A Feature Comparison Study to Evaluate the Modified Processing of Fujifilm's ASPIRE Cristalle with Digital Breast Tomosynthesis Option as Compared to the Original Processing

FUJIFILM Medical Systems U.S.A., Inc.

419 West Avenue

Stamford, Connecticut 06902

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Abbreviations

Abbreviation	Explanation
ACR®	American College of Radiology
BI-RADS®	Breast Imaging Reporting and Data System
CC	Cranio-Caudal
CFR	Code of Federal Regulations
CRF	Case Report Form
DBT	Digital Breast Tomosynthesis
DCF	Data Clarification Form
DMC	Data Management Center
DVIIm	Dynamic Visualization for Mammography
EDR	Exposure Data Recognizer
EDR2m	Exposure Data Recognizer 2 for Mammography
FBP	Filtered Back Projection
FDA	Food and Drug Administration
FFDM	Full-Field Digital Mammography (also known as Digital Mammography)
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
ID	Identification
IRB	Institutional Review Board
ISR	Iterative Super-Resolution Reconstruction
LCC	Left Cranio-Caudal
LMLO	Left Medio-Lateral Oblique
MFP	Multi-Objective Frequency Processing
MFP2	Multi-Objective Frequency Processing 2
MLO	Medio-Lateral Oblique
MQSA	Mammography Quality Standards Act

PHI	Protected Health Information
PMA	Premarketing Approval Application
RCC	Right Cranio-Caudal
RMLO	Right Medio-Lateral Oblique

Definitions

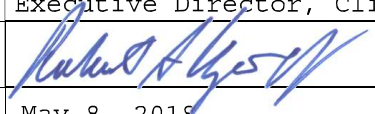
ACR® BI-RADS® Breast Tissue Composition (Density) Categories	a. The breasts are almost entirely fatty b. There are scattered areas of fibroglandular density c. The breasts are heterogeneously dense, which may obscure small masses d. The breasts are extremely dense, which lowers the sensitivity of mammography
ACR® BI-RADS® Assessment Categories	Assigned by reader; **0** = Incomplete - Need Additional Imaging Evaluation and/or Prior Mammograms for Comparison **1** = Negative **2** = Benign **3** = Probably Benign. Management: Short-interval (6-month) follow-up or continued surveillance mammography **4** = Suspicious. Management: Tissue diagnosis. **4A** = Low suspicion for malignancy **4B** = Moderate suspicion for malignancy **4C** = High suspicion for malignancy **5** = Highly Suggestive of Malignancy
ASPIRE Bellus II	Fujifilm mammography viewer (see Appendix A) where the FFDM and DBT images are displayed and reviewed by the physician.
ASPIRE Cristalle with DBT Option	Fujifilm's Mammography Acquisition System (see Appendix A) which generates both FFDM and DBT images.
Benign Case	A case in which all lesions are confirmed as benign by a biopsy or surgery and no other lesions are biopsy-malignant.
Cancer Case	A case in which at least one lesion is confirmed as malignant by biopsy or surgery.
Case	Two views (CC and MLO) of one breast.
DBT Examination	Each DBT Examination has two parts: • Acquisition: Acquisition of DBT images for each of the standard bilateral CC and MLO views (RCC, LCC, RMLO, LMLO) using the ASPIRE Cristalle. • Review: DBT images are displayed and interpreted by the physician on the ASPIRE Bellus II.
DBT Images	A series of mammograms, which are reconstructed from multiple low-dose projection images captured by the ASPIRE Cristalle with the x-ray tube rotated at a number of small offset angles over a limited angular range while the breast remains compressed and unmoved.
DBT Read	The physician reads (interprets) the DBT images displayed on the ASPIRE Bellus II (see Appendix A)
DBT Views	A series of cross-sectional views of the DBT images for each of the CC and MLO views for each breast.

Evaluable Subject	Based on acquisition-site data, an evaluable subject is a subject with known true clinical status and with complete DBT and FFDM examinations (four standard views), in which there is sufficient anatomical coverage, sufficient contrast, no significant motion or other artifacts, limited noise, and similar positioning.
FMSU2013-004A	Acquisition of Digital Mammography and Breast Tomosynthesis Images for Clinical Evaluation of Fujifilm Digital Breast Tomosynthesis
FMSU2017-003	A Feature Comparison Study to Evaluate the Modified Processing of Fujifilm's ASPIRE Cristalle with Digital Breast Tomosynthesis Option as Compared to the Original Processing
Fujifilm	FUJIFILM Medical Systems, U.S.A., Inc.
IA Site DBT Reader	An image-acquisition site reader is an MQSA-qualified radiologist who interprets the DBT images at the time of image acquisition (see FMSU2013-004A).
Image Set	One (1) image with Original Processing, and one (1) image with Modified Processing of two views (CC and MLO) of the same breast.
Modified Processing	Fujifilm's ASPIRE Cristalle with Digital Breast Tomosynthesis Option with a) iterative super-resolution reconstruction (ISR) and b) Dynamic Visualization II for Mammography (DVIIm = EDR2m + MFP2) presentation processing.
Negative Case	A negative case is defined as a case where there are no abnormal areas or malignant (cancer) findings within a year (within 320 to 455 days) from the original screening examination.
Non-Cancer Case	A biopsy benign case, or a recall case, or a normal case.
Original Processing	Fujifilm's ASPIRE Cristalle with Digital Breast Tomosynthesis Option with FDA-approved filtered back projection (FBP) with EDR and MFP presentation processing.
Prior Mammogram	Historical mammogram acquired on any media – including screen-film, digitized image, FFDM and/or DBT.
Recall Case	A case where there is a suspicious area(s) identified in the screening exam that needs additional work-up to determine if the area is cancerous or not. This is determined at the IA site.
Standard views	Standard CC and MLO views for each breast (RCC, LCC, RMLO, LMLO).

Tables and Figures

1. Sponsor Protocol Approval Signature Page

Study Title	A Feature Comparison Study to Evaluate the Modified Processing of Fujifilm's ASPIRE Cristalle with Digital Breast Tomosynthesis Option as Compared to the Original Processing
Protocol Number	FMSU2017-003
Effective Date	May 8, 2018
Study Sponsor	FUJIFILM Medical Systems U.S.A., Inc. 419 West Avenue Stamford, Connecticut 06902

FUJIFILM Medical Systems U.S.A., Inc.	**Approval**
Name, Title	Robert A. Uzenoff Executive Director, Clinical Science
Signature	
Date	May 8, 2018

2. Investigator Agreement Signature Page

Study Title	A Feature Comparison Study to Evaluate the Modified Processing of Fujifilm's ASPIRE Cristalle with Digital Breast Tomosynthesis Option as Compared to the Original Processing
Protocol Number	FMSU2017-003
Effective Date	May 8, 2018
Study Sponsor	FUJIFILM Medical Systems U.S.A., Inc. 419 West Avenue Stamford, Connecticut 06902, U.S.A.
Principal Investigator	Laurie L. Fajardo, M.D., MBA, FACR, FSBI Radiology Consultant 1730 Lucky John Dr. Park City, UT 84060

I, the principal investigator named above, acknowledge the receipt of this protocol. I have read this protocol in its entirety and agree to conduct this study according to this protocol and all applicable regulations/guidelines.

Principal investigator	Laurie L. Fajardo, MD, MBA, FACR, FSBI
Signature	Laurie L. Fajardo
Date	2019-Apr-18

3. Protocol Synopsis

SPONSOR NAME	FUJIFILM Medical Systems U.S.A., Inc.
PROTOCOL NUMBER	FMSU2017-003
STUDY TITLE	A Feature Comparison Study to Evaluate the Modified Processing of Fujifilm's ASPIRE Cristalle with Digital Breast Tomosynthesis Option as Compared to the Original Processing
DEVICE NAME	Fujifilm ASPIRE Cristalle with DBT Option Utilizing ISR and DVIIm
PURPOSE	The purpose of the feature comparison study is to evaluate general mammographic features in images of the same breast when reconstructed with modified (ISR and DVIIm) processing as compared to the original processing (FBP with EDR and MFP). One breast per subject (two views per breast) will be assessed by approximately six (6) readers.
STUDY OBJECTIVES	The following primary objectives will be tested simultaneously, and include: • Non-inferiority in each of 7 general mammographic features of the modified processing
CORE READING CENTER	The feature comparison study will be performed at International HealthCare, LLC in Norwalk, CT.
PRINCIPAL INVESTIGATOR AND READERS	The principal investigator for this study is Laurie Fajardo, MD, MBA, FACR, FSBI. The feature comparison study radiologist readers shall meet all criteria for their respective roles as specified in the investigational plan. The feature comparison study readers will participate in a training session to ensure their understanding of the ASPIRE Bellus II workstation, the protocol, the study CRFs, study processes, GCP, and their obligations as study participants.

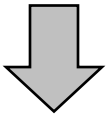
FEATURE COMPARISON STUDY DESIGN	Six MQSA-qualified and board-certified mammographers representing various experience levels, will be shown DBT images of a breast with the modified processing side-by-side the same breast with the original processing. One breast per subject (two views per breast; CC and MLO) will be evaluated by the readers. Readers will be blinded to the image reconstruction and presentation processing methods. Each reader will be given a different sample of cases to review. Approximately 600 total cases (100 cases per reader) will compose the sample. The order of the subjects and location (left or right review workstation high resolution monitor) of the images with modified processing will be randomized for each reader. Readers will compare several general mammographic features. Readers will be asked to grade each feature on each view (CC and MLO) using the following 5-point scale, with specific training to use the score=0 category sparingly: -2 (left image much superior) -1 (left image somewhat superior) 0 (left and right images are equivalent) +1 (right image somewhat superior) +2 (right image much superior)
	Interpretation instructions: The reader will complete the CRFs for each case for both CC and MLO views. The list of individual general mammographic features and lesion specific features are outlined below. Note that the results of the three lesion-specific features as well as diagnostic confidence (#8-11 below) will not be evaluated as part of this study. 1. Exposure, assessing visualization of the adipose and fibroglandular tissues and visualization of breast tissue underlying the pectoralis muscle, separately; 2. Breast composition, assessing overlapping breast structures, uniformity of exposure of fibroglandular tissues, adequacy of penetration of thicker portions of the breast, exposure of thinner areas and motion unsharpness; 3. Image contrast for differentiation of subtle tissue density differences; permitting image contrast assessment adjustment of the window and level settings; 4. Sharpness, assessing the edges of fine linear structures, tissue borders, and benign calcifications; 5. Tissue visibility at the skin line; 6. Noise, i.e., noise obscuring breast structures or suggestive of structures not actually present; 7. Artifacts due to image processing, detector failure and other factors external to the breast on soft-copy displays; and 8. Ability to characterize a Mass (when present) based on conspicuity, margin sharpness, shape; 9. Ability to characterize Calcifications (when present) based on conspicuity, sharpness/shape, distribution; 10. Ability to characterize an Architectural Distortion (when present) based on conspicuity, sharpness. 11. Diagnostic confidence.

STUDY ANALYSIS	The proportion of cases where the readers judged the modified image processing as non-inferior will be calculated. Non-inferiority will be defined as a score of equivalence between modified and original or a score indicating the modified image processing is superior. For each reader, the proportion of cases judged as non-inferior with modified processing will be calculated for each feature and each view. A pooled estimate will also be calculated where the results over all readers and views will be combined. 95% percentile bootstrap CIs will be constructed for the pooled proportions of cases judged as non-inferior with the modified processing. These CIs will be reported for each feature. The primary objective is the readers' assessment for each of the 7 general mammographic features. The null hypothesis is that the pooled proportion of cases judged as non-inferior with modified image processing is $\leq$0.50, versus the alternative hypothesis that the pooled proportion is >0.50. If the 95% CI does not contain values $\leq$0.50, then the null hypothesis will be rejected. These hypotheses will be evaluated for each of the 7 general mammographic features. If all 7 null hypotheses are rejected, then it will be concluded that the modified imaging features are non-inferior to the original imaging

4. Fujifilm FMSU2013/2017 Applicable Series Protocols

Fujifilm Protocol FMSU2013-004A

Acquisition of Digital Mammography and Breast Tomosynthesis Images for Clinical Evaluation of Fujifilm Digital Breast Tomosynthesis



Fujifilm Protocol FMSU2017-003

A Feature Comparison Study to Evaluate the Modified Processing of Fujifilm's ASPIRE Cristalle with Digital Breast Tomosynthesis Option as Compared to the Original Processing

5. Investigators and Study Administrative Structure

Study Personnel:

Principal investigator

Laurie L. Fajardo, M.D., MBA, FACR, FSBI
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6. Background and Rationale

The following software changes have been made to the FDR-3000AWS of the PMA P160031 device; Dynamic Visualization II for mammography (DVIIm) and Iterative Super-Resolution Reconstruction (ISR).

DVIIm consists of EDR2 and MFP2, which are detailed as follows:

- **Exposure Data Recognizer 2 for mammography (EDR2m)** – the EDR2m algorithm analyzes image data and identifies various anatomic structures using a statistical estimation method as opposed to original EDR's histogram analysis method. EDR2m determines the parameters to optimize brightness and contrast of the image based on the analysis result.
- **Multi-Objective Frequency Processing 2 (MFP2)** - MFP2 optimizes the brightness, contrast and sharpness of the image using parameters determined by the EDR2m processing. MFP2 uses additional low frequency tables and a combination of automatic and preset dynamic range control operations.

Iterative Super-Resolution Reconstruction (**ISR**) is a new reconstruction algorithm that uses an iterative method to improve image quality including increased sharpness and lower noise. ISR applies super-resolution technology to improve the visibility of fine structures such as calcifications, and reduces the severity of artifacts.

Note: ISR replaces filtered back projection (**FBP**), and DVIIm (EDR2m and MFP2) replaces EDR and MFP, the methods used in the original PMA P160031 device.

7. Investigational Plan

7.1. Purpose

The purpose of the feature comparison study is to evaluate general mammographic features of the same breast when reconstructed with modified (ISR and DVIIm) presentation processing as compared to the original processing (FBP with EDR and MFP).

7.2. Study Objectives

The **primary objective** is:

- Non-inferiority in each of the seven general mammographic features of the modified processing

7.3. Feature Comparison Study Population

Approximately 600 cases (breasts) will be selected from mammograms that were acquired under Fujifilm protocol FMSU2013-004A. Each of the six (6) readers will evaluate 100 unique cases in randomized order.

Table 1. Image Acquisition Sites and Principal Investigators

Image-Acquisition Site	Principal Investigator's Name	City, State
Elizabeth Wende Breast Care, LLC	Stamatia Destounis, MD	Rochester, NY
Scottsdale Medical Imaging, LLC	Denise Reddy, MD	Scottsdale, AZ
University of Iowa Hospitals and Clinics	Limin Yang, MD	Iowa City, IA
The University of North Carolina at Chapel Hill	Cherie Kuzmiak, DO	Chapel Hill, NC
University of Texas San Antonio	Pamela Otto, MD	San Antonio, TX

7.3.1. Sample Size and Case Mix

Approximately 230 cancer cases and approximately 370 non-cancer cases will be selected by the statistician for this feature comparison reader study from the library of DBT mammograms collected under Fujifilm protocol FMSU2013-004A.

The approximately 370 non-cancer cases will include:

- approximately 190 biopsy benign cases,
- approximately 60 recall cases,
- approximately 60 normal cases, and

- approximately 60 cases lost to follow-up.

7.3.2. Inclusion and Exclusion Criteria

All cases for this feature comparison reader study will meet the following eligibility inclusion and exclusion criteria (see also Appendix B for complete inclusion and exclusion criteria from protocol FMSU2013-004A). Only subjects who were consented and met all inclusion criteria and none of the exclusion criteria were considered evaluable.

Inclusion Criteria

- Eligible subjects under protocol FMSU2013-004A, defined as female subjects with complete FFDM and DBT examinations, in which there is sufficient anatomical coverage, sufficient contrast, and no significant motion or other artifacts, as determined by the image-acquisition sites.
- Meet none of the exclusion criteria under protocol FMSU2013-004A.

Exclusion Criteria

- Subjects who are in violation of protocol FMSU2013-004A.
- Subjects who meet exclusion criteria under Fujifilm protocol FMSU2013-004A.

7.3.3. Case selection and Targeted Distribution

Cases will be randomly selected from Fujifilm's existing library (collected under protocol FMSU2013-004A). A stratified randomization is proposed where the strata and proposed sampling proportions are summarized in Table 2. Within each stratum, cases will be randomly selected so that approximately 10% have extremely dense breasts, 40% have heterogeneously dense breasts, 40% have scattered fibroglandular breasts, and 10% have fatty breasts.

Table 2. Sampling Plan

Stratum, defined by Reference Standard*	# available subjects	Overall sample composition	# cases per reader	Total # cases
Cancer: (N=229)				
Architectural Distortion	21	38%	3-4	21
Microcalcification	86		14-15	86
Asymmetry	19		3-4	19
Mass	95		15-16	95
Other	8		1-2	8
Biopsy Benign: (N=457)				
Architectural Distortion	19	32%	3-4	19
Microcalcification	212		10	60
Asymmetry	43		7-8	43
Mass	158		9	54
Other	25		2-3	15
Recalled/No Biopsy	98	10%	10	60
Negative	234	10%	10	60
Unknown	209	10%	10	60
Total	**1227**	**100%**	**100**	**600**

*There are 1031 biopsied lesions in 894 subjects available for selection for this study. Because there are subjects with multiple lesions, cases in the table are organized first by the presence/absence of a malignant lesion, and then by presence/absence of an AD (and possibly another lesion), microcalcification, asymmetry, mass, and other, respectively. There were 208 subjects with lesions but no definitive biopsy diagnosis, including 24 ADs, 24 microcalcifications, 75 asymmetries, and 49 masses.

7.4 Risk/Benefit Assessment

The probable benefits of the software are based on the data that will be collected in the clinical study being conducted to support PMA supplement approval.

The software has no significant risk of direct harm to the patient.

8. Reader Selection and Training

8.1. Purpose

The purpose of the training process is to ensure that each reader selected for the reading session has been adequately trained to evaluate the DBT image sets on the ASPIRE Bellus II workstation.

8.2. Selection and Qualification Criteria for Readers

This study will be conducted with radiologists of varying experience levels, from both community and academic practices. These radiologists were not associated with the acquisition or original clinical review of cases.

Base qualification criteria: All readers must meet the following base criteria:

- Are board-certified
- Are MQSA-qualified for DBT interpretation

8.3. Conduct of the Training Process

Training will include review of the case report forms to ensure reader understanding of the mammographic features they will be evaluating images based on, as well as the 5-point scale they will be utilizing to grade each image set. Readers will be specifically instructed to use the score=0 sparingly. GCP will also be reviewed and documented via attestation form during the training process.

Training will also consist of a hands-on session at the workstation to provide the readers with an overview of its pertinent DBT-specific functionality.

Following the successful completion of the reader training, the readers will independently review and score each of the approximately 100 image sets at their own designated workstation. Interpretation of mammography images will be performed in a controlled environment with consistent lighting. The review workstations will be preloaded with the cases. The reading time allowed per image set will not be limited. A lunch break will be offered during the reading session, and radiologists will be encouraged to take a 5-10 minute break each hour, as needed. Each reader will dictate their evaluations to a trained scribe, who will enter the dictation onto a paper CRF. Each reader will sign an attestation form verifying the documented information.

8.4 Conduct of the Reading Process

8.4.1 Purpose and Conduct

The purpose of the reading process is for the readers to evaluate, side-by-side, images of the same breast reconstructed with the modified and original processing methods.

Readers will compare several general mammographic features. Readers will be asked to grade each feature on each view (CC and MLO) using the following 5-point scale:

-2 (left image much superior)

-1 (left image somewhat superior)

0 (left and right images are equivalent)

+1 (right image somewhat superior)

+2 (right image much superior)

The list of individual general features and three lesion-specific features is given in Table 3. Note that the results of the three lesion-specific features as well as diagnostic confidence (#8-11 below) will not be evaluated as part of this study. Readers will be specifically instructed to use the score=0 sparingly.

Table 3. Mammographic Features to be Graded

1. Exposure, assessing visualization of the adipose and fibroglandular tissues and visualization of breast tissue underlying the pectoralis muscle, separately;
2. Breast compression, assessing overlapping breast structures, uniformity of exposure of fibroglandular tissues, adequacy of penetration of thicker portions of the breast, exposure of thinner areas, and motion unsharpness;
3. Image contrast for differentiation of subtle tissue density differences; permitting image contrast assessment adjustment of the window and level settings.
4. Sharpness, assessing the edges of fine linear structures, tissue borders, and benign calcifications;
5. Tissue visibility at the skin line;
6. Noise, i.e., noise obscuring breast structures or suggestive of structures not actually present;
7. Artifacts due to image processing, detector failure and other factors external to the breast on soft-copy displays; and
8. Ability to characterize a Mass (When Present) based on conspicuity, margin sharpness, shape;
9. Ability to characterize Calcifications (When Present) based on conspicuity, sharpness/shape, distribution;
10. Ability to characterize an Architectural Distortion (When Present) based on conspicuity, sharpness;
11. Diagnostic confidence.

8.4.2 Core Reading Center

The reading process with 6 radiologists selected for the feature comparison reader study will be conducted at International HealthCare, LLC in Norwalk, CT.

8.4.3 Preparation of Cases for Interpretation

To maintain subject confidentiality, no identifying patient data will be displayed. Unique image identifiers associated with the case ID number will be visible in each DICOM header for tracking purposes. To maintain reader confidentiality, a unique ID number will be assigned to each radiologist participating in the reader study for entry on the CRFs.

8.4.4 Workflow for the Interpretation of Cases

Readers will be shown side-by-side images of the same breast reconstructed with the modified and original processing methods. One breast per subject (two views per breast) will be assessed by the readers. Readers will be blinded to the image reconstruction and processing methods. Each reader will be given a unique sample of cases to review. The order of the subjects and location (left or right review workstation high resolution monitor) of the images with modified processing will be randomized for each reader.

Within each stratum, cases will be randomly selected so that 10% have extremely dense breasts, 40% have heterogeneously dense breasts, 40% have scattered fibroglandular breasts, and 10% have fatty breasts.

Readers may interpret the preloaded cases in their assigned randomized order with the use of barcode scanner/barcodes.

General instructions for the readers are as follows:

The reader is to compare the tomosynthesis image on the left monitor to the tomosynthesis image on the right monitor. One CRF will be completed for each view (CC and MLO) for each case (breast).

For each case that has a lesion, the reader is to document lesion type, quadrant and slice number.

A study scribe representing the sponsor will capture the radiologist's results on the CRFs to ensure completeness and allow the radiologist to focus on evaluation of image sets.

9. Statistical Analysis

The proportion of cases where the readers judged the modified image processing as non-inferior will be calculated. Non-inferiority will be defined as a score of equivalence between modified and original or a score indicating the modified image processing is superior. For each reader, the proportion of cases judged as non-inferior with modified processing will be calculated for each feature and each view in Table 3. A pooled estimate will also be calculated where the results over all readers and views will be combined. 95% percentile bootstrap CIs will be constructed for the pooled proportions of cases judged as non-inferior with the modified processing. These CIs will be reported for each feature.

The null hypothesis is that the pooled proportion of cases judged as non-inferior with modified image processing is $\leq$0.50, versus the alternative hypothesis that the pooled proportion is >0.50. If the 95% CI does not contain values $\leq$0.50, then the null hypothesis will be rejected. These hypotheses will be evaluated for each of the seven general mammographic features. If the null hypothesis is rejected for each of the seven general features, then it will be concluded that the readers' subjective evaluation of the features on the modified imaging is non-inferior to the original imaging.

9.1. Analysis Set

We plan to include all readers' interpretations of all cases in the analysis set. If any protocol deviations or violations occur, Fujifilm will report these to the statistician. The statistician will evaluate these to determine their impact on the validity of the study data and will determine whether any affected data points should be excluded from analysis.

9.2 Analysis of Primary Objective

The primary objective of this study is non-inferiority in each of the seven general mammographic features of the modified processing.

The proportion of cases where the readers judged the modified image processing as non-inferior will be calculated. Non-inferiority will be defined as a score of equivalence between modified and original or a score indicating the modified image processing is superior. For each reader, the proportion of cases judged as non-inferior with modified processing will be calculated for each general mammographic feature. A pooled estimate will also be calculated where the results over all readers will be combined. 95% percentile bootstrap CIs will be constructed for the pooled proportions of cases judged as non-inferior with the modified processing. These CIs will be reported for each of the 7 general mammographic features.

9.3 Sample Size Justification

The following assumptions were made for determining sample size for the primary objectives:

- One breast per subject (two views)
- Each of six readers scores an independent sample of cases; thus, there is no correlation between readers' interpretations.
- 50% of cases have dense breasts
- $\geq$80% power is required

- 2.5% type I error rate (Note that hypothesis rejection depends on the lower bound of the 95% CI being greater than 0.50.)

Based on these assumptions, sample size was determined as follows:

$$M = \frac{\{1.96 \times \sqrt{0.5(1-0.5)} + 0.84\sqrt{p(1-p)}\}^2}{[p-0.5]^2}$$

where *p* is the proportion of comparisons judged as non-inferior under the alternative hypothesis. The sample size is given by N=M/(# readers). Table 4 summarizes the number of subjects needed per reader as a function of the proportion of cases judged as non-inferior with the modified processing.

Table 4. Number of Subjects Needed Per Reader for Tests of Non-inferiority

# readers	Proportion of Comparisons Judged as Non-inferior with Modified Processing (DVIIm plus ISR)			
	0.55	**0.56**	**0.57**	**0.60**
6	131	91	67	33

A study with 600 total subjects (i.e. 100 cases evaluated per reader) is proposed. This sample size would provide slightly more than 80% power to reject the primary null hypothesis, as long as ≥56% of cases are judged non-inferior.

10. Sponsor and Investigational Site Requirements (Study Administration)

10.1 Ethics

10.1.1 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

A description of this clinical trial will be available on ***http://www.ClinicalTrials.gov***, as required by U.S. Law.

10.1.2 Institutional Review Board

The sponsor and investigator(s) shall assure that an IRB, constituted in accordance with 21CFR812 Subpart D and ICH guidelines for GCP (ICH E6 GCP) will provide initial and continuing review of the study.

Prior to enrollment of study subjects in the image acquisition portion of the study, documented IRB approval of the protocol, the informed consent form, and any other written materials supplied to the subjects, including any advertisements for subject recruitment, was obtained and provided to the sponsor or its designated representative(s).

Prior to commencement of the reader study portion of the study, documented IRB approval of the protocol, the reader informed consent form, and any other written materials supplied to the readers must be obtained by the sponsor or its designated representative(s).

The IRB must also be informed of any protocol amendments prior to implementation. The sponsor must provide reports of any change in research activity (e.g., the completion, termination, or discontinuation of the study) to the IRB. Annual review documentation will be submitted to the IRB 90 days prior to the IRB approval expiration.

10.2 Reader Informed Consent

Each reader must provide written informed consent before participating in the reader study of this protocol.

10.3 Protocol Compliance

Except for a change that is intended to eliminate an apparent immediate hazard to a study subject, the protocol shall be conducted as described. Any such change must be reported immediately to Fujifilm or its representative(s) and the governing IRB.

10.3.1 Protocol Amendments

Protocol amendments will be prepared and approved by Fujifilm or its authorized designee. All protocol amendments will be signed by the investigator and submitted to the IRB for review prior to implementation. Documentation of IRB approval must be provided to Fujifilm or its representative. If an amendment significantly alters the study design, increases potential risk to the subject, or otherwise affects statements in the informed consent, the informed consent must be revised and submitted to the IRB for review and approval. The approved informed consent form must be used to obtain consent from new subjects enrolled in the study and must also be used to re-consent subjects already enrolled in the study, if they are affected by the amendment.

10.4 Retention of Study Records

All documents pertaining to the conduct of this clinical study – including CRFs, informed consent forms, source documents, and other records must be retained during the investigation, unless otherwise requested by the sponsor, for a period of 2 years after the later of the following 2 dates [21CFR812.140 (d)]:

- Records are no longer required for the purposes of supporting a regulatory submission to the FDA.

OR

- Following the termination or withdrawal of the regulatory submission.

The principal investigator must contact Fujifilm in writing prior to the destruction of any study records or in the event of accidental destruction or loss of the documents. If the principal investigator leaves the institution where the study is being conducted, the principal investigator must contact the sponsor to arrange for transfer of responsibilities and alternative record storage options, if applicable.

Study documentation includes all CRFs, data correction forms, source documents, monitoring logs, sponsor-investigator correspondence, protocols and amendments, ethics committee correspondence and approvals, signed consent forms, etc. Source documents include all original records or observations, results and activities necessary to reconstruct and evaluate the study.

10.5 Data Collection and Management

10.5.1 General

All data entry will be completed using paper Case Report Forms, following the guidelines established in the Data Management Plan.

The privacy of participating subjects must be maintained in accordance with the HIPAA privacy ruling and disclosed per 24CFR50.

The CRFs will be data entered, and then reviewed for accuracy and completeness by a study monitor representing Fujifilm, as well as reviewed by DMC staff prior to data transfer to the statistician.

10.5.2 Data Management Center

The responsibilities of the DMC will include monitoring and oversight of the collection efforts, performance of the data audits, facilitating data entry into a computerized database, and providing the data to the statistician.

The DMC responsibilities will include oversight of the data collection efforts (excluding image data, which will be collected by Fujifilm or its designees), facilitation of data entry into the computerized database, all final data cleaning, and performance of a final data quality-control audit prior to database lock.

CRFs will be logged and tracked when received by the DMC. CRFs will then be entered and stored in a 21 CFR Part 11 compliant clinical database. Upon completion of the study and resolution of all outstanding DCFs, the database will be locked and datasets necessary for analysis and reporting will be generated and provided to the statistician for final analysis.

10.6 Confidentiality

10.6.1 Subject Confidentiality

To maintain subject confidentiality, no identifying patient data will be displayed. Unique image identifiers associated with the case ID number will be visible on each image for tracking purposes. A unique ID, one per case per modality will be assigned to each case whose images are selected for the reader study and will be the only subject identifier on all study-related documentation.

Prior to the initiation of the study, Fujifilm or its authorized representative will provide the readers with adequate training related to the identification. The subject's unique identifier may be displayed on the softcopy image as an overlay. The overlay may be turned on and off as necessary during the reader studies for reference.

10.6.2 Reader Confidentiality

Information collected during the reader study will be reported in such a way as to preclude identification of any individual radiologist's performance. To maintain reader confidentiality, a unique ID number will be assigned to each radiologist participating in the reader study for entry on the CRF's. A master list of these ID numbers for the radiologists participating in the reader study will be securely maintained by the Fujifilm project manager.

10.6.3 Transfer of Confidential Information to the Sponsor or the DMC

This reader study utilizes data from the Fujifilm library that was obtained in Fujifilm protocol FMSU2013-004A. All data utilized for this study (photocopies of radiology, pathology and clinical reports as well as images) was de-identified prior to removal from the acquisition center(s).

10.7 Study Monitoring

Fujifilm and/or its designees will monitor the study, verify the collection of data, and confirm that the study is being conducted according to the protocol. The CRF data will be recorded.

The study may be audited by representatives from the FDA or other regulatory agencies, who also shall be allowed access to study documents.

If Fujifilm, the principal investigator, the IRB, or a regulatory authority discover conditions arising during the study that indicate that the study should be halted or that the study center's participation in the study should be terminated, this action may be taken after appropriate consultation between Fujifilm, its designee, and the investigator(s).

10.8 Sponsor Audits

Individuals appointed by the sponsor may visit the CRO to conduct an audit of the study GCPs. The purpose of the visit will be to determine adherence to the protocol, applicable regulations and the sponsor's procedures in addition to the assessing the accuracy of the study data (Inspection Readiness). Prior to initiating this audit, the CRO will be contacted by the sponsor to arrange a convenient time for this visit.

10.9 Inspection by a Regulatory Agency

At some point during the study, the investigator may be visited by a regulatory agency (e.g., FDA) to conduct an inspection of the study. The purpose of this visit will be to determine adherence to the protocol and regulatory requirements for conducting clinical studies. The investigator must immediately notify Fujifilm when contacted by a regulatory agency for the purposes of conducting an inspection of the Fujifilm's study.

10.10 Financial Disclosure

In accordance with 21CFR54, the principal investigator and the study readers will provide Fujifilm or its designee sufficient and accurate information on financial interests (proprietary or equity interests and payments exclusive of clinical study costs) to allow complete disclosure documenting lack of conflict of interest. The principal investigator and study readers shall promptly update this information with any relevant changes that occur during the course of the study, at the completion of the study, and for a period of 1 year following the completion of the study.

10.11 Study or Study-site Termination

If Fujifilm, the principal investigator, the IRB, or a regulatory authority discover conditions arising during the conduct of the study that indicate that the study should be halted or that the study center should be closed, this action may be taken after appropriate consultation between Fujifilm and the principal investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- A decision on the part of Fujifilm to suspend or discontinue testing, evaluation, or development of a product.

The study center may warrant closure/termination for the following reasons:

- Failure of the investigator to comply with pertinent regulatory authority regulations.
- Knowing submission of false information from the research center to Fujifilm, study monitor, or a regulatory authority.
- Insufficient adherence to the protocol requirements.

Study termination and follow-up will be performed in compliance with the conditions set forth in 21CFR812.150 (a) (2).

11 Appendices

Appendix A: Fujifilm FFDM and DBT Image Acquisition and Display

Note: The proposed brand and/or configuration of the ASPIRE products are subject to change.

Overview of ASPIRE Cristalle DBT Option and ASPIRE Bellus II

Fujifilm's **ASPIRE Cristalle** DBT Option (**Figure A**) mammography acquisition system generates both FFDM and DBT images. It is comprised of the X-ray exposure unit and acquisition workstation, and is FDA PMA approved (P160031) for 2D mammography and DBT image acquisition.

Fujifilm's **ASPIRE Bellus II** (**Figure B**) mammography review workstation displays and supports the physician's review of 2D mammography and DBT images. It is composed of the display accessories of the ASPIRE Cristalle and includes the major components of a PC (with image review and manipulation software installed), a console monitor, and two high-resolution grayscale diagnostic display monitors, and is FDA cleared (K171463)

Figure A. ASPIRE Cristalle DBT Option - Fujifilm's mammography acquisition system.

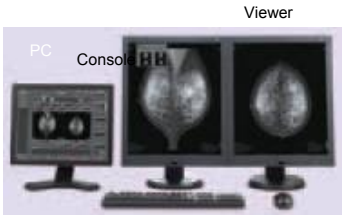

Figure B. ASPIRE Bellus II - Fujifilm's mammography viewer.

Acquisition of FFDM and DBT Images by ASPIRE Cristalle DBT Option (Figure A)

All FFDM and DBT images of the enrolled study subjects were acquired on the ASPIRE Cristalle system with DBT option. For each study subject, the DBT and FFDM images were acquired under the same breast compression for each of the LCC, RCC, LMLO and RMLO views.

Display of FFDM and DBT Images on ASPIRE Bellus II (Figure B)

Mammography images are displayed on the ASPIRE Bellus II for the physician's review. The console allows the user to manage various aspects of the system configurations and setup, including the modality work list, local archive, communications, and the selection of images to be displayed on the two high-resolution grayscale diagnostic display monitors. The viewer supports typical image-manipulation functions, such as windowing, leveling, zooming, etc.

Appendix B: Inclusion and Exclusion Criteria from FMSU2013-004A

Study Population

All female subjects, of any ethnic or racial origin, who are appearing for a routine screening examination or have been referred for further diagnostic evaluation after a screening examination (within 60 days) or have a 4-view mammogram (within 60 days) due to clinical concerns and receive a BI-RADS assessment of category 4 or 5 after diagnostic workup and are scheduled for biopsy will be eligible to participate in the study.

Subjects will receive a written explanation of the study and will be asked to provide written informed consent to participate. Once eligibility is confirmed and informed consent has been obtained, the subjects will be enrolled in the study.

Inclusion Criteria

Subjects enrolled must meet all the following inclusion criteria:

- Screening Subjects
  - Be at least 40 years of age, are
  - Asymptomatic,
  - Scheduled for a routine screening mammogram,
- Recall Subjects
  - Be at least 18 years of age
  - Received a BIRADS 0 within the last 60 days
  - Are recalled for additional imaging
- Diagnostic Subjects
  - Be at least 18 years of age,
  - Scheduled for a biopsy due to an assessment of BI-RADS® 4 or 5 after diagnostic work-up of a suspicious screening or clinical finding within the last 60 days.
- Have the ability to understand the requirements of the study, to provide written informed consent, and to comply with the study protocol, and
- Meet none of the exclusion criteria.

Exclusion Criteria

Subjects will be excluded from participating in the study if they meet any one or more of the following exclusion criteria:

- Presence of a breast implant.
- Women with only a single breast; for example, post mastectomy patients.
- Is pregnant or believes she may be pregnant.
- A woman who has delivered and who has expressed the intention to breast-feed or is currently breast-feeding.
- A woman who has significant existing breast trauma within the last one year.
- Has self-reported severe non-focal or bilateral breast pain affecting subject's ability to tolerate digital mammography and/or breast tomosynthesis examinations.
- A woman who has had a mammogram performed for the purpose of therapy portal planning within the last year.
- Cannot, for any known reason, undergo follow-up digital mammography and/or breast tomosynthesis examinations (where clinically indicated) at the participating institution.
- Is an inmate (see *US Code of Federal Regulations 45CFR46.306*)