to enrollment if conducted within 30 days of DBT.

\*\* Concordant histological and imaging findings for benign lesions or evidence of negative 1-year follow-up will serve as truth for non-cancer.



### 6.1.2. Study Design Details:

Open-Label	<input checked="" type="checkbox"/>	<i>Interventions are known to researchers and subjects</i>
Blinded	<input type="checkbox"/>	
Double-Blinded	<input type="checkbox"/>	
Single-site	<input type="checkbox"/>	
Multi-site	<input checked="" type="checkbox"/>	<i>Data will be pooled from multiple studies (e.g. ADAPT-SCR &amp; ADAPT-BX) at multiple sites</i>
Randomization Procedure:	<input checked="" type="checkbox"/>	<i>Reading order of DBT and FFDM will be random</i>
Not randomized:	<input type="checkbox"/>	
Single arm	<input type="checkbox"/>	
Comparator	<input checked="" type="checkbox"/>	<i>Diagnostic accuracy of DBT vs FFDM will be assessed in a separate protocol (ADAPT-BIE)</i>
Parallel	<input type="checkbox"/>	
Crossover	<input checked="" type="checkbox"/>	<i>This is a within-subject crossover study</i>
Prospective	<input checked="" type="checkbox"/>	<i>Subjects are enrolled and then undergo study procedures</i>

### 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 the last subject is imaged in the one-year follow-up. Total participation for each subject is expected to be 10-16 months, unless completed early due to truth determination of cancer status. The Investigator shall not begin study until the applicable EC/IRB approval has been obtained.

### 6.3. Controls and Minimization of Bias

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

- Selection bias in allocating subjects to interventional groups will be limited by attempting to enroll consecutively eligible subjects; subjects may be recalled for further work-up based on positive screening interpretations on either FFDM or DBT.
- 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.
- Interpretation bias will be managed by randomizing the order that DBT and FFDM are read for subjects as these will usually occur during the same visit.



## **7. STUDY SUBJECTS**

### **7.1. Number of Subjects**

Up to 250 routine screening mammography (Enrollment ceiling per site will be 150 subjects) subjects will be enrolled from two (2) centers in the US. Data will be pooled with other sources to achieve the target number of positive cancer and non-cancer cases required for analysis, as described in Section 10.1.1 Sample Size Justification.

### **7.2. Subject Population**

Study subjects will be adult women ( $\geq 30$  years of age) clinically scheduled for routine screening mammography that are 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). Each subject will be assigned a randomized order for reading of their DBT and FFDM images such that approximately half of the subjects will have their DBT images interpreted first and the other half will have their FFDM images interpreted first. A subject will be considered enrolled when determined eligible, informed consent is signed, and randomized read order is assigned, 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 ( $\geq 30$  years old);
2. Asymptomatic women scheduled for screening mammography or have completed a screening mammogram within the past 30 days;
3. Mammography completed on a GE FFDM system (with CC and MLO views) at the site or another clinical facility<sup>1,2</sup>;
4. Are able and willing to comply with study procedures;
5. Have signed and dated the informed consent form;
6. Are either surgically sterile or post-menopausal<sup>3</sup> or, if of childbearing potential, the possibility of pregnancy is remote based on a documented negative patient history and, optionally, a negative urine pregnancy test (if subject requests one).

## 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 a history of breast cancer and are in active treatment. However, subjects with a prior lumpectomy ( $\geq 5$  years prior) who receive only routine screening mammography views can be included;
3. Have breasts too large to be adequately positioned on 24 x 31 centimeter (cm) FFDM digital receptor without anatomical cut off during either FFDM or DBT 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 recruited from asymptomatic populations undergoing routine screening mammography at each site, in accordance with local EC/IRB recruitment policy. Enrollment decisions will be based on 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

<sup>1</sup> If prior mammographic examinations were not conducted at the recruiting site, review of those images by the Investigator must confirm that the subject qualified for this study (CC and MLO views present) and access to the images in DICOM digital format by GE must be granted.

<sup>2</sup> Subjects who had prior imaging on non-GE equipment may be enrolled if they agree to undergo repeat imaging on a GE FFDM system

<sup>3</sup> Post-Menopausal is defined as documented 12 months of spontaneous amenorrhea.



compliance with applicable laws, regulations, and standard procedures at the investigational site.

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1 If prior mammographic examinations were not conducted at the recruiting site, review of those images by the Investigator must confirm that the subject qualified for this study (CC and MLO views present) and access to the images in DICOM digital format by GE must be granted.  
2 Subjects who had prior imaging on non-GE equipment may be enrolled if they agree to undergo repeat imaging on a GE FFDM system  
3 Post-Menopausal is defined as documented 12 months of spontaneous amenorrhea.





## 8. PROCEDURES FOR RESEARCH STUDY

**Table 1: Study Schedule of Events for Study Subjects**

Variables	Pre – Study Imaging	Study Imaging	Post - Study Imaging
Informed Consent	X		
Entry Criteria	X		
Demographic Information <sup>a</sup>	X		
Review Relevant Medical/Surgical History	X		
Randomized Read Order Assigned	X		
DBT Imaging		X	
Collection of Prior Screening FFDM Imaging	X		
Screening FFDM Imaging <sup>b</sup>		X	
Safety Assessments (AE, SAE, device malfunctions) <sup>c</sup>		X	
Image assessment by site radiologist			X
Histopathology (if applicable)			X

DBT = Digital Breast Tomosynthesis; FFDM = Full-field digital mammography; AE = adverse event; SAE = serious adverse event;

a: Including age, menopausal status and history of surgical breast intervention. b: Only if prior images are not available or were not obtained on a GE FFDM system. c: Device-related AEs and SAEs

### 8.1. Pre-Study Imaging Procedures

All enrolled subjects will undergo the following procedures prior to receiving their study-specific 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 the subject had her questions answered, read, signed and dated and has 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 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 and randomized reading order will be assigned.

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

### 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 images will be collected from each subject's medical record or, if necessary (because prior screening mammography images are not available or were not performed with GE FFDM equipment), a subject may also need to undergo



repeat FFDM; if so, this will be 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 FFDM image acquisition (both CC and MLO views) will be performed within 30 days of each other, regardless if FFDM was performed before or after the subject 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 FFDM (if repeated) to be recorded in the source document and CRF. Device malfunctions shall be sent to the Sponsor as per Section 12.5 - Management of Device Complaints.

Proper equipment checks as noted in the SenoClaire® - GE Breast Tomosynthesis Operators Manual will be performed prior to imaging 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 the CC position, where it is essential that the breast is lifted away from the chest wall and gently pulled forward, in order to visualize the maximum amount of breast tissue.

### **8.3. Post-Study Imaging Procedures**

The following assessments will be performed:

- DBT and FFDM images will be assessed at the study site in randomized order by one or more MQSA-qualified radiologists, as per institutional standard practice;
- If clinically indicated based on screening imaging results, subjects will undergo institution's standard practice of diagnostic work-up of findings seen, which may include surgical intervention and breast tissue histopathological analysis.



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

### **8.3.1. On-Site Image Interpretation**

DBT and FFDM images of all included subjects will be assessed at the study site by one or more MQSA-qualified radiologist(s) on an IDI MammoWorkstation. The 2-D FFDM or 3-D DBT results may result in a recommendation that breast lesions be worked-up by diagnostic evaluation or biopsied.

The results of DBT alone, however, will not be used as a basis to cancel plans for biopsy of any lesion that would be otherwise recommended based on routine mammography with FFDM.

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

- Breast density (as defined by BI-RADS® density categories)
- Finding characteristics, to include breast location, lesion type, depth, quadrant and size. In the case of multiple findings, a maximum of three (3) most suspicious findings will be scored and localized.
- Screening BI-RADS® score (BI-RADS 1, 2, 3, 4, 5), scores of 0 (indeterminate) should be approximated to the closest definition score of 1 to 5 for each breast based on DBT and FFDM separately

### **8.3.2. Additional Diagnostic Imaging**

If a subject is called back for further diagnostic assessment, the additional FFDM views will be recorded on the CRF. In addition, any other imaging which the subject undergoes will be recorded (e.g., ultrasound or magnetic resonance imaging [MRI]).

## **8.4. Biopsy Procedures**

Biopsy(ies) will be completed for subjects whose screening mammography (DBT and/or FFDM) and subsequent diagnostic work-up results provide a clinical indication for biopsy. No biopsies will be performed solely for research purposes as part of this study.

Percutaneous and/or 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 on 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. 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, 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. If available, one-year follow-up data will be used to determine truth status in lieu of concordance assessments.

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, the subject will be followed at approximately one year (10-16 months).

## **8.5. Follow-up (Month 10-16) Procedures**

All subjects will be followed at approximately one year (10-16 months) unless positive cancer status is histologically determined or imaging and histology are deemed concordant prior to one year follow-up. For any subject who undergoes one-year follow-up procedures, the follow-up results will be considered truth for non-cancer or cancer status.

Applicable 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 images 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.

If the initial GE FFDM and/or DBT imaging or incidental standard of care procedures conducted prior to one-year follow-up reveals suspicious findings that could indicate breast cancer, the subject will undergo standard of care diagnostic work-up (e.g. clinically indicated MRI, ultrasound, biopsy, or other exams). Cancer status should be reported using all available clinical information, according to the Investigator's medical judgment. Positive cancer results from diagnostic work-up, biopsy and histology will be considered truth of positive cancer status, and no additional follow-up will be required once truth is established.

## **8.6. Incidental Findings**

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



## **8.7. Withdrawal and Discontinuation Criteria**

### **8.7.1. Subject Withdrawal Rules**

The subject's medical care shall take precedence over any research imaging or other procedures associated with the study. If it is determined during the exam that the research imaging will in any way 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.

Subjects withdrawn after consent is signed and randomized read order is given 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 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 dates 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 recording of data on case report forms (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-BX and ADAPT-Enrich).

In this study, for an enrollment of 250 screening subjects, it is assumed, based on the GE-190-001 experience, that 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.

Based on the GE-190-003 experience, for an enrollment of 275 subjects recommended for breast biopsy, approximately 33% are expected to have a proven cancer and 33% will have a benign lesion. So, at least 90 cancer cases and 90 benign cases are expected to be accrued in the ADAPT-BX study.

In the ADAPT-ENRICH study, for a target enrollment of 200 subjects recommended for breast biopsy, it is assumed, based on the GE-190-003 experience, that approximately 33% are expected to have a proven cancer. Thus, at least 66 cancer cases are expected from the ADAPT-ENRICH study.

In the combined protocols (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.

The data from this study will be pooled with data from other subjects who will be recruited from other sources (e.g. ADAPT-BX). If necessary, data from other sources may also be included to



achieve the required number of cancer and non-cancer cases. The accrued screening 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 the 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/randomized, 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.

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 data 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:**

Critical deviations are protocol 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, the Investigator shall consider this a critical deviation and report the event to the Sponsor and the EC/IRB within 5 working days of the occurrence.

**Non-Critical Deviations:**

Non-critical deviations are 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 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 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.

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 subject's 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](mailto: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 Affairs 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](mailto: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 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 that the subject has ample time to review the ICF and has all questions answered to her 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 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. These data and images collected as part of this research study may also be transported to countries outside of the United States for purposes of future research, engineering development, and global regulatory submissions in other countries.

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

### **15.2. Subject De-identification**

Each enrolled subject will be assigned a unique Subject Identification number that is used to provide a means for subject randomization and 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.





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## 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, which are not expected to impact the safety profile or scientific integrity of the study. Changes made to the protocol include:

- Addition of documented concordance assessments for truth determination of negative/benign histology cases;
- Inclusion of data collection for non-cancerous lesions;
- Updates to accrual target for the overall GEHC DBT program; and
- Discussion of additional ADAPT case collection study (ADAPT-ENRICH).

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	<p>An open-label, multi-center, accrual study collecting DBT and FFDM screening images from up to 250 asymptomatic women aged ≥30 years undergoing routine breast cancer screening will be conducted. CC and MLO views from bilateral GE DBT and GE FFDM (conducted before or after enrollment) within a 30 day window will be collected and assessed on-site by qualified radiologist(s) for clinical management purposes. BI-RADS® scores will be recorded. Results of biopsy(ies) and histopathology, including lesion characteristics, will be recorded.</p> <p><del>A positive histology result will be considered truth of cancer.</del></p> <p>Subjects with negative or benign <u>imaging findings (histological and/or imaging)</u> will be followed for approximately one year (10-16 months) by <u>FFDM and any additional standard of care imaging to determine cancer status performed per standard of care. 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 or evidence of negative one-year follow-up will be considered truth for non-cancer status. A positive histology result will be considered truth for cancer.</u></p> <p>...</p>	<p>Added assessment of histologic concordance with imaging for truth status of negative/benign histology cases.</p> <p>Clarified how truth will be determined for cancer and non-cancer status.</p>
2.	Section 1. Study Synopsis – Brief Description of Study Purpose	<p>This study is being conducted to accrue breast cancer screening cases of asymptomatic women for a subsequent blinded reader study comparing the diagnostic <del>superiority, accuracy and performance, and reading time</del> of digital breast tomosynthesis (DBT) performed with the GE SenoClaire® - GE Breast Tomosynthesis (DBT) compared to conventional GE full-field digital mammography (FFDM) in asymptomatic women. The study also provides data for exploratory analysis of cancerous <u>and non-cancerous</u> lesion characteristics detected by DBT and FFDM systems. This statistically powered study</p>	<p>Revised to accurately reflect intent of the blinded reader study.</p> <p>Updated to include non-cancerous lesion characteristics.</p>



Item	Section	Revision or Clarification	Justification
		is being conducted to support regulatory claims to expand the labeling of the DBT system.	
3.	Section 1. Study Synopsis – Primary Endpoints	The primary endpoint will be the site's diagnosis of cancer status (positive or negative/benign) for each subject based on DBT and FFDM at baseline (0 months) and 10-16 months, and/or (if clinically indicated) histology and surgical findings. <u>Histologic concordance with imaging will be assessed for benign lesions, when applicable, and at any point after enrollment.</u> DBT and FFDM image sets will be assessed using BI-RADS® scores.	Revised to include histologic concordance with imaging for determining truth status of benign lesions.  Clarified that FFDM and DBT image sets will be assessed.
4.	Section 1. Study Synopsis and 5.3.2. – Characteristic Endpoints	Characteristic endpoints for <del>all subjects with positive cancer status</del> will include <del>invasive/non-invasive characteristics and histology findings and</del> , size, lesion type, <u>and other lesion characteristics</u> based on image appearance <del>and other lesion characteristics</del> . Technical factors of 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 will be collected based on image appearance.
5.	Section 1. Study Synopsis and 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 as needed, repeat FFDM) <u>that occur during the study</u> will be collected. No other clinical safety assessments will be performed.	Reporting period defined for safety endpoint.
6.	Section 1. Study Synopsis – Sample Size	Sample size is determined by the need to accrue at least <del>70-120</del> cancer cases and 250 non-cancer cases for the overall GE Healthcare (GEHC) DBT program (ADAPT-BIE), for which accrual of 200 biopsy cases (ADAPT-BX <u>and other sources</u> ) and 250 screening mammography cases (ADAPT-SCR <u>and other sources</u> ) are required.	Revised accrual target based on power analysis for the overall GEHC DBT program.  Updated to clarify that other sources may be pooled for subsequent BIE study.
7.	Section 1. Study Synopsis – Research Manager	<b>Address:</b> <u>3562 Lookout Court #478</u> <u>Oceanside, CA 92056-5259, US</u> <del>3200 N Grandview Blvd</del> <del>Waukesha, WI 53188-1678</del> <b>Telephone:</b> <u>+1-414-379-4201</u> <del>1-414-721-4393</del> <b>E-mail:</b> <u>Tanya.Carrillo@ge.com</u>	Updated Research Manager's contact information.
8.	Section 1. Study Synopsis – Medical Monitor	<b>Address:</b> <u>1100 Technology Park Drive</u> <u>Billerica, MA 01821-4111, US</u> <del>3200 N Grandview Blvd</del> <del>Waukesha, WI 53188-1678</del> <b>Telephone:</b> <u>+1-617-669-3200</u> <del>781-262-5579</del>	Updated Medical Monitor's contact information.



Item	Section	Revision or Clarification	Justification
		E-mail: <a href="mailto:Ron.VonJako@med.ge.com">Ron.VonJako@med.ge.com</a>	
9.	Section 2.1. Literature Review – Introduction	... This protocol is one of <del>two</del> <u>multiple</u> 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 <del>two</del> 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 <u>some</u> who have been recommended for breast biopsy because of one or more radiographically detected suspicious lesions.	Updated to clarify that other sources may be pooled for subsequent BIE study.  Clarified that all subjects are not expected to be recommended for biopsy.
10.	Section 5.2.2. Characteristic Objectives	An exploratory aim is to describe <del>positive cancer and non-cancer</del> cases identified in this accrual study based on <del>cancer characteristics</del> <u>histology findings</u> and lesion type.	Updated to include non-cancerous lesion characteristics.
11.	Section 5.3.1. Primary Endpoints	The primary endpoint will be the site's diagnosis <del>for each patient</del> of cancer status (positive or negative/benign) <u>for each subject</u> based on DBT and FFDM at baseline (0 months) and 10-16 months, and/or (if clinically indicated) histology and surgical findings. <u>Histologic concordance with imaging will be assessed for benign lesions, when applicable, and</u> DBT and FFDM image sets will be assessed using BI-RADS® scores.	Revised to include histologic concordance with imaging for determining non-cancer truth status of benign lesions.  Revised to mirror language in Section 1. Study Synopsis – Primary Endpoints.
12.	Section 6.1.1. Study Type	This study (ADAPT-SCR) is an open-label, multi-center, within-subject crossover, randomized, prospective clinical research study, <u>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.</u> Study subjects will be asymptomatic adult women aged ≥30 years undergoing routine screening mammography. ... <b>Figure 1: Study Design and Procedures</b>	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 lesions. Clarified that 1-year follow-up will



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		<p><i>*FFDM may be collected prior to enrollment if conducted within 30 days of DBT.</i></p> <p><i>** Concordant histological and imaging findings for benign lesions or evidence of negative 1-year follow-up will serve as truth for non-cancer.</i></p>	<p>include standard of care imaging.</p> <p>Added footnote clarifying non-cancer truth determination.</p>
13.	Section 6.1.2. Study Design Details	<p>...</p> <p>Multi-site: <i>Data will be pooled from 2-multiple studies (e.g. ADAPT-SCR &amp; ADAPT-BX) at multiple sites</i></p> <p>Comparator: <i>Diagnostic accuracy of DBT vs FFDM <del>is</del> will be assessed in a separate protocol (ADAPT-BIE)</i></p> <p>...</p>	<p>Clarified that other sources may be pooled for analyses.</p> <p>Clarified that ADAPT-BIE will be conducted subsequently.</p>
14.	Section 6.2. Study Timeframe	<p>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 the last subject is imaged in the one-year follow-up. Total participation for each subject is expected to be 10-16 months, unless completed early due to <del>incidental cancer finding</del> <u>truth determination of cancer status</u>. The Investigator shall not begin study until the applicable EC/IRB approval has been obtained.</p>	<p>Revised to reflect update to non-cancer truth determination.</p>





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15.	Section 7.1. Number of Subjects	Up to 250 routine screening mammography (Enrollment ceiling per site will be <u>150</u> subjects) subjects will be enrolled from two (2) centers in the US. Data will be pooled with other sources to achieve the target number of positive cancer and non-cancer cases required for analysis, as described in Section <u>10.1.1 Sample Size Justification</u> <del>9.1.1 Sample Size Justification.</del>	Updated section reference.																																																
16.	Section 8. Procedures for Research Study	<p><b>Table 1: Study Schedule of Events for Study Subjects</b></p> <table> <tr> <th>Variables</th><th>Pre – Study Imaging Mammography</th><th>Study Imaging Mammography</th><th>Post – Study Imaging 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 <sup>a</sup></td><td>X</td><td></td><td></td></tr> <tr> <td>Review Relevant Medical/Surgical</td><td>X</td><td></td><td></td></tr> <tr> <td>Randomized Read Order Assigned</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 Screening</td><td>X</td><td></td><td></td></tr> <tr> <td>Screening FFDM Imaging <sup>b</sup></td><td></td><td>X</td><td></td></tr> <tr> <td>Safety Assessments (AE, SAE, device malfunctions) <sup>c</sup></td><td></td><td>X</td><td></td></tr> <tr> <td>Image assessment assessment by</td><td></td><td></td><td>X</td></tr> <tr> <td>Histopathology (if applicable)</td><td></td><td></td><td>X</td></tr> </table>	Variables	Pre – Study Imaging Mammography	Study Imaging Mammography	Post – Study Imaging Mammography	Informed Consent	X			Entry Criteria	X			Demographic Information <sup>a</sup>	X			Review Relevant Medical/Surgical	X			Randomized Read Order Assigned	X			DBT Imaging		X		Collection of Prior Screening	X			Screening FFDM Imaging <sup>b</sup>		X		Safety Assessments (AE, SAE, device malfunctions) <sup>c</sup>		X		Image assessment assessment by			X	Histopathology (if applicable)			X	<p>Revised table headers to clarify procedures are related to study-specific imaging.</p> <p>Corrected typographical error.</p>
Variables	Pre – Study Imaging Mammography	Study Imaging Mammography	Post – Study Imaging Mammography																																																
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17.	Section 8.1. Pre-Study Imaging Procedures	<p><del>8.1. Pre-Mammography Study Imaging Procedures</del></p> <p>All enrolled subjects will undergo the following procedures prior to receiving their <u>study-specific</u> DBT (and, if necessary, FFDM) mammogram(s):</p> <ul style="list-style-type: none"> <li>A notation will be made in the subject's medical chart that the subject is participating in the clinical trial. Additionally, the notation should indicate the subject had her questions answered-, read, signed and dated and has been given a copy of the Informed Consent Form (ICF);</li> <li>Study entry criteria, demographic information (including age), relevant reproductive medical/surgical history such as oophorectomy, hysterectomy, or other reproductive or breast surgeries (e.g. aspiration, core biopsy, breast reduction, implant removal surgery, or other surgery) and pregnancy/menopausal status will be reviewed;</li> <li>A subject number and randomized reading order will be assigned.</li> </ul> <p><del>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.</del></p> <p>There is no special subject preparation required to perform DBT or FFDM screening mammography. <del>Subjects undergoing a</del></p>	<p>Revised section title for consistency with Table 1 headings.</p> <p>Clarified procedures relate to study-specific imaging.</p> <p>Deleted language regarding Investigator comments to reflect approved format of CRFs.</p> <p>Deleted inconsequential language for the study protocol. Appropriate language presented in the informed consent forms.</p>																																																





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		<del>mammography examination often feel apprehensive because of the examination and the ensuing diagnosis. Consequently, a simple but precise explanation of the procedure is provided to reassure the subject. The subject should be comfortably positioned to remain motionless throughout the examination.</del>	
18.	Section 8.2. Baseline (Month 0) Digital Breast Tomosynthesis (DBT) and Full Field Digital Mammography (FFDM) Examinations	... <ul style="list-style-type: none"> <li>Positioning the breast properly in FFDM 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.</li> </ul>	Generalized statement since CC views apply to both DBT and FFDM.
19.	Section 8.3. Post-Study Imaging Procedures	8.3 Post-Mammography Study Imaging Procedures	Revised section title for consistency with Table 1 headings.
20.	Section 8.3.1. On-Site Image Interpretation	DBT and FFDM images of all included subjects will be assessed at the study site by one or more MQSA-qualified radiologist(s) on an IDI MammoWorkstation. The 2-D FFDM or 3-D DBT results may result in a recommendation that breast lesions be worked-up by diagnostic evaluation or biopsied. ...	Added FFDM to accurately reflect study procedures.
21.	Section 8.4. Biopsy Procedures	Biopsy(ies) will be completed for subjects whose screening mammography (DBT and/or FFDM) and subsequent diagnostic work-up results provide a clinical indication for biopsy. No biopsies will be performed solely for research purposes as part of this study.  Percutaneous and/or 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 on 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. The interpretation of the local pathologist will be recorded on the CRF.  <u>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. If available, one-year follow-up data will be used to determine truth status in lieu of concordance assessments.</u>  <u>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</u>	Added procedure for histologic concordance with imaging for negative/benign histology cases.



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		<u>concordance assessment of the rebiopsy will be used to determine the subject's cancer status. If rebiopsy is not recommended, the subject will be followed at approximately one year (10-16 months).</u>	
22.	Section 8.5. Follow-up (Month 10-16) Procedures	<p>All subjects will be followed at approximately one year (10-16 months) unless positive cancer status is histologically determined <u>or imaging and histology are deemed concordant</u> prior to one year follow-up. <u>For any subject who undergoes one-year follow-up procedures, the follow-up results will be considered truth for non-cancer or cancer status.</u></p> <p><u>Applicable</u> <del>Subjects</del> 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 <del>FFDM</del> images completed at another clinical site. If no suspicious findings are observed at one-year <del>FFDM</del> 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.</p> <p>...</p>	<p>Added histologic concordance with imaging for negative/benign histology cases.</p> <p>Specified that one-year follow-up results will be used for truth determination, when available.</p> <p>Clarified that standard of care imaging will be conducted at follow-up.</p>
23.	Section 10.1.1. Sample Size Justification	<p>The projected sample size is determined by the need to accrue at least <del>70-120</del> cancer cases and 250 non-cancer cases for the overall GE Healthcare SenoClaire® - GE Breast Tomosynthesis (DBT) development program. <u>To achieve these overall accrual targets, the data from this study will be pooled with data from other studies (e.g. ADAPT-BX and ADAPT-Enrich).</u></p> <p>In this study, for an enrollment of 250 screening subjects, it is assumed, based on the GE-190-001 experience, that 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.</p> <p>Based on the GE-190-003 experience, for an enrollment of <del>200-275</del> subjects recommended for breast biopsy, approximately 33% are expected to have a proven cancer and 33% will have a benign lesion <del>with normal 1-year follow-up</del>. So, at least <del>66-90</del> cancer cases and <del>66-90</del> benign cases <del>with normal 1-year follow-up</del> are expected to be accrued in the ADAPT-BX study.</p> <p><u>In the ADAPT-ENRICH study, for a target enrollment of 200 subjects recommended for breast biopsy, it is assumed, based on the GE-190-003 experience, that approximately 33% are expected to have a proven cancer. Thus, at least 66 cancer cases are expected from the ADAPT-ENRICH study.</u></p> <p><del>Thus, in</del> In the combined protocols (ADAPT-SCR and, ADAPT-BX, and ADAPT-ENRICH), it is expected that at least <del>70-120</del> cancer cases and</p>	<p>Updated total accrual targets for the overall GEHC DBT program.</p> <p>Revised to include ADAPT-ENRICH and to clarify strategy for combining cancer and non-cancer cases from different sources to achieve the overall program targets.</p> <p>Updated enrollment targets for ADAPT-BX (protocol version 4.0, dated 08/Mar/2016).</p>



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		<p>250 non-cancer cases will be accrued <u>for the overall GEHC DBT development program</u>.</p> <p>The data from this study will be pooled with data from other subjects who will be recruited from other sources, <del>such as the separate protocol</del> (e.g. ADAPT-BX). If necessary, data from other sources may also be included to achieve the required number of cancer and non-cancer cases. The accrued screening 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.</p> <p>...</p>	

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