GE Healthcare

Clinical Study Protocol:

Patient-Assisted Compression in 3D – Impact on Image Quality and Workflow (Study NO. 124.03-2017-GES-0005)

Version: 1.0; 09/Nov/2017

Sponsor: General Electric Company, acting through its GE Healthcare Business
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Investigational Product: Patient-assisted Compression (PAC), Senographe Pristina 3D

Modality: Imaging, Women's Health

FOR QUALIFIED INVESTIGATORS, STUDY STAFF, AND THEIR ETHICS COMMITTEE(S) ONLY

The Sponsor and Investigator have approved this protocol version, and I confirm hereby to conduct the study according to the protocol and in accordance with applicable principles of the World Medical Association Declaration of Helsinki and Good Clinical Practice (GCP) guidelines as per ISO 14155:2011, any conditions of approval imposed by the reviewing EC or governing regulatory body, and applicable laws and regulations. The investigator should not deviate from this protocol except for emergency use. I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Principal Investigator at study site:

Investigator Signature	Date
Print Name	
Site Name, Department, 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 every relevant change by indicating what changes were made.

Revision	Date	Revision Author	Comments/Changes
1.0	09/Nov/2017	Carrie Lauer	Clinical Writer – This is the initial version.

LIST OF ABBREVIATIONS AND TERMS

2D	Two dimensional
3D	Three dimensional
AE	Adverse Event
ADE	Adverse Device Effect
ALARP	As Low as Reasonably Practicable
CA	Competent Authority
CAPM	GE Clinical Affairs Project Manager
CC	Craniocaudal
CCG	Case Report Form Completion Guidelines
CFR	Code of Federal Regulations
CHF	Clinical History File (synonymous with e-Trial Master File)
CRF	Case Report Form
DBT	Digital Breast Tomosynthesis
EC	Ethics Committee
eCRF	Electronic case report form
FDA	United States Food and Drug Administration
FFDM	Full-field Digital Mammography
GCP	Good Clinical Practice (see ISO 14155:2011) [1]
GE	General Electric
GEHC	General Electric Healthcare
Guidance	Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Full-Field Digital Mammography System (2012)
ICF	Informed Consent Form
ISO	International Standards Organization
MLO	Mediolateral Oblique
MQSA	Mammography Quality Standards Act
MWS	GE MyWorkshop Internal Documentation System
PAC	Patient-assisted Compression
PI	Principal Investigator
Reader	Interpreting Physician, as defined under U.S. FDA 21CFR §900.12(a)(1)(i)(B)(2)
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
TC	Technologist-controlled
U.S.	United States
USADE	Unexpected Serious Adverse Device Effect

STUDY SYNOPSIS

Sponsor:	General Electric Company, acting through its GE Healthcare Business
Research Type:	This is a Clinical, single-blind, randomized, prospective research study.
Regulatory Status:	This is a pre-market research study of the following products: Post-market: **Patient-assisted Compression (PAC) on Senographe Pristina 3D** (Senographe Pristina FFDM with PAC is FDA-cleared; thus, PAC is being used off-label for the purposes of this DBT-focused study, indicating the pre-market nature of the research.) **Technologist-controlled compression on Senographe Pristina 3D**
Background and Rationale:	Patient-assisted compression (PAC) allows the patient to participate in controlling the amount of compression force during mammography and is a personalized approach that has demonstrated successful reduction in discomfort experienced during mammography. GE Healthcare's Senographe Pristina, an innovative mammography platform that provides both two-dimensional (2D) and three-dimensional (3D) imaging capabilities, offers both standard and patient-assisted compression modes. This study will evaluate image quality and clinical workflow as it relates to use of PAC with the Senographe Pristina 3D. Study are intended to support regulatory submissions.
Procedures/ Methods:	The study population will consist of adult asymptomatic women presenting for screening 2D mammography. One breast of each subject will be identified as the "breast of interest," which will undergo study-specific 3D imaging consisting of two-view (craniocaudal and mediolateral oblique) PA compression and image acquisition, followed by two-view technologist-controlled (TC) compression and image acquisition. The breast of interest will be randomly assigned to either the first breast imaged during the exam or the second breast imaged. TC compression and imaging, and procedures performed on the subject's other breast will be conducted per standard of care. Following image acquisition, 3D image quality evaluation will be conducted by MQSA-qualified readers. Prior to the reading session, images will be de-identified and the following information will be removed from the DICOM header to blind readers to the compression mode used during acquisition: time stamp, compression force, and breast thickness. The image sets will also be randomized for presentation during the image attribute reviews. Two (2) readers will evaluate each PAC and TC compression image set collected from each subject's breast of interest and assess the acceptability of image attributes, as defined in the Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Full-Field Digital Mammography System (2012). A third reader will provide adjudication, if there is disagreement for a given image set's overall clinical image quality. Workflow data, including the incidence of technologist intervention during acquisition and need for repeat image acquisition, will also be collected. The proportion of PAC image sets that are of equal or higher acceptability than TC image sets will be calculated. A 95% confidence interval will be calculated using asymptotic method with continuity correction. The proportion of image sets indicated for repeated

	image acquisition when using PA mode or TC mode will be summarized. Other endpoint data will be summarized using descriptive statistics. No statistical hypothesis is being tested in this study.
Objectives:	The **primary objective** is to compare the acceptability of overall image quality in unilateral two-view (CC and MLO) breast images acquired using PAC and TC compression modes. The **secondary objectives** are: • To evaluate the need for repeat image acquisition when using PAC and TC compression modes; and • To evaluate acceptability of mammographic attributes for unilateral two-view breast images acquired using PAC and TC compression modes, per the *Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Full-Field Digital Mammography System* (2012). The **exploratory objectives** are: • To collect workflow data for PAC and TC compression, and • To collect breast thickness, radiation dose, and compression force for images acquired using PAC and TC compression. The **safety objective** is to collect safety information, including adverse events (AEs), serious adverse events (SAEs), and product issues.
Endpoints:	The **primary endpoint** is the overall image quality acceptability on a per subject-basis using a binary response of either acceptable or unacceptable for unilateral, two-view PAC and TC compression image sets. The **secondary endpoints** are: • Number of incidences per image set when the technologist and/or readers indicate a repeat acquisition for PAC and TC compression; and • Acceptability of mammographic attributes, as defined in the *Guidance* and as described in this protocol. The **exploratory endpoints** will be collected per subject for each study-specific 3D PAC and TC compression. The endpoints are: • Type and incidence of technologist interventions (e.g. technologist uses footswitch to increase compression); and • Breast thickness, radiation dose, and compression force. The **safety endpoints** are the type and number of AEs, SAEs, and device issues.

Eligibility criteria:	1) Are women aged 40 years or older; 2) Are asymptomatic and scheduled for screening mammography; 3) Have left and right breasts; 4) Have breast sizes compatible with the dimensions of a 24 x 31 cm image detector, without anatomical cut-off; 5) Are documented as non-pregnant based on the investigator's medical judgment and in consideration of local clinical practice standards for evidence of non-pregnancy; 6) Are able and willing to comply with study procedures; and 7) Are able and willing to provide written informed consent to participate.	1) Have been previously included in this study or are participating in another study expected to interfere with study procedures or outcomes; 2) Participated in the GE Healthcare study that investigated PAC with the Senographe Pristina FFDM system (Study Number: 124.03-2017-GES-0002; Study Title: Patient-Assisted Compression – Impact on Image Quality and Workflow); 3) Have undergone diagnostic or surgical intervention(s) or procedure(s) on either breast, including breast biopsy, lumpectomy, or reconstruction, within five (5) years (≤ 5 years) of the study exam date; 4) Are currently undergoing radiotherapy or chemotherapy, or have a history of prior radiotherapy treatment on either breast; 5) Are currently lactating; or 6) Have breast implants.
Sample size and Sites:	Up to 36 subjects from one (1) site will be included as part of this study to achieve the targeted number of complete and evaluable subjects. The target sample size for this study is 30 subjects, providing 60 evaluable 3D image sets for the image attribute review (30 PAC image sets and 30 TC compression image sets). The number of subjects was determined based on Sponsor discussions with a U.S. FDA Medical Officer, who indicated that, during MQSA re-accreditation, sites are requested to submit sample images. If an issue is identified with the sample images, an Advanced Mammographic Review occurs, where the quality of 30 images is assessed to determine whether the issue was isolated or systemic.	
Study duration:	The study is expected to last approximately three (3) months.	

ADMINISTRATIVE STRUCTURE OF INVESTIGATION		
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1. BACKGROUND AND JUSTIFICATION

1.1 Screening Mammography and Patient-Assisted Compression

Leading authorities on breast cancer recommend regular screening mammography for women aged 40 years and older as a means of early detection for breast cancer, leading to increased survival rates and more treatment options. [2, 3, 4] Numerous randomized trials have demonstrated that regular mammographic screening reduces breast cancer mortality, [5, 6, 7, 8, 9] with more than 40% reduction in breast cancer deaths. [10, 11] Amidst the success of screening mammography, clinicians struggle to maintain patient participation in regular screening programs. Notably, a systematic review by Whelehan, et al. concluded that pain experienced during screening mammography (e.g. compression pain) contributed to reduced rates of repeat participation in regular screening programs. [12]

Adequate breast compression during mammography creates uniform thickness and flattens tissues, [4] which is necessary to obtain sufficient image quality [4, 13, 14] and reduce radiation dose. [4, 15] Various methods are being investigated to maintain sufficient compression while reducing pain/discomfort associated with mammography. Specifically, studies have shown that a personalized approach to compression can significantly reduce pain intensity and discomfort experienced by patients while maintaining diagnostic image quality. [16, 17, 18]

Patient-assisted compression (PAC) allows the patient to control the amount of compression force during mammography and is a personalized approach that has demonstrated successful pain reduction in mammography. [16] GE Healthcare's Senographe Pristina, an innovative mammography platform that provides both two-dimensional (2D) and three-dimensional (3D) imaging capabilities, offers standard and patient-assisted compression modes. The study described herein is being conducted to compare the image quality of DBT breast images obtained using standard (i.e. technologist-controlled) compression and PAC in an asymptomatic female population undergoing 2D and 3D (i.e. "combo mode") screening mammography. PAC, which is marketed as Pristina Dueta™ in some countries, was recently cleared by the U.S. FDA for use with Senographe Pristina FFDM (2D) system and is the first of its kind in the medical device industry. This study will evaluate image quality and clinical workflow as it relates to use of PAC with the Senographe Pristina 3D (DBT option). Study results are intended to support regulatory submissions.

1.2 Controls and Minimization of Bias

Due to the inherent difference in utility of standard and PAC modes, study subjects and study staff will not be blinded to the compression mode. However, the following bias control methods will be employed in this study:

- Selection bias will be limited by consecutively enrolling eligible subjects.
- Spectrum bias will be limited by using a population expected to represent the general population at the investigational site, without regard to race or ethnicity.
- PAC will be randomly assigned to either the first or second breast imaged to mitigate subject-learning bias associated with the amount of compression required for image acquisition.
- Reading order bias will be limited by randomizing the order of image set presentation to the readers.
- Readers conducting image quality evaluations will be blinded to the compression mode used to obtain the images.
- A minimum of three (3) radiology technologists will conduct the study procedures to mitigate bias introduced by technologist-specific practices.

2. DEVICE/PRODUCT DESCRIPTION

2.1 Identity, Mechanism, and Function of Investigational Device

Name: Patient-assisted Compression (PAC), Senographe Pristina 3D

Modality/Type: Imaging, Women's Health

Manufacturer: GE

Software version: Senographe Pristina 1.0, Axis version 1.50

Regulatory Status: Post-market device (PAC) used off-label in this pre-market research study

Note: A record of number of products issued, along with applicable identification numbers (e.g. serial/lot/batch) and components/accessories used in this study will be retained by the Sponsor as part of the clinical history file (CHF), as required by applicable laws and regulations.

Senographe Pristina is a commercial mammography medical device consisting of the Senographe Pristina FFDM system (2D) and Senographe Pristina 3D (DBT option). The platform is an evolution of the cleared/approved Senographe Essential FFDM system (2D) and SenoClaire DBT option (3D). Senographe Pristina includes the same clinical applications as traditional mammography systems and is designed to improve workflow while maintaining imaging capabilities and image quality of FFDM and DBT breast imaging. The DBT option will be the focus of this study, as PAC is FDA-cleared for use with the Senographe Pristina FFDM system.

Senographe Pristina includes the hardware and software components required for multi-modality functioning and is designed to improve patient experience, patient throughput, and radiographer experience. The system offers two compression modes – standard mode and the optional PAC mode

. PAC enables the patient to personally refine breast compression using a hand-held remote control (Figure 1


) after the compression has been initiated by the operator, which is required to ensure proper breast positioning.

Figure 1 –Senographe Pristina mammography device with remote control for PAC.

The research device (i.e. Senographe Pristina 3D with PAC), instructions for use, or packaging shall indicate that the research device is for use in a research investigation, in accordance with applicable regulations in the U.S., including U.S. FDA 21 CFR and other applicable laws and regulations. Senographe Pristina 3D with PAC will be exclusively used for research purposes.

The results of this study are intended to support regulatory submissions for PAC use with Senographe Pristina 3D. Results may be used to help commercialize the product in other global regions in the future, at the discretion of the Sponsor.

2.2 Mammography Review Workstation

An FDA-cleared mammography review workstation or other image review system will be used in this study to display images during reader evaluations of the image sets. Review workstations/systems are not a component of Senographe Pristina or PAC.

The study-specific images will be labelled for research use only, and the investigational image sets will be exclusively used for research purposes.

2.3 Intended Use

Senographe Pristina 3D is indicated for acquisition of multiple projection views to produce 3D digital mammography images suitable for use in screening and diagnosis of breast cancer; however, screening mammography is the focus of this study. Study procedures are intended for research purposes and are not intended as a substitute for required medical care.

2.4 Comparator

The comparator is the technologist-controlled compression mode of Senographe Pristina 3D (referred to as "TC compression" hereafter). This is considered the "standard" compression mode, which is currently approved for use with Senographe Pristina 3D.

2.5 Concomitant/Ancillary Administrations

2.5.1 Medications and Biologic Products

No medications or biologic products will be administered as part of study procedures.

2.5.2 Laboratory Tests and Sample Processing

No laboratory tests or sample processing is planned as part of the study procedures.

2.6 Accountability

Accurate and adequate records will be maintained for all devices/products, from time of shipment to the site until return or disposal of all devices issued by the Sponsor as part of this study, as required by applicable laws and regulations. The Principal Investigator (PI) will be ultimately responsible for the security and integrity of research devices/products at the investigational site during the study.

2.6.1 Issuance

The PAC product will be provided by the Sponsor. Site will be encouraged to use equipment owned by the site, such as the Senographe Pristina and image review workstations, if available. If the site does not own the required equipment, the Sponsor may provide devices for study use.

2.6.2 Disposition

Product(s) provided to the site by the Sponsor will be returned to the Sponsor, in accordance with applicable laws and regulations.

2.7 Anticipated Risks and Benefits

The device under study has undergone risk assessment, in accordance with International Standards Organization (ISO) 14971:2012. Risks have been mitigated to levels as low as reasonably possible (ALARP) and are not expected to exceed risks associated with the routine clinical breast cancer screening procedures that the subject has been prescribed outside of the study. The operator's manual highlights warnings, cautions, and potential conventional risks associated with the exam.

Breast imaging procedures will be conducted using post-market Senographe Pristina systems with post-market PAC installed. Breast imaging procedures will be conducted per the site's standard of care, with the exception of the

investigational imaging, which will consist of unilateral two-view (craniocaudal [CC] and mediolateral oblique [MLO]) acquisitions using PAC during DBT imaging. There will be no repeat imaging administered using PAC.

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. Post-trial care and follow-up are not required by this study.

There is no expected benefit to study subjects participating in this research. The results of this study may benefit future patients by increasing knowledge about PAC with Senographe Pristina 3D.

2.7.1 Risk Category and Rationale

The Senographe Pristina 3D system with PAC, as used in this study, is not considered a significant risk device per the 21 CFR §812.3 definition:

1) it is not intended as an implant;
2) is not purported or represented to be for a use in supporting or sustaining human life;
3) is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health; and
4) 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 the data obtained will not be used as the sole measure of diagnosis without distinct confirmation from conventional methods, such as mammography on an approved/cleared device or other standard of care procedures at the investigational site.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Purpose of the Study

The purpose of this study is to collect clinical evidence associated with image quality and workflow to support regulatory submissions for PAC use with Senographe Pristina 3D.

3.1.1 Primary Objective

The primary objective is to compare the acceptability of overall image quality in unilateral two-view (CC and MLO) breast images acquired using PAC and TC compression modes.

3.1.2 Secondary Objectives

The secondary objectives are:

- To evaluate the need for repeat image acquisition when using PAC and TC compression modes; and
- To evaluate acceptability of mammographic attributes for unilateral two-view breast images acquired using PAC and TC compression modes, per the *Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Full-Field Digital Mammography System* (2012; hereafter referred to as the "*Guidance*").

3.1.3 Exploratory Objectives

The exploratory objectives are:

- To collect workflow data for PAC and TC compression, and
- To collect breast thickness, radiation dose, and compression force for images acquired using PAC and TC compression.

3.1.4 Safety Objective

The objective is to collect safety information, including adverse events (AEs), serious adverse events (SAEs), and product issues.

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoint is the overall image quality acceptability on a per subject-basis using a binary response of either acceptable or unacceptable for unilateral, two-view PAC and TC compression image sets.

3.2.2 Secondary Endpoints

The secondary endpoints are:

- Number of incidences per image set when the technologist and/or readers indicate a repeat acquisition for PAC and TC compression; and
- Acceptability of mammographic attributes, as defined in the *Guidance* and as described in Section 6.2 Image Attribute Review Data.

3.2.3 Exploratory Endpoints

The exploratory endpoints will be collected per subject for each study-specific 3D PAC and TC compression. The endpoints are:

- Type and incidence of technologist interventions (e.g. technologist uses footswitch to increase compression); and
- Breast thickness, radiation dose, and compression force.

3.2.4 Safety Endpoints

The safety endpoints are the type and number of AEs, SAEs, and device issues.

3.3 Summary of Study Design

This is a pre-market, clinical, single-blind, prospective, randomized research study conducted at one (1) site in the U.S.

4. STUDY DESIGN

4.1 Study Population

The study population will consist of asymptomatic adult women presenting for screening breast imaging, which is representative of the general population expected to use Senographe Pristina 3D in clinical practice.

4.2 Number Subjects

Up to 36 subjects will be enrolled into this study at one (1) site to achieve the targeted number of 30 complete and evaluable subjects.

4.3 Protection of Vulnerable Subjects

Vulnerable subjects are individuals whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate.

The Sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s), or other parties participating in, or contributing to, the clinical investigation.

All investigators shall avoid improper influence on, or inducement of, the subject, Sponsor, monitor, other investigator(s), or other parties participating in, or contributing to, the clinical investigation.

This study does not examine any groups of subjects who are considered to be vulnerable subjects in the country in which the study is being conducted.

4.4 Eligibility Criteria

4.4.1 Inclusion Criteria

Subjects who meet all the following inclusion criteria may be included:

1) Are women aged 40 years or older;
2) Are asymptomatic and scheduled for screening mammography;
3) Have left and right breasts;
4) Have breast sizes compatible with the dimensions of a 24 x 31 cm image detector, without anatomical cut-off;
5) Are documented as non-pregnant based on the investigator's medical judgment and in consideration of local clinical practice standards for evidence of non-pregnancy;
6) Are able and willing to comply with study procedures; and
7) Are able and willing to provide written informed consent to participate.

4.4.2 Exclusion Criteria

Subjects who meet any the following exclusion criteria will be excluded:

1) Have been previously included in this study or are participating in another study expected to interfere with study procedures or outcomes;
2) Participated in the GE Healthcare study that investigated PAC with the Senographe Pristina FFDM system (*Study Number: 124.03-2017-GES-0002; Study Title: Patient-Assisted Compression – Impact on Image Quality and Workflow*);
3) Have undergone diagnostic or surgical intervention(s) or procedure(s) on either breast, including breast biopsy, lumpectomy, or reconstruction, within five (5) years (≤ 5 years) of the study exam date;
4) Are currently undergoing radiotherapy or chemotherapy, or have a history of prior radiotherapy treatment on either breast;
5) Are currently lactating; or
6) Have breast implants.

4.5 Recruiting and Screening

Subjects will be recruited for potential enrollment into this study from an adult asymptomatic female population scheduled for screening at the site. Subjects will be screened for enrollment against the inclusion and exclusion criteria,

and enrollment determinations will be made by the PI. Recruitment, screening, and enrollment will be conducted per the standard procedures of the investigational site. All subject participation will be voluntary.

Following recruitment, a subject will be considered enrolled (the point of enrollment) once she signs and dates the informed consent form (ICF). Once enrolled, the subject will be assigned a unique subject number, which will not contain information that could identify her (e.g. subject name or date of birth). The unique subject number will be used to label case report form (CRF) data for the subject throughout her participation in the study.

4.6 Breast of Interest Randomization

One (1) breast per subject will undergo study-specific procedures (hereafter referred to as "breast of interest") while the second breast will be imaged per standard of care. The breast of interest will be randomized across all subjects so that approximately half the subjects will be assigned to the first imaged breast and the other half will be assigned to the second imaged breast (Figure 2).

Site technologists conducting the study will perform each subject's mammography exam per standard practice. Thus, the laterality of the breast of interest will solely depend on which breast (left or right) the technologist images first and second in standard practice.

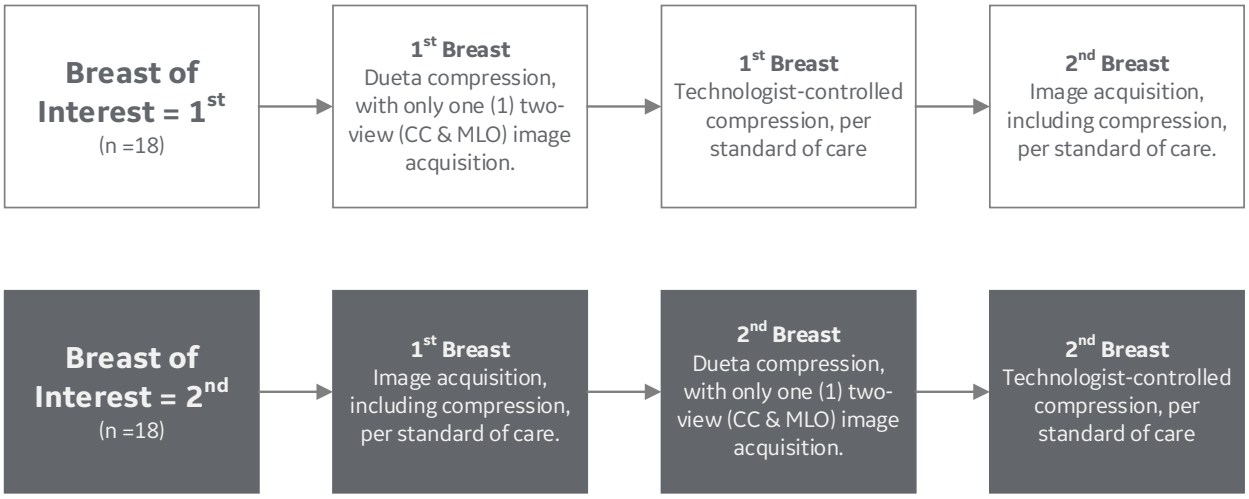

Figure 2 – Schematic showing image acquisitions based on the randomly-assigned breast of interest (i.e. first or second breast).

4.7 Criteria for Withdrawal/Discontinuation

A subject may withdraw from study participation at any time, for any reason, and the investigator may withdraw a subject at any time, for any reason. The reasons for withdrawal and discontinuation for any subject shall be recorded on a case report form (CRF) and reported to the Sponsor. The Ethics Committee (EC) should be notified per their notification-of-subject-withdrawal policy.

A subject shall be withdrawn from the study if a study-related PAC in either CC or MLO view is not completed (i.e. no image is acquired due to inadequate compression or positioning). If a subject withdraws or is withdrawn, all efforts will be made to complete and report study data up to the time of withdrawal. A complete final evaluation at the time of the subject's withdrawal shall be made and recorded on a CRF. If the reason for withdrawal is related to an adverse event (AE) or serious adverse event (SAE), monitoring of the subject will continue until the outcome is evident.

Any data collected for the subject, up until the time of withdrawal or discontinuation, may still be included in the study results and provided to the Sponsor, unless the subject requests that their data not be used. The site shall document all requests by subjects regarding their data use.

5. STUDY PROCEDURES

5.1 Diagram of Procedures

Figure 3 shows a high-level sequence of study procedures that will be conducted in this study.

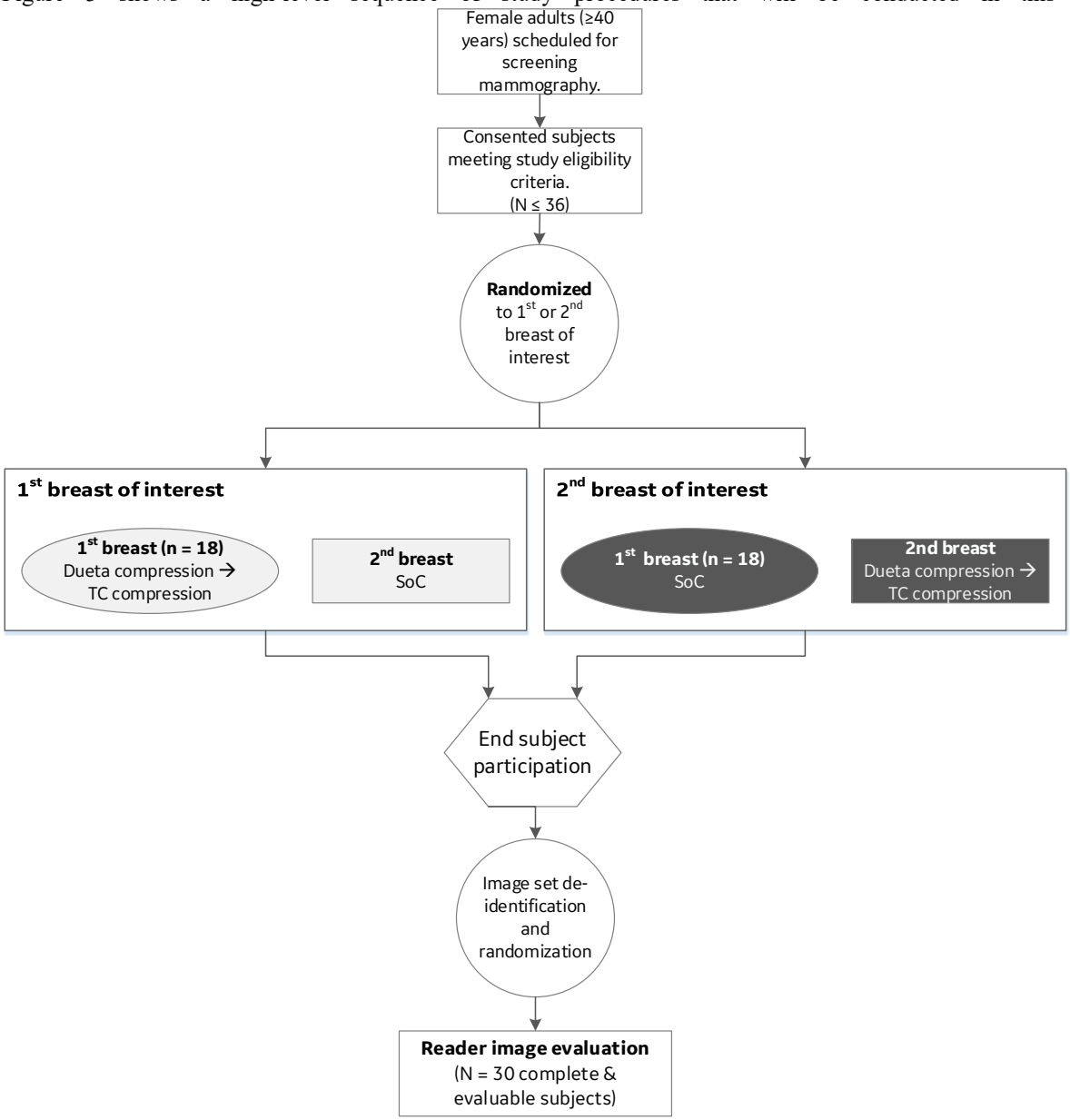

Figure 3 – Diagram of study procedures.

5.2 Subject Preparation

Study staff will confirm that the subject is eligible and willing to comply with applicable site requirements prior to starting study procedures. Demographic information, clinical history data, and pregnancy/menopausal status will be collected prior to the mammography exam.

No preparation for the breast imaging exam beyond that usually required by the investigational site is needed before procedures. After consenting, however, the study staff will show the subjects how to use the PAC mode prior to starting the exam.

5.3 Description of Study Procedures

5.3.1 Image acquisitions

Each subject will undergo her regularly scheduled breast imaging exam per standard practices at the investigational site, with the exception of the study-specific image acquisitions using PAC. The site uses combo mode (2D and 3D imaging) for screening mammography, and does not decompress between 3D and 2D imaging for a given view. Additionally, 3D acquisitions are conducted first per standard of practice. Thus, the sequence of imaging procedures will be conducted for the breast of interest, as shown in Figure 4. There shall be no repeat imaging administered using PAC mode, and standard of care will be used for imaging of the subject's other breast.

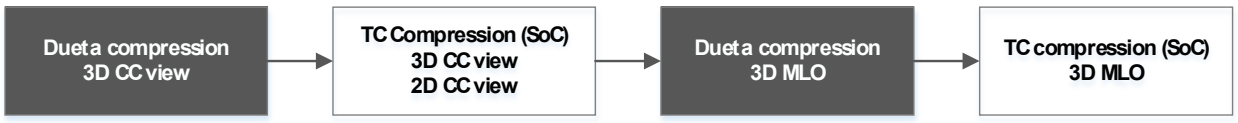

Figure 4 – Sequence of imaging procedures for the breast of interest (dark boxes = PAC, study-specific imaging, white boxes = standard of care (SoC) at the site).

A minimum of three (3) site technologists will perform the image acquisitions and related study procedures. Study procedures shall not impact the order in which the left and right breasts are imaged during the subjects' exams.

There will be two (2) study-specific image sets of the breast of interest for each subject. Image sets will consist of CC and MLO views obtained using PAC and CC and MLO views obtained using TC compression.

5.3.2 Image attribute review

Following acquisition, study-specific 3D images will be de-identified, and the time stamp, compression force, and breast thickness will be removed from the DICOM header to ensure the readers are blinded to the compression mode used for each image set. The image sets will be randomized for presentation during the image attribute reviews.

The 3D PAC and TC compression image sets will be evaluated by two (2) MQSA-qualified readers, with a third reader to provide adjudication if disagreement is observed between the two (2) readers' evaluations of "overall clinical image quality" (i.e. item number 9 in Section 5.3.2 Image attribute review). Images will be displayed on site-provided mammography review workstations/systems per the previously defined randomization scheme. Each reader will evaluate each image set independently from other reader(s) and have the freedom to navigate between views, as he/she would do in clinical practice.

In addition to the images, the following case data will be available to the readers for each image set during image attribute review:

- Techniques (anode, filter, kVp, mAs, half-value layer)
- Estimated average glandular dose per view (mGy)

5.4 Follow-up

No follow-up will be conducted in this study.

6. STUDY DATA COLLECTION AND ASSESSMENTS

6.1 Image Acquisition Data

The following data will be collected on a study CRF during the mammography exams:

1) Date of mammography exam
2) Demographic information, including age and ethnicity
3) Menopausal status
4) Size of paddle used for imaging (per breast) – 24 x 29.8 cm or 19 x 23 cm
5) Breast of interest – First breast imaged or Second breast imaged
6) Laterality of the breast of interest – Right or Left

When a subject's mammography exam is complete, the following data will be collected on a study CRF:

1) Considering PAC only, did the technologist intervene while the subject was controlling the compression? Yes or No. If yes, please indicate which of the following interventions were done:
    a. Use footswitch to increase compression
    b. Used footswitch to decrease compression
    c. Used manual knobs to increase compression
    d. Used manual knobs to decrease compression
2) Considering PAC only, would you have repeated the image acquisition? Yes or No. If yes, please select the option below that best describes the reasoning.
    a. Positioning
    b. Compression
    c. Motion
    d. Other, please explain.
3) Considering the TC compression only, did you repeat image acquisition? Yes or No. If yes, please select the option below that best describes the reasoning.
    a. Positioning
    b. Compression
    c. Motion
    d. Other, please explain.
4) Compression force (daN) – obtained from DICOM header
5) Breast thickness (mm) – obtained from DICOM header
6) AGD (mGy) – obtained from DICOM header
7) Per-view acquisition parameters (mAs and kVp) – obtained from DICOM header

6.2 Image Attribute Review Data

Following training (see Section 7. Qualification and Training Plan), readers will evaluate all image sets from all cases by classifying each of the following image attributes as either "**Acceptable**" or "**Not Acceptable**" on CRFs.

1) Breast positioning, assessing coverage of the breast on craniocaudal and mediolateral oblique view, separately
2) Exposure, assessing visualization of the adipose and fibroglandular tissues, and visualization of breast tissue underlying the pectoralis muscle, separately
3) Breast compression, assessing overlapping breast structures, uniformity of exposure of fibroglandular tissues, adequacy of penetration of thicker portions of the breast, and exposure of thinner areas
    a. If you answered "not acceptable," was breast compression acceptable or not? If not, would you request repeat imaging in standard clinical practice? Yes or No.
    b. If you answered "not acceptable," was there another reason it was unacceptable? If not, would you request repeat imaging in standard clinical practice? Yes or No.
4) Sharpness due to motion
    a. If you answered "not acceptable," would you request repeat imaging in standard clinical practice? Yes or No.
5) Image contrast for differentiation of subtle tissue density differences
6) Sharpness, assessing the edges of fine linear structures, tissue borders, and benign calcifications
7) Tissue visibility at the skin line
8) Noise, i.e., noise obscuring breast structures or suggestive of structures not actually present
9) Artifacts due to image processing, detector failure and other factors external to the breast on hard-copy and soft-copy displays
10) Overall clinical image quality
    a. If you answered "not acceptable" for overall clinical image quality, would you request repeat imaging in standard clinical practice? Yes or No.
    b. If yes, which view would you request for repeat imaging? CC only, MLO only, or both CC and MLO?

If an issue is encountered by any reader during the image attribute review of any image set, an explanation of the issue will be documented on a CRF by the reader.

Readers will also classify the breast density of each image set as follows:

1) Almost entirely fatty
2) Scattered areas of fibroglandular density
3) Heterogeneously dense
4) Extremely dense

6.3 Safety Assessments

The description, severity, and device relatedness of any AE or SAE during the study will be recorded. Subjects will, if necessary, be provided with emergency care. In the event of any device issues, the event will be recorded. Safety reporting will be conducted as described in this protocol.

7. QUALIFICATION AND TRAINING PLAN

7.1 Staff Qualifications

All members of the study staff participating in the conduct of the clinical investigation shall be qualified by education, training and/or experience to perform their tasks, and this shall be documented appropriately, as per ISO 14155:2011. Specifically, readers shall be MQSA-qualified.

7.2 Training Plan for the Protocol and Research Product

Before starting the study, study staff will be trained on the requirements and procedures set forth in this study protocol, including completion of ICFs, CRFs, and other study documentation. Training will also be provided to ensure appropriate storage and handling of data, and 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 will be stored in the Site Regulatory Binder and provided to the Sponsor for inclusion in the Sponsor's CHF. Documentation of training will include:

- Title of Training
- Training objectives
- Training logistics (trainer and training methods)
- Documentation of trainees
- Training content (e.g. device operation, protocol review and CRF completion)

Study staff directly operating the PAC product will be qualified based on mammographic experience and trained to use PAC by a GE application specialist.

The Principal Investigator will be ultimately responsible for execution of this study in accordance with the protocol and for device use in this study by members of the study staff.

8. SAFETY

8.1 Anticipated Adverse Events

Mammography is an x-ray examination of the breasts. As with all x-ray exams, mammography involves ionizing radiation. The amount of radiation from a standard screening mammography exam, even with the addition of the study-specific unilateral, two-view imaging, is small and equal in cancer risk to the total body radiation received naturally from the environment over a period of a few months.

There are no known additional medical risks or side effects from Senographe Pristina 3D with PAC mode beyond those of similar conventional clinical procedures on other commercial mammography devices. Foreseeable AEs that apply to mammography and are also applicable to digital mammography using Senographe Pristina 3D with PAC may include, but are not limited to:

- Bruising (uncommon);
- Skin irritation (uncommon), abrasions (uncommon), or tears (rare);
- Discomfort (common).

The study staff conducting the research is trained to recognize these reactions, and should it be necessary, other medical care is available at the site. Subjects will be followed for AEs from the time they enter the imaging suite for their exam until the time they exit the imaging suite after the exam.

It is generally agreed that the risk to a fetus from radiation in a screening mammography exam is minimal [19]; however, it is standard clinical practice 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.

There is always a chance of unexpected risks. Throughout the study, the Sponsor will evaluate and update safety information in study documents.

8.2 Adverse Event Definitions

Adverse Event (AE): 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 [ISO 14155:2011 3.2]. This includes events related to the investigational device or the comparator and to the procedures involved. For users or other persons, this is restricted to events related to the investigational medical device.

Serious Adverse Event (SAE): an adverse event that led to death; led to a serious deterioration in the health of the subject, that either resulted in a life-threatening illness or injury, a permanent impairment of a body structure or a body function, or in-patient or prolonged hospitalization, or medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function; or led to fetal distress, fetal death or a congenital abnormality or birth defect. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol without serious deterioration in health, is not considered a SAE [ISO 14155:2011 3.37].

Adverse Device Effect (ADE): an adverse event related to the use of an investigational medical device [ISO 14155:2011 3.1]. This includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This includes any event that is a result of a user error or intentional misuse of the investigational device [ISO 14155:2011 3.43].

Serious Adverse Device Effect (SADE): an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event [ISO 14155:2011 3.36].

Device deficiency: an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance, such as malfunctions, use errors, and inadequate labelling [ISO 14155:2011 3.15].

Unanticipated serious adverse device effect (USADE): a serious adverse device effect, which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report [ISO 14155:2011 3.42]. In the United States, 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 study documents, will be reported in accordance with 21 CFR §812.3 and applicable laws and regulations.

8.3 Documentation of Safety Events

All adverse events (AE), including all serious adverse events (SAE), are required to be collected, investigated, and documented during the study reporting period, as defined in the study procedure set forth in this protocol. Documentation will include:

- Description of Event
- Date of onset and resolution
- Severity (mild, moderate, or 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)
- Causal relationship to investigational medical device? (not related, possibly related, or related)
    - *Not related*: 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.
    - *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, or no action)
- Anticipated (yes/no)

8.4 Reporting of Safety Events and Device Deficiencies/Complaints

The following events are to be reported to the Sponsor within 72 hours of the event occurrence and to the EC per their policy:

- All SAEs and USADEs
- All device issues that could possible lead to an SAE

Additional follow-up information may be requested by the Sponsor. In addition, safety information may be shared with regulatory agencies and other participating sites, as required by applicable law and regulation.

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 per their policy.

Sponsor contact for SAEs and UADEs:

Ron von Jako, MD, PhD

Fax: 1-800-888-3983

E-mail: SAE@ge.com

8.5 Device Deficiencies/Complaints

Device deficiencies/complaints should be reported to the study Sponsor contact identified on the cover page of this protocol. All device deficiencies/complaints will be collected, fully investigated, and documented in the source document and appropriate Sponsor document during the study reporting period. The PI is responsible for notifying the Sponsor in the event that there is any device issue that could potentially lead to a SAE.

9. ETHICAL CONDUCT OF THE STUDY

The study will be carried out in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki; the guidelines of Good Clinical Practice (GCP) for medical devices, as set forth by ISO 14155:2011 and ISO 14971:2012; applicable sections of U.S. FDA 21 Code of Federal Regulations (CFR); and applicable regulatory authority's requirements of the U.S.

The study will be conducted and reported in accordance with applicable policies of the EC and governing regulatory authorities.

9.1 Ethics Committee

The PI will ensure that approval from an appropriately constituted EC is attained for the clinical study prior to enrolling subjects, and PI will ensure that documentation of approval is maintained for the duration of the study.

The PI will ensure that the Sponsor is notified of any withdrawal of EC approval within 5 working days of such occurrence. If approval is terminated or suspended, the Principal Investigator will promptly notify the Sponsor and provide written explanation.

9.2 Regulatory Agencies and Competent Authority(ies)

The Sponsor will obtain approval from the local regulatory agency and competent authority (CA) before the start of the clinical trial, if necessary, per applicable local laws and regulations. Any additional requirements imposed by the EC or regulatory authority shall be followed, if applicable.

9.3 Management of Protocol Modifications and Amendments

Substantial amendments will only be implemented after approval of the EC.

A deviation is any instance(s) of failure to follow, intentionally or unintentionally, the requirements of the protocol. Under emergency circumstances, deviations from the protocol to protect the rights, safety, and wellbeing of human subjects may proceed without prior approval of the Sponsor and the EC/competent authority (CA). Such deviations shall be documented and reported to the Sponsor and the EC as soon as possible. Deviations will be reported as:

- **Critical Deviations:** Deviations that significantly affect the safety, efficacy, integrity, or conduct of the study. These deviations must be reported to the Sponsor no later than 5 working days from awareness of occurrence and reported to the EC per the deviation reporting policy.
- **Non-Critical Deviations:** Protocol deviations that do not significantly affect the safety, efficacy, integrity, or conduct of the trial. These deviations must be documented on the CRF Protocol Deviation page and will be reviewed by the study monitor.

Non-substantial modifications may be made during the normal course of device optimization, maintenance, and feasibility testing. Non-substantial modifications will be communicated to the CA as soon as possible, if applicable, and to the EC per their policy.

9.4 Participant Information and Informed Consent

The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration of exposure to the investigational product (if applicable), the potential risks and benefits, and any potential discomforts. Each participant will be informed that participation in the study is voluntary, that she may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical assistance and treatment. The participant must be informed that her medical records may be examined by authorized individuals other than their treating physician.

All participants for the study will be provided an ICF, describing the study and providing sufficient information to allow the participant to make an informed decision about her participation in the study. Informed consent documents will be subject to approval by the EC prior to enrolling subjects in the study.

The participant should read and consider the statement before signing and dating the ICF, and shall be given a copy of the signed document. The ICF must also be signed and dated by the PI (or his/her designee), and it shall be retained as part of the study records.

9.5 Early Termination of the Study

The Sponsor may terminate the study prematurely according to certain circumstances. Examples of such circumstances include ethical concerns, insufficient participant recruitment, participant safety concerns, alterations in

accepted clinical practice that make the continuation of a clinical trial unwise, early evidence of benefit or harm of the research product, or for any other reason.

10.STATISTICAL METHODS

10.1 Statistical Hypothesis

No statistical hypothesis is being tested in this study.

10.2 Sample Size Determination

The target sample size for this study is 30 subjects, providing 60 evaluable image sets for the image attribute review (30 PAC compression image sets and 30 TC compression image sets). The number of subjects was determined based on Sponsor discussions with a U.S. FDA Medical Officer, who indicated that, during MQSA re-accreditation, sites are requested to submit sample images. If an issue is identified with the sample images, an Advanced Mammographic Review occurs, where the quality of 30 images is assessed to determine whether the issue was isolated or systemic.

With a sample size of 30 image pairs, the 95% confidence interval width for the proportion of PAC image sets with equal or higher acceptability than TC image sets will be no wider than 13%, when the proportion is 95%.

10.3 Statistical Analysis

10.3.1 General Statistical Methods

The study data will be summarized using descriptive statistics. The descriptive statistics for continuous variables will include mean, standard deviation, median, Q1 and Q3, minimum, maximum, and sample size, as appropriate. Categorical variables will be described with counts, percentages, and sample size, as appropriate. A 95% confidence interval may be presented, when necessary.

10.3.2 Analysis of Primary Endpoint

The proportion of PAC image sets that are of equal or higher acceptability than TC image sets will be calculated. A 95% confidence interval will be calculated using asymptotic method with continuity correction. This analysis will also be performed for subgroups defined by the randomized breast of interest (i.e. breast of interest imaged first versus breast of interest imaged second).

Proportion of images with acceptable overall image quality will be summarized for PAC image sets and TC image sets separately, with 95% confidence interval using asymptotic method with continuity correction.

10.3.3 Analysis of Secondary and Exploratory Endpoints

The proportion of image sets indicated for repeated image acquisition when using PAC mode or TC mode will be summarized. This analysis will also be performed for subgroups defined by the randomized breast of interest.

The acceptability for individual mammographic attributes will be summarized by attribute.

Patient characteristics (demographics, breast thickness) and procedural characteristics (radiation dose, compression force) will be summarized using descriptive statistics. Compression force analysis will also be performed for subgroups defined by the randomized breast of interest.

10.3.4 Safety Analysis

AEs, SAEs, and devices issues will be provided in listings and will be summarized descriptively, as deemed necessary.

10.3. Interim Analysis

No interim analyses are intended to be conducted as part of this study.

10.4 Handling of Missing Data

Analysis will be based on collected data, and no imputation will be done for missing data.

10.5 Deviation(s) from the Original Statistical Methods

Any changes or deviations from the original statistical plan specified in this protocol will be described and justified in the final study report per ISO 14155:2011.

11. QUALITY ASSURANCE AND CONTROL

11.1 Data Management

Data management processes for handling study data will be maintained by the Sponsor.

11.1.1 Completion of Case Report Forms (CRFs)

The data reported on the CRFs shall be derived from source documents and be consistent with these source documents. Electronic CRFs (eCRFs) will be used to collect data. The Sponsor will provide eCRFs and train study staff on completion of eCRFs using Good Documentation Practices (GDP). CRF Completion Guidelines (CCG) may be provided by the Sponsor to help facilitate training.

eCRFs are to be completed as information becomes available at the site. eCRFs should be signed by indicated parties, in indicated area(s), to certify the contents of the form. The PI is ultimately responsible for ensuring completion of eCRFs.

If discrepancies are discovered on the eCRFs, whether during monitoring or during data review by the study team, a query will be raised, and the site shall make the correction within the electronic database, noting the reason for change. Data will be considered clean once all queries are answered and closed.

If the Sponsor discovers discrepancies on eCRFs, a query will be raised and necessary corrections will be made by the site. The reason for any changes will be noted. All queries will be resolved prior to study completion.

11.1.2 Data Handling and Record Keeping

All documents and data shall be produced and maintained in a manner that assures control and traceability.

11.1.3 Source Data and Documents

Source data includes information in original records, certified copies of original records of clinical findings, observations, or other activities for the study. Source documents for each subject must be retained throughout the investigation, including printed or electronic documents containing source data. Elements should include:

- **Source data and documentation** relevant to data recorded for subject screening and CRF corroboration.
- **Subject records** containing the completed ICFs and eCRFs.
- **Regulatory binder** containing the protocol and any subsequent amendments, EC submissions and approvals, blank ICF(s), and site logs.
- **Reference manuals** such as investigator responsibilities, Sponsor, AE/SAE and informed consent guidelines, applicable training materials, and operator manual for PAC.

The Principal Investigator or institution shall provide direct access to source data during and after the clinical investigation for monitoring, audits, EC review, and regulatory authority inspections.

11.1.4 Archiving

All study data must be archived for a minimum of three (3) years after study termination or premature termination of the clinical trial. No source documents or study records will be destroyed without Sponsor notification and approval.

12.MONITORING PLAN

In collaboration with the site, the Sponsor will ensure proper monitoring of the study to confirm that all the research requirements are met. Monitoring visits will oversee the progress of a clinical investigation and ensure that it is conducted, recorded, and reported in accordance with the protocol, written procedures, Good Clinical Practice (GCP) ISO 14155:2011, and the applicable regulatory requirements.

12.1 Confidentiality and Data Protection

The investigator affirms and upholds the principle of the participant's right to privacy, and the investigator shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing data in scientific journals.

Individual subject medical information obtained as a result of this study will be considered confidential, and disclosure to third parties will be prohibited. Subject confidentiality will be further ensured by utilizing subject identification code numbers. For data verification purposes, authorized representatives of the Sponsor, a competent authority, or an EC may require direct access to parts of the medical records relevant to the study, including subject medical history.

12.1.1 Storage of Images and Associated Health Data

Images and associated data will be collected and disclosed to the Sponsor as part of this study. Fully de-identified data, which has had all personal identifying information removed, may be stored and used by the Sponsor indefinitely. The Sponsor and/or its authorized representatives may use any de-identified data collected in this study for future technology and engineering development, marketing purposes, education, regulatory submissions, publications, or other possible uses.

12.2 Publication Policy

The results of this study may be used in future publications. If applicable, the conditions of publication shall be described in a separate contractual agreement.

REFERENCES

1. ISO. *Clinical investigation of medical devices for human subjects - Good Clinical Practice*: International Organization for Standardization; 2011. ISO 14155:2011(E).

2. American Cancer Society. *Breast Cancer Facts & Figures 2015-2016*. United States: American Cancer Society; 2015.

3. American Cancer Society. *Global Cancer Facts & Figures 3rd Edition*. Atlanta: American Cancer Society; 2015.

4. Nelson HD, Cantor A, Humphrey L, et al. *Screening for Breast Cancer: A Systematic Review to Update the 2009 U.S. Preventive Services Task Force Recommendation*. Rockville: Agency for Healthcare Research and Quality; 2016. 14-05201-EF-1.

5. Shapiro S, Strax P, Venet L. Periodic breast cancer screening in reducing mortality from breast cancer. *JAMA*. 1971;215(11):1777-1785.

6. Thurfjell E, Lendgren J. Breast cancer survival rates with mammographic screening: similar favorable survival rates for women younger and those older than 50 years. *Radiology*. 1996;201(2).

7. Hendrick R, Smith R, Rutledge J, Smart C. Benefit of screening mammography in women aged 40-49: a new meta-analysis of randomized controlled trials. *J Natl Cancer Inst Monogr*. 1997;22:87-92.

8. Tabar L, Vitak B, Chen H, Yen M, Duffy S, Smith R. Beyond randomized controlled trials: organized mammographic screening substantially reduces breast carcinoma mortality. *Cancer*. 2001;91(9):1724-1731.

9. The Swedish Organized Service Screening Evaluation Group. Reduction in breast cancer mortality from organized service screening with mammography: 1. Further confirmation with extended data. *Cancer Epidemiol*. 2006;15(1):45-51.

10. Coldman A, Phillips N, Wilson C, et al. Pan-Canadian Study of Mammography Screening and Mortality. *Journal of the National Cancer Institute*. Oct 2014;106(11):1-7.

11. Hofvind S, Ursin G, Tretli S, Sebuødegård S, Møller B. Breast cancer mortality in participants of the Norwegian Breast Cancer Screening Program. *Cancer*. Sep 2013;119(17):3106-3112.

12. Whelehan P, Evans A, Wells M, Macgillivray S. The effect of mammography pain on repeat participation in breast cancer screening: a systematic review. *Breast*. Aug 2013;22(4):389-394.

13. Dullum JR, Lewis EC, Mayer JA. Rates and correlates of discomfort associated with mammography. *Radiology*. Feb 2000;214(2):547-552.

14. Gupta R, Nayak M, Khoursheed M, Roy S, Behbehani AI. Pain during mammography: impact of breast pathologies and demographic factors. *Medical principles and practice*. Jul-Sep 2003;12(3):180-183.

15. Poulos A, Rickard M. Compression in mammography and the perception of discomfort. *Australasian Radiology*. Aug 1997;41(3):247-252.

16. Kornguth PJ, Rimer BK, Conaway MR, et al. Impact of patient-controlled compression on the mammography experience. *Radiology*. Jan 1993;186(1):99-102.

17. de Groot JE, Broeders MJ, Brandenhorst W, den Heeten GJ, Grimbergen CA. Mammographic compression after breast conserving therapy: controlling pressure instead of force. *Medical Physics*. Feb 2014;41(2).

18. de Groot JE, Branderhorst W, Grimbergen CA, den Heeten GJ, Broeders MJM. Towards personalized compression in mammography: A comparison study between pressure- and force-standardization. *Euorpean Journal of Radiology*. Mar 2015;84(3):384-391.

19. Sechopoulos I, Suryanarayanan S, Vedantham S, D'Orsi C, Karellas A. Radiation Dose to Organs and Tissues from Mammography: Monte Carlo and Phantom Study. *Radiology*. 2008;246:434-443.

APPENDIX A – STUDY SCHEDULE

Table A.1 - Schedule of Study Procedures

Evaluation	Subject Visits*		Post Image Acquisition
	Screening & Enrollment**	Visit 1**	
Written Informed Consent	X		
Patient Demographics	X		
Inclusion criteria	X		
Exclusion criteria	X		
Combo Mode Screening Exam, including PAC for the breast of interest		X	
Image acquisition data collection		X	
Image attribute review			X

*Subjects will be followed for AE reporting purposes from the time when they enter the imaging exam room until the time when they leave the imaging exam room at each visit. There will be no follow-up.

** Screening, enrollment, and procedures may be conducted on the same day for study subjects.

APPENDIX B – STUDY SITE AND INVESTIGATOR LIST

The following investigators at each study site will be responsible for the conduct of this study:

Investigator(s):[1]	**Kathy Schilling, MD, Principal Investigator** *Tel*: 1-561-955-5000 *e-mail*: kschilling@brrh.com	**Boca Raton Regional Hospital** Christine E. Lynn Women's Health and Wellness Institute *Address*: 690 Meadows Road Boca Raton, FL, 33486 U.S.

[1] The role of the ***Principal Investigator*** is to implement and manage the conduct of the investigation as well as ensure data integrity and the rights, safety, and well-being of humans involved in the study [ISO 14155:2011 9.1].