Breast Compression:
Evaluating Image Quality and Comfort of an Investigational Curved Paddle Compared to a Standard Paddle

Protocol Number:	**2016-03 (NCT03611543)**
Sponsor:	Hologic, Inc. 250 Campus Drive Marlborough, MA 01752
Revision	3.0
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Key Protocol Terms

Term or Abbreviation	*Definition*
2D Imaging	Mammographic imaging on a 2D FFDM system
3D or Tomosynthesis Imaging	Mammographic imaging on a 3D or tomosynthesis system
BIRADS	Breast Imaging-Reporting and Data Systems
Breast Density BIRADS	The classification of density into 4 groups with ratings 1-4 based on the composition of the breast tissue. Where a 1 is almost entirely fatty, a 2 has scattered fibroglandular densities, a 3 is defined as heterogeneously dense, and a 4 is extremely dense
CC	Cranio- Caudal – the top to bottom view of a mammogram
Combo Images	2D and 3D images acquired under one compression
C-Paddle	Curved paddle; This is the investigational paddle.
FFDM	Full-field digital mammography
MLO	Medio-lateral Oblique- the side view of a mammogram
SOC Paddle	Standard of Care (conventional) compression paddle
Tomosynthesis	Set of images reconstructed at 1 mm intervals from a set of 2D images acquired as the x-ray source moves in an arc above the breast. The set of 1 mm images composes a 3D data set.

Executive Overview

Protocol Version and date	Revision 3.0 Dated: January 15th, 2018
Objective:	To evaluate a new investigational curved paddle to be used in mammography at compression forces to achieve tautness in the breast to determine a reduction in pain from the current standard of care paddle
Study Goals:	1. To achieve a mammographic procedure that reduces discomfort for patients.
Primary Endpoint:	1. Comfort with the investigational curved paddle will be improved to that of the standard paddle based on pain scale data recorded for each paddle type
Secondary Endpoint:	1. The curved paddle allows for an increase in tissue coverage as compared to the standard paddle 2. Image quality when using the curved paddle is non-inferior to the image quality of the standard paddle
Brief Inclusion/ Exclusion Criteria (see page 13- for full detailed listing)	*Inclusion Criteria* • Subject is female of any race and ethnicity • Screening Subject is at least 40 years old, Diagnostic subjects are at least 25 years old • Subject will be referred for a screening or a diagnostic work-up with tomosynthesis as part of the exam *Exclusion Criteria:* • Subjects who are pregnant or who think they may be pregnant • Subjects lactating or presenting with discharge • Women too large for the detector • Subjects who cannot give informed consent
Number of Subjects	Up the 650 subjects at 4-5 collection sites in the United States
Study Type	Multi-Center, Controlled
Study Duration	24 months

1. INTRODUCTION

Routine two-dimensional x-ray mammography has been used for the screening and diagnosis of breast cancer for approximately 30 years, and is accepted as the best test for the early detection of breast cancer for the general population. The effectiveness of screening, however, is greatly dependent on sustained compliance to yearly screening, which is reportedly approximately 64% in the United States [1]. The evolution of mammography technology has seen improvements over time, culminating in the introduction of full-field digital mammography systems in 2000 and the approval of 3D imaging, or Breast Tomosynthesis in 2011. Despite vast improvements in image quality and the change to digital acquisition, an element of breast imaging that has seen very little investigation or progress is the optimization of breast compression. The woman's perception of breast compression during mammography ranges from mild discomfort to severe pain [2] and breast compression has been shown to be a barrier to compliance for routine screening [3]. The MammoPad, a soft cushion that attaches to the detector has had some degree of success to address discomfort from the detector and edges, but there has been limited changes to the design of the compression paddle to offer a decrease in discomfort for patients.

Furthermore, whereas analog film mammography required flat paddles for good image quality, digital mammography and in particular tomosynthesis imaging do not have this requirement. This leaves open the opportunity to investigate curved paddles that may improve patient comfort without adversely affecting image quality.

2. OBJECTIVE

The goal of this study is to evaluate patient comfort during compression with a standard flat mammographic paddle and an investigational curved paddle. This is a study that will be performed with x-ray imaging and will be used to determine if an overall reduction in pain can be appreciated in patients without loss in image quality as compared to the current standard mammogram. Another benefit of the curved paddle may be an increase of perceivable and measurable tissue capture.

3. BACKGROUND INFORMATION

Imaging the breast is complex. The breast varies widely in size, composition and glandular to fat ratio over the female population and breast cancer varies in presentation. The breast differs in consistency from quite firm and fixed on the chest wall to soft and malleable, able to be pulled easily from the chest wall.

Breast compression reduces motion un-sharpness by immobilizing the breast, decreases breast thickness reducing exposure time, geometric un-sharpness, dose and unwanted scatter radiation, and creates a more homogeneous thickness for uniform x-ray exposure, thereby allowing a relative assessment of breast tissue. Another important contribution resulting from breast compression is the separation of glandular structures, which reduces structure overlap (structure noise). Structure noise has been shown to reduce the accuracy of mammography as overlapped structures can imitate as well as hide a cancer or

an area of suspicion. Compression also aids in pulling and holding the breast forward onto the image receptor.

Two-dimensional full-field digital mammography resolves some of the issues of its analog counterpart. Because of the limited dynamic range of analog film imaging it was necessary to compress the breast to nearly uniform thickness. The wider dynamic range of digital mammography and the ability to post-process the image reduces the need for uniform compression thickness. However, digital mammography is a two-dimensional technology and is still confounded by structure noise.

Three-dimensional (3-D) breast imaging referred to as breast Tomosynthesis [4-11] has been approved by the FDA for breast cancer screening in combination with digital mammography. With tomosynthesis, the breast is imaged from a number of different angles and from these images a series of 1-mm reconstructed slices are created and combined with the ability to scroll through each slice. 3-D reduces the problem of structure noise that may hide a breast cancer or cause unnecessary recalls. Some compression of the breast tissue will be needed with both 2D and 3D imaging to hold the breast stationary and to reduce overall thickness.

Figure 1: Acquisition of breast tomosynthesis image. Projection images are acquired as the x-ray tube moves in an arc above the breast. These projection images are reconstructed to create the reconstructed slices.

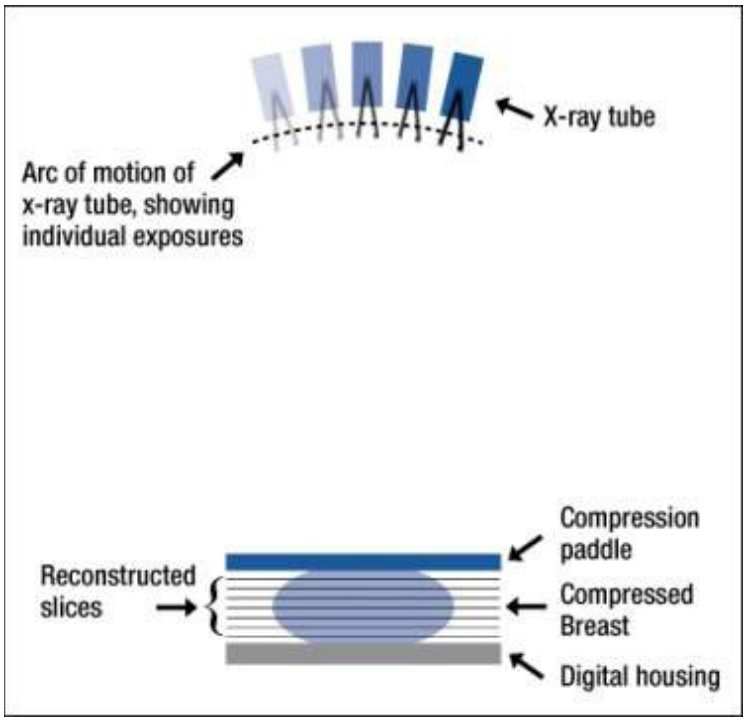


Figure 2: Hologic Dimensions tomosynthesis system. This system will obtain both 2D and 3D images.

3.1 Current Compression Standards and Methods

For standard mammography, the breast is positioned on the image receptor, with compression applied from above using a flat, clear, minimally attenuating plastic paddle, which normally remains parallel to the image receptor. The technologist typically holds the breast in place on the image receptor and applies compression using a foot control that controls the compression force until the compression paddle is holding the breast in position. Once the breast is held in place, the technologist then may apply final compression electronically, or manually with hand-controls. As force is applied, the breast thickness is reduced and the breast spreads out allowing better visibility of internal breast structures. MQSA (Mammography Quality Standards Act) mandates technologist training for breast positioning and compression. MQSA [13] loosely provides guidelines for the compression of the breast, stating only, “A compression force of at least 111 newtons (25 pounds) shall be provided” and

"the maximum compression force for the *initial* power drive shall be between 111 newtons (25 pounds) and 200 newtons (45 pounds)." There is no recommendation for applied final force and no correlate between force, compression thickness, dose, breast spread and tissue separation.

4. STUDY RATIONALE

Despite improvements in image acquisition and display methods, compression is still applied to 3D and 2D digital imaging as it was for 2D analog imaging and has changed little over the last 30 years. One company (Hologic, Inc., Bedford, MA) has taken advantage of the post-processing of digital imaging employing a "flex" paddle, which is similar in appearance to the standard compression device, but flexes as the breast is compressed. This provides better compression at the anterior breast in women with firm breasts and a slight improvement in comfort for the patient. Another company developed and implemented single-use, minimally attenuating cushions (BioLucent, CA) that may be applied above and/or beneath the breast. However, the cushion applied above the breast is rarely used, as it impedes positioning. Small gains in patient comfort are realized with the use of the lower pad.

The amount of required compression applied is subjective and continues to be a barrier to screening due to the perception women have or from having experienced pain during screening procedures. Most technologists that perform imaging aim to achieve tautness of the breast to demonstrate adequate compression force.

Standard compression methods apply most of the compression to the central portion of the breast since the breast is thicker in the center. The curved compression paddles being investigated allow for a more even compression of the breast.

The primary aim of this research is to determine if the curved paddle will provide an improvement in patient comfort without a loss in image quality.

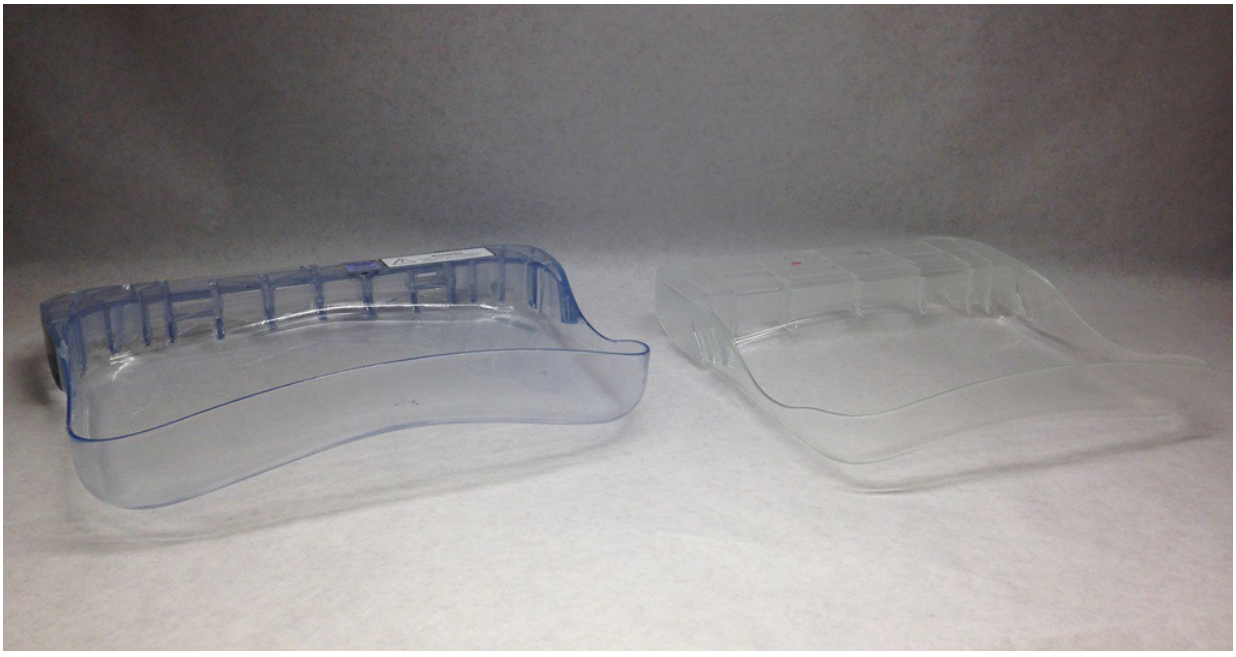
5. PRIMARY HYPOTHESIS

The patient reported pain score will decrease with the use of the investigational curved paddle compared to the patient reported pain score reported with the use of the current standard of care paddle.

6. INVESTIGATIONAL DEVICE DESCRIPTION

Image processing software and an investigational curved paddle will be employed on a commercially approved Hologic Selenia Dimensions mammography system. The investigational paddle is made from a plastic material shaped with a curve to conform better to breast anatomy. The breast tomosynthesis system is a digital mammography system that is capable of producing standard two-dimensional (2D) images and three-dimensional (3D) tomosynthesis images. The Hologic Dimensions system is a commercial product approved by the FDA. The image processing software will only be applied to images acquired with the investigational paddle which is identified via an RFID tag on the paddle when it is attached to the Dimensions.

Figure 3: Investigational paddles of different sizes showing the curved shape



7. DATA ANALYSIS

7.1 Primary Endpoint

The curved paddle results in less discomfort than the standard paddle in screening and diagnostic patients as demonstrated by comparing pain scores between the 2 paddles on each patient. Statistical analysis with a students paired t-test and ANOVA analysis to compare the pain scores from the current flat paddle to the new curved paddle will be conducted.

7.2 Secondary Endpoints

1. Tissue volume imaged with curved paddle is greater than that for standard paddle
2. Image quality when using the curved paddle is non-inferior to the image quality of the standard paddle

This study will investigate and measure the potential reduction in pain to the breast with the curved paddle when compressing breast tissue to tautness as compared to the standard of care paddle compressing breast tissue to tautness. The potential improvement in the comfort of a mammographic exam for patients while looking at ease in positioning for technologists, without a loss in image quality, would offer a less painful, high quality procedure, which may potentially increase mammography compliance rates.

8. STUDY OVERVIEW

The proposed study is designed to evaluate the following parameters and how they may affect pain during a mammogram: breast thickness, breast spread and compression force with the investigational curved paddle using compression force to achieve tautness for imaging. (The current standard for mammographic compression is to compress to tautness which may be determined by observing or touching the skin surface. The same parameters will be captured for the standard paddle at tautness. (Tautness compression captured as a function of force may differ between the two paddles based on the curved design of the investigational paddle versus the flat design of the standard paddle.)

9. STUDY DESIGN

The study will be conducted in the United States at up to 5 centers. The study will enroll up to 650 subjects. The number of subjects was chosen to allow evaluation of screening and diagnostic patients with a variety of breast densities (fatty, scattered densities, heterogeneously dense or extremely dense) and women with a range of breasts sizes that fit on the current detector. The evaluation of pain reduction will be the primary endpoint, while examining the potential of increased tissue capture without a compromise in image quality will be assessed as secondary endpoints. The enrollment will be consecutive for subjects who sign informed consent to participate. Women participating in the study will present for a screening or diagnostic imaging exam.

All women participating in this study will undergo imaging with the standard and the investigational paddles in a randomized order. This is so that neither the standard paddle nor the investigational curved paddle always have a set order. The intent to randomize is to reduce any bias for either paddle; in that if one is always first the second compression may be more painful, because the woman has been under compression for a number of minutes before having the second set of compressions taken.

Each patient who agrees to participate and is consented and is undergoing a routine screening mammogram will receive 4 view 2D plus 3D combination imaging (LCC, LMO, RCC, RMLO) mammogram, with the current standard paddle. In addition she will also receive a cranio-caudal (CC) and a mediolateral oblique (MLO) in one of her breasts as determined by a randomization scheme with the investigational curved paddle. The amount of compression applied to both mammograms will be that to achieve tautness.

Patients who agree to participate, are consented and are undergoing a diagnostic exam will have diagnostic 2D plus 3D combination imaging as well as a CC or MLO with both the standard paddle and the investigational curved paddle compressed to tautness on the breast of interest. The order of the paddles will be randomized and the view (CC or MLO) will be based in the visibility of the area of interest for which the diagnostic imaging was ordered. (It is possible that one of the views is superior to assess the area of interest).

650 women who are at least 40 years of age will be enrolled. Data will be recorded for compression related parameters such as compression force, thickness, and comfort for both conventional and investigational paddle designs. A standardized 10 point pain scale will be used to record comfort. The investigational paddle that will be tested has been constructed with the natural shape of the breast in mind, rather than current paddles which are straight and flat to try to flatten the breast. In order to obtain the necessary information related to the images, radiologists will be asked to evaluate overall image quality between the standard of care paddle and the investigational paddle.

Each subject will be instructed on the use of the pain scale. The investigational imaging using the Curved Paddle (C-paddle) will be conducted on one breast in either the screening or the diagnostic study population for this study.

At the time of enrollment all screening subjects must be at least 40 years of age and all diagnostic patients must be at least 25 years of age, and be scheduled to have a mammogram as part of their routine clinical care. All subjects will be required to sign an informed consent form prior to enrollment and undergoing imaging with the investigational paddle in the study. All exams will be conducted on the same day. At the

conclusion of the procedure each subject will be asked a few questions related to her overall experience during the visit and her preference for which paddle she preferred.

9.1. Subject Inclusion/Exclusion Criteria:

Inclusion criteria for all subjects are as follows:

Inclusion Criteria

- Subject is female (born XX) of any race and ethnicity
- Screening Subjects are ≥40 years old and diagnostic subjects are ≥ 25 years old
- Subject will have had a combination 2D plus 3D exam
- If Subject is having a diagnostic workup she has had a 2D plus 3D imaging exam within the last 60 days
- Subject is either having a screening mammogram or presenting for a diagnostic imaging evaluation

Exclusion Criteria

- Subject is unable or unwilling to undergo informed consent
- Subject is pregnant
- Subject is breast-feeding
- Subject is unable to be imaged on a standard detector; breasts are too large

10. DETAILED STUDY PROCEDURE

A study flow chart is shown below. The study will include 650 subjects. After determining eligibility and informed consent is obtained, the subjects presenting for screening will undergo (2D plus 3D) with the current paddle and 2 views of one breast with the curved paddle (CC and MLO in 2D plus 3D).

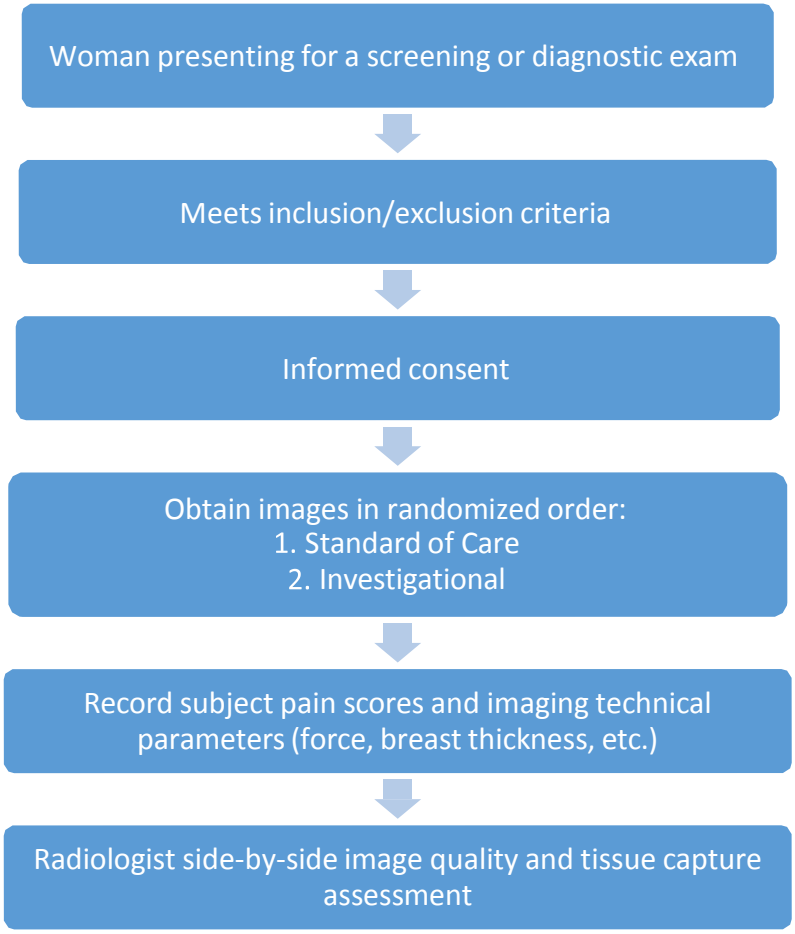
If the patient is undergoing diagnostic imaging she will have her prescribed diagnostic views followed by a combination (2D plus 3D) CC or MLO with both the standard paddle and the investigational curved paddle compressed to tautness on the breast of interest.

In both the screening and the diagnostic populations, the paddle order will alternate so that for the first subject the order would be standard of care, followed by the investigational paddle. The next subject would have the investigational first followed by the standard of care. The order is changed to prevent distortion in the recorded pain scores since women may find the first compression more or less painful than subsequent compressions.

Both sets of compression on the curved paddle and the standard of care paddle will be to tautness. The force will not be matched exactly since the curved compression paddle may allow imaging of more breast

tissue and forcing the compression level to match the standard of care may result in unnecessary pain to achieve tautness. The technologist will strive to achieve a similar compression without causing excess pain.

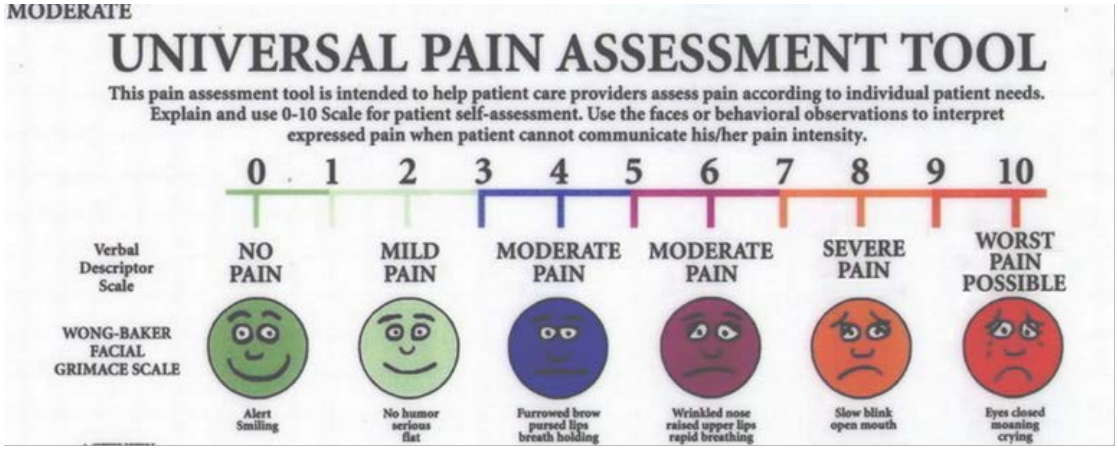
Figure 4: Flowchart showing the enrollment and imaging process



The technical factors such as kilovoltage, tube current and filtration will be determined using AEC (automatic exposure control) in the same manner as conventional 3D exams.

At the completion of each compression for each view and each paddle (the standard procedure and the investigational procedure(s)) each patient will be asked to rate her pain on a 0-10 pain scale. The result will be pain scores for the breast being compressed with both paddles. Additionally, each patient will be asked to point out any specific areas of discomfort on a breast diagram that is experienced during the course of the compression procedures.

Figure 5: Pain score used for comfort evaluation



The investigational images will not be used to recommend biopsy and will not be used to cancel work-up or biopsy of any index lesion of concern that was recommended based on the standard of care (SOC) mammograms. However, the investigational images may characterize the index lesion of concern as more suspicious than standard diagnostic imaging and further standard work-up (including targeted extra views, sonography or MRI) may be recommended. The subject and the subject's doctor will be informed of any new finding(s). The subject is not required to undergo further testing.

The investigational images may also allow detection of a new suspicious finding and further standard work-up (including targeted extra views, sonography or MRI) may be recommended. The subject and the subject's doctor will be informed of any new finding(s). The subject is not required to undergo further testing.

If a patient is recalled based on her standard of care imaging, her follow-up procedures will be outside of this study and be conducted as per institutional policy for patient care.

The study technologist conducting the study imaging will then complete a series of questions regarding their experience with the procedures for both paddles using a 5 point Likert scale to compare the investigational procedures against the Standard of Care procedures for areas including but not limited to:

- Overall Ease in positioning for each view on each paddle
- Ability to maintain positioning
- Ability to get high into the Axilla
- Ability to get further back on the chest wall
- Ability to pull in more tissue
- Ability to decrease skin folds
- Ability to decrease neck pulling
- Ability to decrease breast sagging
- Ability to hold the breast in the optimal MLO position

After the images have been acquired a study radiologist will conduct a side by side image comparison of the standard of care images to the investigational images using a 5-point Likert scale to assess the images for:

- Overall Image quality
- Lesion Visibility
- Tissue separation of structures
- Patient Motion

The radiologist will also assess breast density separately on the standard of care and on the investigational images.

11. ANALYSIS FOR THE ACQUISITION STUDY

This study is designed to evaluate the use of the new curved paddle including image quality, patient comfort and tissue coverage. Data in the form of questionnaires will be collected from the subject, technologist and radiologist. A synthetic 2D image may be created for all 3D images and will be included in the image review. The Hologic synthetic 2D image is called C-View and is FDA approved. The investigational C-View images for the curved paddle will be used for image comparison only and not for clinical evaluation.

Each patient will have their images reviewed by an appointed study radiologist who will be asked to rate and compare the standard of care images to the investigational images using a 5 point Likert scale for:

- Overall Image quality
- Lesion visibility
- Tissue separation of structures
- Tissue coverage (especially at the Chest wall, axilla and Infra-mammary fold)
- Patient Motion

The radiologist will also assess breast density separately on the standard of care and on the investigational images.

The image review will consist of a side-by-side comparison with the standard-of-care image displayed on one display monitor and the matching investigational image on another display monitor.

No formal power calculation has been performed, because of the descriptive nature of the trial. A total of 650 patients will be enrolled in the study.

All variables will be tabulated using descriptive statistics. Continuous variables will be presented as means and standard deviations with 95% confidence intervals, as well as medians and ranges. For categorical variables, relative frequencies and 95% confidence intervals will be provided.

12. STUDY DURATION

Subjects will be accrued over a 24-month period. The amount of time each subject will actively participate, inclusive of the consenting process, will be approximately 30-60 minutes. Once imaging is complete, the subject will be cleared to leave the facility per standard Imaging protocol. Subjects will be considered as enrolled subjects from the time they complete and sign the informed consent until the time they complete the imaging procedures or ask to be withdrawn from the study.

13. QUALITY CONTROL

The Hologic Selenia Dimensions Digital Mammography Systems with the investigational paddle will be checked by a qualified medical physicist prior to any testing or imaging of subjects to assure the system is operating correctly. A Study Technologist will review the tomosynthesis images, obtain phantom images and check system operation on a periodic basis to ensure system performance. The quality control procedures described in the systems' operator manuals will be used throughout the trial. If there is any noticeable degradation in system performance, a Hologic engineer will be called immediately to recalibrate or repair the system.

Routine QC procedures will be run on the system per the manufacturer instructions.

14. POTENTIAL RISKS AND ANTICIPATED BENEFIT TO THE SUBJECT

An immediate benefit to the subject being enrolled in the study is not anticipated, although participation in this study may lead to the use of a more comfortable, more specific tool for evaluating breast disease for the benefit of future patients. It is possible that the additional imaging tests could identify a significant additional lesion not identified by the standard imaging paradigm.

14.1. Radiation risk

Although the 2D and 3D mammograms are FDA approved imaging modalities, a risk of the proposed study is the additional radiation exposure for enrolled subjects in having an additional two 2D/3D combination image pairs of one breast. The estimated mean glandular radiation dose for each 2D plus 3D image will be 2.9 mGy for an average breast size (4.2 cm compressed breast thickness). For two investigational images, the imaged breast would receive on average about 5.8 mGy (=2.9 mGy x 2) of radiation dose. The *average* additional breast dose would be half this, 2.9 mGy, since the other breast is not imaged with the investigational paddle.

To calculate risk from radiation, the most common approach is to relate the radiation dose to a whole body exposure. The International Commission on Radiation Protection states that exposure to the breasts results in a risk approximately equivalent to 12% of that from whole body exposure [1].

To calculate the equivalent whole body radiation dose of the investigational exam, the average breast dose would be 2.9 mGy. Therefore the expected whole body equivalent dose based on two investigational combo images would be; 2.9 mGy x 12% = 0.35 mSv.

The additional radiation from participation in this study is very low and may be compared to natural background radiation dose that is approximately 1.5 mSv per year in the US. This value includes background radiation from cosmic radiation and radon. The additional radiation dose from this study is therefore equivalent to about 3 months of the average background radiation dose or less and is therefore not considered to be a significant risk to the subject.

Therefore, it is felt that participation in the clinical study will not present a significantly increased risk to participating subjects.

14.2. Other potential risks

Other potential risks of the research mammograms are those similar to having standard mammography and include the possibility of bruising, infection and skin irritation, and abrasion wounds from compression of the breasts, but this is extremely unlikely. Millions of mammograms are performed each year with a very low occurrence of such incidences.

15. NEW FINDINGS

The investigational images may reveal a new suspicious finding and additional imaging (mammograms, sonography or MRI) may be recommended. The participant subject and her doctor will be informed of any new suspicious finding on the study mammograms, but the subject is under no obligation to undergo further testing. The new finding may prove to be an otherwise occult cancer, thus providing for an earlier detection. Early detection of breast cancer is associated with reduced morbidity and an improved outcome. Conversely, the new suspicious finding detected on the study mammograms may prove to be normal or benign. In this case, the participant subject may incur unnecessary additional time and anxiety.

The likelihood of new suspicious findings is low because the standard imaging already includes 3D imaging.

16. COMPENSATION

Subjects will may be compensated for participation in this study. If site allows, subjects will be

compensated up to the amount agreed upon in the Clinical Trial Agreement and Informed Consent Form.

17. ALTERNATIVE PROCEDURES

No diagnosis or treatment is offered in this study. The alternative is to not participate in the research study. Not participating will not affect the subject's relationship with her physician, nor the subject's right to health care or other services to which she is otherwise entitled.

Participation in this study will in no way delay the standard care for the patient.

18. RESEARCH MATERIALS, RECORDS AND CONFIDENTIALITY

18.1. Data and Image Collection

The following data and images will be collected for data analysis

- Date of Birth
- Race/Ethnicity
- Breast health related data inclusive of density and BI-RADs
- Day of menstrual cycle, if applicable
- Whether MammoPad was used
- Related screening and diagnostic mammographic images in the "For Processing" and "For Presentation" states
- 2D and 3D Radiographic imaging datasets in the "For Processing" and "For Presentation" states
- Prior screening images 2D or 2D plus 3D from previous mammogram if present
- Imaging reports (screening, diagnostic, ultrasound and MRI)
- Pathology reports (as applicable)
- Medical history as necessary related to subject's overall health for study inclusion
- Any documentation related to the occurrence of an adverse event

All data will be stripped of subject identifiers for the study folders.

18.2. Data and Image Archiving

All images required for the study (current mammogram, investigational mammogram, diagnostic mammogram and prior mammograms as necessary) will be stored in a secure location at the study site. Access to this server will be password protected. Any paper documents will be kept in a file identified by a unique study ID. The data will be stored in a secure location. No study specific information will be stored in the patient's electronic medical record or digital archiving system.

18.3. Privacy and Confidentiality

All image data will be maintained in an Excel or Excel-like spreadsheet. The subject will be issued a unique ID number. Only this spreadsheet will connect an assigned study ID with the patient's medical record number. This database will be password protected and maintained in a secure location. All data and data forms will be collected using the study ID number only. Only the research team will have access to subject identifiers. No information will be disclosed to others without written permission, except:

- If necessary to protect the rights or welfare of the subject (for example, if the subject is injured and in need of emergency care); or
- If required by law

When the results of the research are published or discussed in conferences, no information will be included that would reveal subject identity. Authorized representatives of the FDA, the IRB, or the ethics committee may need to review records of individual subjects.

A copy of the anonymized research images and other associated breast images and reports will be provided to Hologic, Incorporated (Bedford, MA); the manufacturer of the investigational machine and the study sponsor. However, subject identifiers will be removed from the images and records prior to transferring them to the sponsor.

19. PRINCIPAL INVESTIGATOR STUDY OVERSIGHT OBLIGATIONS

The Principle Investigator will perform the following tasks to assure the safety of subjects and the good conduct of the study:

19.1. Awaiting Approval

Investigators will not obtain informed consent or commence enrollment of subjects until IRB and sponsor approvals are secured. The Investigator will provide the sponsor with written documentation of a properly constituted IRB committee's approval of the protocol and the subject's informed consent form. The IRB approval must refer to the consent form, the study by title and protocol number (including revision level and date) as given by the sponsor. The Investigator, if a member of the IRB committee, is not to participate in the approval decision for the study. This non-participation is to be noted in the approval letter. The Investigator must promptly report to the sponsor any withdrawal of the IRB's approval of the study.

19.2. Supervising Investigational Device Use

Investigators are responsible for ensuring that only authorized and Hologic-trained study personnel use the investigational device. All approved study personnel will be trained on the use of the equipment and the techniques for this study. All appropriate study staff members, including the study PI, the study technologists, and the study coordinator(s) shall be listed on the study authorization form. Training for the use of the equipment will be documented by the Hologic representative conducting the training. Personnel not trained to use the equipment shall not be permitted to do so.

19.3. Investigator Records

The Investigator will maintain the following accurate, complete and current records relating to the study:

- Correspondence with other Investigators, IRB, Hologic, Hologic study monitors, and FDA;
- Records of device use (i.e., CRFs)
- Training records
- Subject records, documents demonstrating informed consent, and for any use of the investigational device without informed consent, a brief justification for not obtaining informed consent;
- A copy of the protocol;
- Records of reasons and dates for deviations from the protocol.

These records may be requested by Hologic, the reviewing IRB or the FDA at any time and are to be provided in a timely manner. For any requests for information or documents pertaining to the investigation received by the reviewing IRB or FDA, the investigator is to promptly notify Hologic.

Records shall be retained by the Investigator for a two (2) year period after the latter of the following two dates:

Following the written termination, discontinuation or withdrawal of the study by the sponsor; or after the records are no longer required for the purpose of supporting a submission to the FDA for approval of the device.

If an Investigator retires, moves, or withdraws from the investigation, the responsibility for maintaining records may be transferred to another person (sponsor or other Investigator) who will accept responsibility. Hologic must be notified and agree to the change prior to its implementation. Further, no disposition of any Investigator records may be made without prior approval by Hologic.

The Investigator is responsible for ensuring that the study data is secure, loss free, and its access is restricted to appropriate study personnel.

20.3.1 Monthly Duties

- Review the study binder to assure all documents, approvals and communications are up to date
- Review the Inclusion/Exclusion forms for completeness and compliance to study protocol
- Review case report forms for completeness and compliance to study protocol with due diligence to study timelines.
- Review the Quality Control testing results for the tomosynthesis system
- Monitor the accrual rate and recruiting efforts
- Ensure records are available for routine monitoring visits from the sponsor
- Allow for time to meet with the sponsor representatives during routine monitoring visits including but not limited to: study initiation, scheduled visits throughout the conduct of the study and study close out.

20.4 Investigator Reports

The Investigator reporting requirements include:

- To the Sponsor:
    - Notification should the IRB disagree with the non-significant risk assessment of the device and/or protocol.
    - Notification within 48 hours of all severe/serious adverse event and all unanticipated adverse events.
    - Notification as soon as possible of IRB approval.
    - Notification within forty-eight (48) hours of any Unanticipated Adverse Device Effect.
    - Notification within forty-eight (48) hours after use of the investigational device without obtaining informed consent
    - Notification within forty-eight (48) hours of withdrawal of approval by the reviewing IRB.
    - Immediate (within 48 hours) notification of any requests for information made by the IRB or the FDA.
    - Immediate (within 48 hours) notification of any inspection or contact by the FDA.
- To the IRB:

    - Notification as soon as possible, but no later than ten (10) working days after first learning of an Unanticipated Adverse Device Effect.
    - Notification within five (5) working days after use of the investigational device without obtaining informed consent.
- Submit regular progress reports to the monitor, at least annually, to include the number of subjects enrolled and a statement regarding the occurrence of adverse events that would require termination of the study.
- Submit a final report to the sponsor within three (3) months after the termination or completion of the study.

20.5 Permission to Review Source Subject Records

The Investigator agrees to maintain appropriate subject records and agrees that Hologic and its employees or agents and authorized FDA employees will have the right, from time to time, both during and after the course of this study, to audit and review subject records, medical records and device use records relating to the clinical study.

20.6 Financial Disclosure

All device applications submitted to the FDA after February 1, 1999, must conform to a new federal regulation. Sponsors are required to determine if clinical Investigators (primary and co-Investigators) and their immediate families have substantial proprietary and/or financial interests in the outcome of the studies they conduct. The reporting period includes the time during which the actual study is being carried out, and one year following the completion of the trial. According to the regulations, the financial arrangements that must be disclosed include the following:

- *Compensation made to the Investigator in which the compensation amount is dependent on the study outcome (i.e., higher compensation for a favorable outcome).*
- *Clinical Investigators or their institutions that have received payments from Hologic in excess of $25,000, exclusive of research grants, equipment, ongoing consultation, or honoraria, over the cost of conducting the trial.*
- *Clinical Investigators that have a proprietary interest in the device, such as a patent, trademark, copyright, or licensing agreement.*
- *Clinical Investigators, their spouses and dependent children who own more than $50,000 of Hologic publicly traded stock or stock options.*
- *Names of clinical Investigators who were full or part-time employees of Hologic while they conducted the trial.*

It is the responsibility of Hologic to gather this information, should it be requested, and it is the Investigator's responsibility to provide this data when requested.

21 PATIENT RECRUITMENT PROCESS

A radiologist who is the patient's health care provider, or research staff member authorized to do so, may approach the subject and ask if she is interested in hearing about the research study. If the patient answers in the affirmative that they wish to be contacted, the radiologist investigator (or designated staff member) will determine the potential subject's eligibility using the defined *Inclusion/Exclusion criteria*. If the patient meets the Inclusion/Exclusion criteria, and upon the patient's agreement to participate, the informed consent process will begin.

22 INFORMED CONSENT PROCEDURE

A board-certified radiologist, who is an investigator or an appointee, will discuss the following information with the subject:

- The purpose of the study.
- The investigational nature of the device.
- Foreseeable risks and potential benefits, which might occur with the use of the Investigational Device.

In addition the subject will be informed by the physician Investigator (or designated staff member) that:

- Medical records are subject to review by representatives of the IRB and the FDA as necessary.
- Information obtained during the study will be used to evaluate the feasibility of the Investigational Device as compared to other devices.
- Confidentiality will be maintained at all times.
- Patient is free to refuse study participation or to withdraw from the study at any time without compromising future medical care.

Signed, dated and witnessed informed consent for each subject will be obtained prior to any study procedures being performed on the subject. One copy of the informed consent document must be given to the subject, one copy will be inserted into the subject's medical record, and one copy is to remain in the study record at the study site, depending on the policy of the institutional IRB 2 originals are signed or 3 originals are signed.

The governing IRB must approve the informed consent form for use at the study site. The study will be conducted in full compliance with the informed consent regulations in Title 21 Code of Federal

Regulations, Part 50, Protection of Human Subjects, Subpart B – Informed Consent of Human Subjects, and according to the ICH and GCP guidelines.

The Investigator is responsible for informing the subject whenever important information becomes available that may be relevant to the subject's informed consent.

23 ADVERSE EVENTS

An adverse event is an undesirable clinical event occurring in a subject enrolled in the study, regardless of the relationship to the investigational device. All adverse events are to be reported, followed and documented whether or not they are considered to be related to the investigational device.

23.4 Definitions

23.4.1 Adverse Event

Any undesirable clinical event occurring in a subject enrolled in the study, regardless of the relationship to the investigational device.

23.4.2 Unanticipated Adverse Event

Any undesirable clinical occurrence in a subject, whether or not it is considered to be device related, that is not identified in nature, severity or frequency in the study protocol.

23.4.3 Serious Adverse Event

An adverse event will be classified as serious if it is: fatal or life-threatening; permanently disabling; requires inpatient hospitalization; or results in a persistent or significant disability/incapacity or a congenital anomaly/birth defect.

23.4.4 Unanticipated Adverse Device Effect

An unanticipated adverse device effect is an adverse event, which has not been previously identified as a possible event in the clinical investigation/protocol and is determined to be "probably related" or "definitely related" to the investigational device.

23.5 Assessment of Adverse Event

All adverse events, irrespective of their relevance or severity, shall be documented on the Adverse Event CRF. Adverse events will be given a grading of mild, moderate or severe, and a determination made as to whether or not the event was device related.

Subjects experiencing adverse events will be followed until the event is resolved, or in the Investigator's opinion, the event is no longer considered to be clinically significant for the study.

23.6 Relationship to Investigational Device

The Investigator will make the determination whether or not the adverse event is related to the investigational device on the basis of the following considerations and his/her clinical judgment. The following definitions will be used to assess relationships:

- Not Related: No relationship exists
- Unknown: Unable to determine relationship
- Possibly Related: Follows a logical response pattern to the investigational device but may have been produced by the subject's clinical condition or other treatment/intervention
- Probably Related: Follows a logical response pattern to the investigational device and is unlikely to have been produced by the subject's clinical condition or other treatment/intervention
- Definitely Related: Follows a logical response pattern to the investigational device and where physical evidence exists of the relationship.

23.6.1 Seriousness of Adverse Event

An adverse event will be classified as serious if it is: fatal or life-threatening; permanently disabling; requires inpatient hospitalization; or results in a persistent or significant disability/incapacity or a congenital anomaly/birth defect.

23.6.2 Severity of Adverse Events

The investigator will make a determination regarding the severity of the adverse event. The choices are Mild, Moderate or Severe.

23.7 Follow-up of Adverse Events

Subjects must be carefully followed until the adverse event/condition resolves and/or, in the Investigator's opinion, the event is no longer considered to be clinically significant for the study.

23.8 Subject Deaths

Although highly unlikely to occur in this trial, all subject deaths are considered serious adverse events and should be reported to the sponsor immediately, regardless of cause.

23.9 Reporting of Adverse Events

All serious adverse events must be immediately (within 48 hours) to the IRB and reported to the Manufacturer via telephone or facsimile.

- All complications and adverse events, device related or not, must be reported and recorded per the procedures at the study site.

- Adverse events which are considered to be serious, unanticipated or device related must be submitted immediately (within 48 hours) to the IRB per their reporting requirements. As well as the device manufacturer. Contact the regulatory affairs group:

  Hologic Inc.

  250 Campus Drive

  Marlborough, MA 01752

  Phone: 781-999-7300

  Fax: 781-280-0662

  Toll Free: 1-800-343-9729

24 DEVICE HANDLING

24.1 Reporting of Device Defects or Malfunctions

The performance of the Imaging System will be assessed by the authorized study personnel during each use. The Investigator is responsible for reporting any device defects or malfunctions to the sponsor.

A device defect is defined as any defect that is identified during the inspection, QC or preparation of the device (prior to actual human use), whereas, a device malfunction is defined as a device occurrence during the actual use of the Investigational System during the study.

A device defect or malfunction includes any situation where any part of the device is noted to be physically defective, all situations where the device fails to function as intended, and all situations where the device physically deforms or breaks – even if caused by user error.

In the event a device defect or malfunction harmed the subject, caused or potentially contributed to an adverse event, and Adverse Device Effect report will be completed.

25 DEVICE DISTRIBUTION

Hologic will provide the investigational software and hardware to the site. All investigational applications will be installed by Hologic and maintained at the investigational site. The investigational application will only be used for subjects who have signed the Informed Consent and are under the supervision of the Investigator or his/her designated representative.

The following individuals may be contacted in instances when the system may require servicing, upgrades or repairs:

Device/ Technical Service Contacts:

Tim Stango
Mechanical
Engineer 203-
731-8384
Tim.stango@hologic.com

Image Collection/Storage, Hologic issued MIMs concerns :
Christine Jerome
Technical Assistant, Clinical Data
Management 781-999-7392
Christine.jerome@hologic.com

26 REFERENCES

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13. http://www.fda.gov/CDRH/MAMMOGRAPHY/frmamcom2.html

Declaration of Acceptance of Protocol

Principal Investigator:

Institution:

Sponsor:	Hologic Inc. 250 Campus Drive Marlborough, MA 01752
Protocol Number:	2016-03 Rev. 3.0 Date: January 18th, 2018
Protocol Title:	**Breast Compression:** **Evaluating Image Quality and Comfort of an Investigational Curved Paddle Compared to a Standard Paddle**

This is to acknowledge that I have received the above-identified protocol, that I have read and understood its content, and that I agree to conduct the clinical trial at (**INSTITUTION**) in accordance with the procedures outlined therein.

If I have been involved in a clinical investigation, which was terminated for non-compliance at the insistence of a sponsor, an IRB or the FDA, an explanation of the circumstances is attached.

_____ _____

Physician Signature Date

_____

Physician Name (*please print)*

Protocol Revision - Summary of Changes

Protocol Revision	Change Summary
02	• Language has been updated to reflect accurate standard of care which differs at the Investigational Sites participating in this study. • Subjects may be compensated for participation in study, as agreed upon in Clinical Trial Agreement/Informed Consent Form. • Clarification of the roles of Investigational Site Staff during Patient Recruitment & Informed Consent Process. • Removed Kathy Willison from, "Image Collection/Storage, Hologic issued MIMs concerns" section.
3.0	• Increased the number of subjects to 650 to meet study objective.