AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK
ACRIN 6652
DIGITAL VS. SCREEN-FILM MAMMOGRAPHY

PARTIAL PROTOCOL— CONTACT ACRIN PROTOCOL DEVELOPMENT AND REGULATORY COMPLIANCE FOR A COMPLETE PROTOCOL

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INDEX

SCHEMA

1.0 ABSTRACT 4

2.0 BACKGROUND AND SIGNIFICANCE.....4

3.0 SPECIFIC AIMS 22

4.0 PARTICIPANT SELECTION AND ACCRUAL.....23

5.0 DATA COLLECTION AND MANAGEMENT 26

6.0 STUDY MAMMOGRAM ACQUISITION.....38

7.0 DIGITAL AND SCREEN-FILM MAMMOGRAPHY INTERPRETATION 39

8.0 FOLLOW-UP OF STUDY PARTICIPANTS' MAMMOGRAMS.....44

9.0 COST-EFFECTIVENESS ASSESSMENT 46

10.0 PARTICIPANT HEALTH-RELATED QUALITY OF LIFE ASSESSMENT.....47

11.0 STATISTICAL CONSIDERATIONS REMOVED FROM WEB VERSION 51

12.0 ADVERSE EVENT REPORTING 51

REFERENCES 54

APPENDIX I SAMPLE CONSENT FORM 60

APPENDIX II STAGING SYSTEM 67

APPENDIX III ELIGIBILITY CHECKLIST 69

APPENDIX IV PARTICIPATING INSTITUTIONS 71

APPENDIX V DMIST SOURCE DOCUMENTATION 73

APPENDIX VI DMIST ANNUAL FOLLOW-UP 80

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

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SCHEMA

RANDOMIZATION

Arm 1: Undergo Screen-Film then Digital Mammography

Arm 2: Undergo Digital then Screen-Film Mammography

INTERPRETATION of MAMMOGRAM

Suspicious lesion → Additional workup

Follow-up at one year With screen film or digital mammography

Eligibility *(See Section 4.0 for details)*

- All consecutive women presenting for screening mammography at the participating institutions
- Women must undergo follow-up screen-film mammography at the participating institution or provide mammograms from another institution for review for one year after study entry
- No focal dominant lump or a bloody or clear nipple discharge
- No history of breast cancer treated with lumpectomy
- No breast implants
- Not pregnant
- Signed study-specific informed consent prior to registration

Required Sample Size: 49,500

1.0 ABSTRACT

The primary aim of this three-year protocol is to compare the diagnostic accuracy of digital mammography vs. screen-film mammography for the purpose of breast cancer screening. A total of 49,500 asymptomatic women presenting for screening mammography will be enrolled into the trial at at least 35 centers in the U.S. and Canada. All women will undergo both digital and screen-film mammography. Each examination will be interpreted independently and work-up will proceed based on the findings of either study. Truth regarding breast cancer status for all participants will be determined either through the results of breast biopsy, if that occurs, or as a result of one year of follow-up without clinical evidence of disease. All pathologic specimens will be reread by an expert breast pathologist.

Secondary aims include the measurement of the relative cost-effectiveness of both technologies, and the measurement of the effect on participant quality of life from the expected reduction of false positive mammograms with digital mammography. Seven controlled reader studies will be used to measure the following: 1) the diagnostic accuracy of softcopy vs. printed film display for digital mammography; 2) the effect of disease prevalence on reader interpretation performance; 3) the effect of breast density on the diagnostic accuracy of digital mammography vs. screen-film mammography; and, 4) the diagnostic accuracy of each of the four individual digital mammography units versus screen-film mammography.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 Digital vs. Screen-Film Mammography

Screen-film mammography has been studied extensively for the last thirty years, and because of many large randomized screening trials, it is known to reduce breast cancer mortality by approximately 18-30%. [Nystrom, Hendrick 1997A] The rate of breast cancer death in the last few years has begun to decline, likely due in part to the widespread use of this imaging test. [Graves, Letton] However, while standard screen-film mammography is very good, it is neither perfectly sensitive nor highly specific. Dense breast tissue and diffuse involvement of the breast with tumor tends to reduce the sensitivity of screening mammography. [Laya, Burrell 1996A, Hollingsworth] Approximately 10-20% of breast cancers that are detected by self-breast examination or physical examination are not visible by screen-film mammography. [Baker, Brekelmans, Burrell 1996A] In addition, when lesions are detected by mammography and biopsy is recommended by experienced radiologists, only 5-40% of lesions prove to be malignant. [Sickles, Lidbrink, Burrell 1996B] Clearly, there is room for improvement in both breast cancer detection and lesion characterization.

A major limitation of screen-film mammography is the film itself. The film serves as the medium of image acquisition, storage and display. Breast cancer is often quite similar in x- ray absorption to surrounding normal dense breast tissue. Digital detectors offer improved detection because of improved efficiency of absorption of the incident x-ray photons, a linear response over a wide range of incident radiation intensities, and low system noise. [Pisano 1998A, Feig] Thus, digital mammography has the potential to improve breast cancer detection and breast lesion characterization. [Shtern]

In addition, once a screen-film mammogram is obtained, it cannot be significantly altered. Contrast loss due to film underexposure, especially of dense glandular tissues, cannot be regained through film display. Radiologists cannot manipulate the image directly. Improvements in image display involve acquiring more images with magnification or focal compression *(and thus exposing the participant to more radiation)*, or looking at the images with a hot light or magnifying glass.
What you see is what you get.

Digital acquisition systems directly quantify x-ray photons and decouple the process of x-ray photon detection from image display. Digital images can be processed by a computer and displayed in multiple formats, on film or on a monitor. Lesion conspicuity can be affected by these contrast manipulations. Image processing has been shown to improve visualization of details within medical images in at least one other application. [Rosenman] Since the steps of image acquisition and display are separated, each can be optimized. In addition, image storage, transmission and retrieval can be improved. Software to assist the radiologist in interpreting the images can also be utilized.

2.2 Technical Overview

All four of the currently available full-field digital mammography systems are based on the absorption of x-rays by a phosphor material with subsequent conversion of the absorbed energy to electronic charge. The charge signal is then digitized and stored as a matrix in computer memory to represent the image.

2.2.1 *Fischer Imaging*

The system manufactured by Fischer Imaging employs a thallium-activated cesium iodide [CsI*(Tl)*] phosphor and fiber-optic coupling to a Charge-Coupled Device *(CCD)*. Optical de-magnification is not employed. The x-rays are collimated into a fan beam, which matches the format of the detector array. Image acquisition is carried out by scanning the detector in synchrony with the x-ray beam laterally across the breast. The detector is sufficiently long to cover the breast in the antero-posterior direction, but is only about 1 cm wide in the scanning direction. Acquisition takes place using a time-delay integration *(TDI)* mode in which charge is accumulated in storage wells in the CCD and then shifted down CCD columns from row to row at the same rate and opposite direction as the detector and x-ray beam move across the breast. The detector element size is approximately 54 microns in standard resolution mode with 12bits/pixel digitization. A high-resolution mode provides a limited field of coverage with a detector element of 27 microns.

This system employs a completely dedicated x-ray unit with a tungsten anode tube and a choice of three filter materials, molybdenum, rhodium or aluminum. The x-ray beam is collimated into a slot 14 mm wide and is scanned across the breast during the exposure. Typically, a higher kilovoltage *(e.g., 31 kVp)* is employed than that used with the other molybdenum or rhodium target systems. Currently, exposure control is manual, based on technique charts. The Fischer system provides standard contrast enhancement.

2.2.2 *Fuji*

The current system is based on the original Fuji Computed Radiography product, introduced in 1981, with subsequent advances in imaging plate technology and image processing. The detector is a flexible plastic sheet coated with a photostimulable x-ray absorbing phosphor material, typically BaFBr. The imaging plates, available in standard cassette sizes, are loaded in cassettes for exposure in a standard screen-film mammography Bucky tray. In response to absorption of x-rays, electronic charges are stored in “traps” in the crystalline phosphor where they remain stable for some time. After exposure, the image is read by precision scanning of the imaging plate by a laser beam. The red laser light “discharges” the traps, causing stimulated emission of blue light. The blue light is collected by an efficient light guide and detected by a photo-multiplier tube. The resulting signal is logarithmically amplified, digitized and processed for film or softcopy display. The imaging plate is erased by exposure to

white light in the image reader for reuse. The resultant image has a pixel size of 50 microns with a digitization precision of 10 bits after logarithmic compression.

This system uses a conventional mammography system. Technique factors are similar to those used for conventional mammography with a slight increment in kilovoltage. The automatic exposure control is that of the mammography unit being used. Lorad and Bennett are among the more commonly used in mammography units used with the Fuji system, but any acceptable unit may be employed.

The Fuji system provides two modes for image processing: 1. Standard Fuji processing *("Gradation")* with scaling of data *(to avoid truncation errors)* followed by contrast enhancement; and 2. Multiscale processing *(MFP)* with image divided into subscales with nonlinear processing at each scale and re-synthesis of images.

2.2.3 *General Electric*

This system incorporates a large area matrix of photodiodes on an amorphous silicon substrate. The entire detector is coated with a layer of CsI*(Tl)*. Each light-sensitive diode element is connected by a thin film transistor switch to a control line and a data line such that the charge produced on the diode in response to light emission from the phosphor is read out and can be digitized. The detector element size is approximately 100 microns and digitization is performed to a precision of 14 bits/pixel.

This system uses a mammography unit that is essentially identical to the GE DMR mammography system used for screen-film mammography. The selectable x-ray target-filter combinations are identical to those used for screen-film mammography: molybdenum target with molybdenum or rhodium filtration and rhodium target with rhodium filtration. Like the screen-film DMR system, the Senographe 2000D digital system is equipped with an Automatic Optimization of Parameters *(AOP)* mode that permits selection of Contrast, Standard, or Dose Mode. Each of these three AOP modes employs a very brief test pre-exposure to assess breast thickness and total attenuation. In AOP mode, the target/filter/kVp combination is automatically selected based on the measured breast thickness and composition. The mAs at which exposure is automatically terminated is determined by the automatic exposure control device *(incorporated in the digital detector)*. In the GE system, a 15 cm by 16 cm area of the digital detector serves as the AEC detector. Within that region, the mAs is set to provide adequate signal to most attenuating region with the breast. Contrast, Standard, and Dose modes are selectable to modify the beam quality and mAs slightly to allow the user to select slightly higher image contrast *(Contrast Mode)*, slightly lower dose *(Dose Mode)*, or a compromise between the two *(Standard Mode)*.

For image processing, the GE system applies a logarithmic rescaling and a proprietary peripheral equalization algorithm to the images after dark subtraction and flat-fielding. Both the raw *(dark subtraction and flat-fielding only)* and processed *(rescaled and peripherally equalized)* images are available to the user.

2.2.4 *Lorad (formerly Trex)*

The Lorad digital detector system is a mosaic of 3 by 4 smaller detector modules. The Lorad digital detector system is now used only with the Lorad M-IV. Each module consists of a CsI*(Tl)* phosphor layer on the input surface of a fiber optic taper, providing optical de-magnification on the order of 50%. Each taper couples light from the phosphor to an area CCD array bonded to its exit surface.

This system produces a full size image of the breast with 41 micron pixels. The image is digitized to 14 bits/pixel. The Lorad digital detector system is now used only with the Lorad M-IV. This employs molybdenum anode tubes and molybdenum or rhodium filters. The exposure technique is determined by an AEC system that determines exposure time termination based on the integrated charge in one of the 12 detector modules during a short pre-exposure.

For image processing, the LORAD system applies dark subtraction, de-warping, and flat fielding before monitor display. Proprietary processing occurs before laser printing.

2.3 Previous Work: Technical Characterization Accomplished to Date

2.3.1 *Work Involving or Applicable to More than One Detector*

Under funding from the Office of Women's Health *(Etta Pisano, University of North Carolina, Principal Investigator (PI))*, the International Digital Mammography Development Group *(IDMDG)* has completed technical characterization of the Fischer, GE and Lorad machines. This has included measurement of Modulation Transfer Function *(MTF)*, noise, participant dose, and geometrical factors such as distortion. Temporal variation of these quantities has been monitored. Some of these results and methods have been published or will be published shortly [Yaffe 1998, Critten 1996, Shen 2000]. While the MTF of digital mammography is less than that of screen-film systems, the DQE of the digital systems is higher, providing improved signal-to-noise ratio and allowing substantial improvement of contrast.

Martin Yaffe of the University of Toronto and Mark Williams of the University of Virginia have led the scientific team that has completed this work. Other scientists who have contributed to this work are Dev Chakraborty of the University of Pennsylvania, Eugene Johnston at the University of North Carolina, Carolyn Kimme-Smith of the University of California-Los Angeles, Andrew Maidment of Thomas Jefferson University, Gordon Mawdsley of the University of Toronto, and Loren Niklason, a consultant to General Electric.

In addition, this same group has already developed a digital mammography phantom and a Quality Control *(QC)* program for digital mammography, including some automated QC techniques. This device allows for monitoring of noise power spectrum uniformity, stitching and/or scanning artifacts, spatial resolution, low contrast resolution, and dynamic range. A separate test device is provided for measurement of MTF. These physicists have also written a digital mammography QC manual. This program includes frequent tests of MTF, limiting spatial resolution, scatter-to-primary ratio, image non-uniformity, noise power spectrum, and tests that simulate those required for screen-film systems under the 1992 U.S. Federal Mammography Quality Standards Act *(MQSA)*. The IDMDG clinical pilot study described below utilized this quality control program during participant accrual. [Yaffe 1998].

The IDMDG group's work is continuing under funding from the Department of Defense. *(Laurie Fajardo, Johns Hopkins University (JHU), PI)* Specifically, the assessment of optimum radiographic technique for each machine and for each participant breast type for digital mammography is currently ongoing. The choice of filtration material for each machine is also being studied carefully.

Some additional preliminary work on the optimum spectrum for digital mammography

indicates that the optimum factors may be significantly different than those used for screen-film mammography, at least for the GE system. One would expect these results to hold for any system utilizing a CsI phosphor detector. [Venkatakrishnan, Chakraborty]

In addition, Niklason [1998A] and Edward Hendrick [1997B] of the University of Colorado Health Sciences Center have carefully studied the advisability of the use of a radiographic grid for the General Electric system. Using contrast-detail and other phantoms and measuring scatter fraction and signal-to-noise ratios *(SNR)* with and without grids, they concluded that a conventional antiscatter grid would be beneficial for breast thickness greater than 5 cm. For breasts less than 5 cm., use of a conventional grid resulted in a loss of SNR. Niklason suggested that use of a grid with higher primary transmission would be beneficial for a wider range of breast thickness. These results should apply to the Lorad and Fuji systems, as well as any large area detector system. Grids are not applicable to the Fischer scanning-slot system.

Carolyn Kimme-Smith of the University of California-Los Angeles *(UCLA)*, under DOD funding, has developed a phantom designed to be read automatically, and has tested a version of it on the Lorad, GE and Fischer systems. The phantom differs from the IDMDG phantom in that the signal to noise ratio and calcification conspicuity is tested for each of the 12 CCD's in the Lorad detector separately. For the Lorad system, the signal to noise ratio varied across the CCD's by 12%, rising to 20% when the system was not operating correctly, and varied temporally up to 6% for the same CCD depending on radiographic technique. The phantom was also used to investigate the optimal radiographic technique. It was found that the signal to noise ratio increased with photon flux to the image receptor, either by increasing mAs, kVp, or using Rhodium filtration. For the GE system, signal to noise ratios varied across the image receptor by almost 14%, but dropped to 7% for some radiographic techniques. Calcification conspicuity matched that of the Lorad and Fischer systems. For the Fischer system, a higher kVp was employed and the signal to noise ratio ranged from 8-37% across the 4 CCD's. [Kimme-Smith]

2.3.2 *Work Specific to the GE Detector*

Hendrick and Cynthia Landberg of GE Corporate Research and Development *(GE-CRD)* have developed a QC program and manual for the GE system similar to the program developed by the IDMDG.

Contrast-detail phantoms have also been used by Hendrick and collaborators to compare the low-contrast detection capabilities of the GE digital system to optimized screen-film mammography for a range of breast thickness and tissue compositions. They found that the 100 micron GE detector with a grid had superior low-contrast detection to screen-film mammography with a grid at matching breast doses *($p<0.01$)*. [Hendrick 1997B] This study, however, did not compare digital to screen-film mammography for the detection of calcifications.

2.3.3 *Work Specific to the Lorad Detector*

In addition, Stephen Feig and colleagues at Thomas Jefferson University, under National Cancer Institute funding, have evaluated the image quality and conspicuity of normal anatomic features for 324 Lorad digital mammograms compared to screen-film mammograms of the same women. All digital mammograms were found to have better and more uniform exposure of the whole breast and improved image contrast. Sharpness of anatomic features and lesions was better in all digital mammograms of

women with fatty breasts, and better in 40% of women with dense breasts. Conspicuity of calcifications was better in 25% of digital mammograms, and equal in the other 75%. A manuscript with these results is being prepared for publication.

2.3.4 *Work Specific to the Fuji Detector*

The Fuji system was evaluated for mammography in 1994 [Workman]. While the MTF of the digital system was found to be lower than that of Fuji's screen-film product, DQE was similar and was maintained over a wider range of exposure, and contrast-detail performance was superior. Cowen, et al. have devised a QC phantom for the Fuji system. [1992] In addition, the company has developed a Quality Control program for digital mammography that is based on MQSA, including use of the American College of Radiology mammography phantom. The company has developed recommended radiographic techniques for use with their product, which includes the use of a radiographic grid.

2.3.5 *Average Glandular Dose and Imaging Parameters*

The average glandular dose for each of the digital mammography units depends on the type of breast *(composition and thickness)* being imaged. For imaging the ACR Accreditation Phantom, mean glandular doses and typical technique factors for the four digital mammography systems are shown in the first few columns of Table 1. In each case, mean glandular dose to a standard breast has ranged between 1.5 and 2.0 mGy *(150-200 mrad)* per image. Thus, the total breast dose to a standard breast from 2-view screening digital mammography for digital mammography has been measured between 3.0 and 4.0 mGy *(300-400 mrad)*.

Table 1: Imaging Technique Factors and Display Parameters for Digital Systems Used in the ACRIN Screening Trial of Digital Mammography

Machine Type	MGD *(mGy)*	Target/Filter/kVp	Grid Use?	Soft Copy Display Monitors/ Graphics Cards	Hard Copy Display*
GE	1.5-2.0	Mo/Mo /28	Yes	2 x Siemens Monitors *(each 2K x 2.5K)*/ Dome MD5 Graphics Cards	Kodak DryView 8600 or AGFA LR5200
Fischer	1.5-2.0	W/Al/31	No – slot scan design *(14 mm slot width)*	2 Barco Monitors *(each 2K x 2.5K)*/ Dome dual head graphics card	Kodak Dryview 8600 or AGFA LR5200
Fuji	1.5-2.0	Mo/Mo/28 *(approx. 2kVp higher than screen-film technique)*	Yes	Synapse *(Fuji 2Kx2K)* or CEMAX/ICON Autorad Barco *(2.5K x 2K)* with Metheus card, DICOM 3 gray scale display standard	Fuji Dry Laser or FLIM/D wet laser printer
LORAD	1.5-2.0	Mo/Mo/26	Yes	1 x 21 inch monitor	AGFA LR 5200

MGD = mean glandular dose

* Note that this will depend on the choice of the specific site.

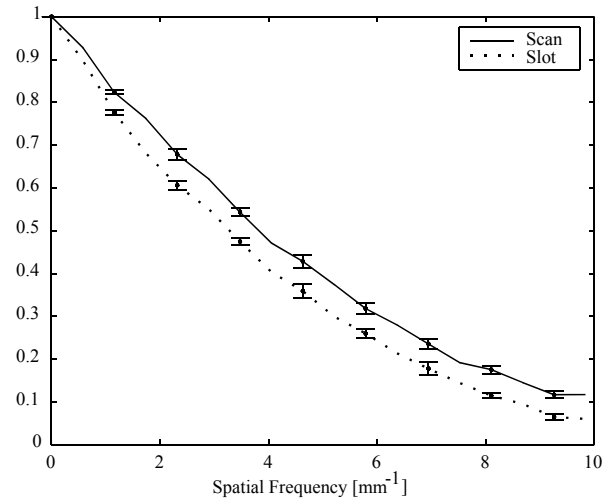
2.3.6 *Performance Characterization*

2.3.6.1 *Fischer Performance Characterization*

Please Note: These measurements were made on a pre-commercial prototype system. Updated measurements for the improved current system are in progress.

MTF and DQE measurements were performed on a clinical slot-scanned digital mammography system *(1996)*, manufactured by Fischer Imaging *(Denver Co.)*, which utilizes a cesium-iodide phosphor coupled to a CCD. The measurements yield a *system* MTF and DQE, which are expected to be lower than those of a detector alone.

Modulation Transfer Function (MTF)
The MTF was measured using the IDMDG MTF tool, behind 4cm of Lucite, using a slanted edge to obtain the pre-sampled MTF [Yaffe 1998, Critten 1996, Shen 2000].



MTF of Fischer prototype machine measured at 40 kVp in both slot and scan directions

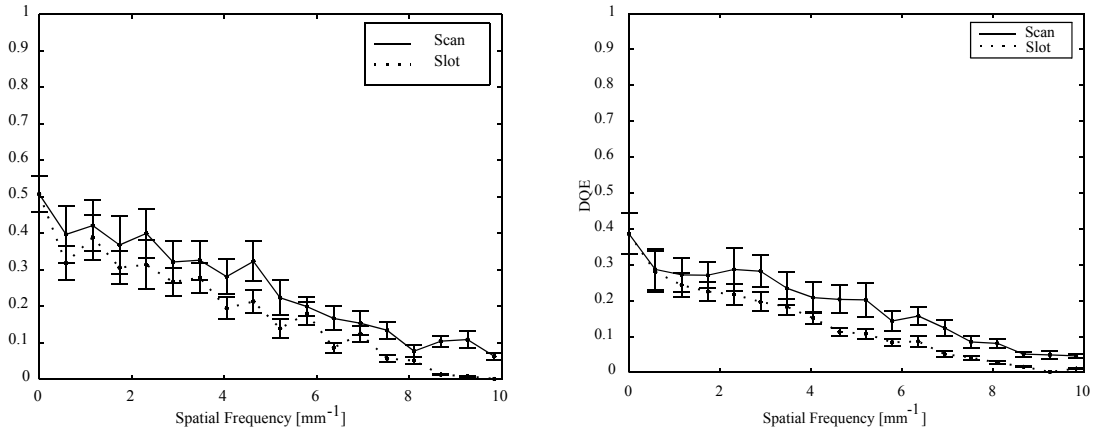
Detective Quantum Efficiency (DQE)
DQE was obtained using:

$$DQE(f) = \frac{S^2 \cdot MTF^2(f)}{\phi \cdot NPS(f)}$$

where S is the mean signal *(in ADU)* of the flat-field image, NPS is in units of ADUxmm^2, ϕ is the fluence in photons/mm^2. The fluence was calculated from the exposure and the mean energy of the incident x-rays.

The flat-field images for noise power spectrum measurement were taken using 4cm of Lucite. The x-ray energy spectra were measured behind 4cm of Lucite using the CZT spectrometer *(Amptek XR100T-CZT).* The exposures were measured behind 4cm Lucite using a Radcal dosimeter *(from the OBSP kit).* The incident fluence was calculated using the mean energy from the measured spectrum and the exposure.

The clinical digital mammography system exhibited a zero spatial frequency DQE of 50% for 26 kVp and 40% for 40 kVp. For the higher x-ray energy, the x-ray absorption efficiency of the phosphor is lower, thereby reducing the DQE. However, all of these detectors exhibit DQE measurements that exceed or are equivalent to screen-film mammography.

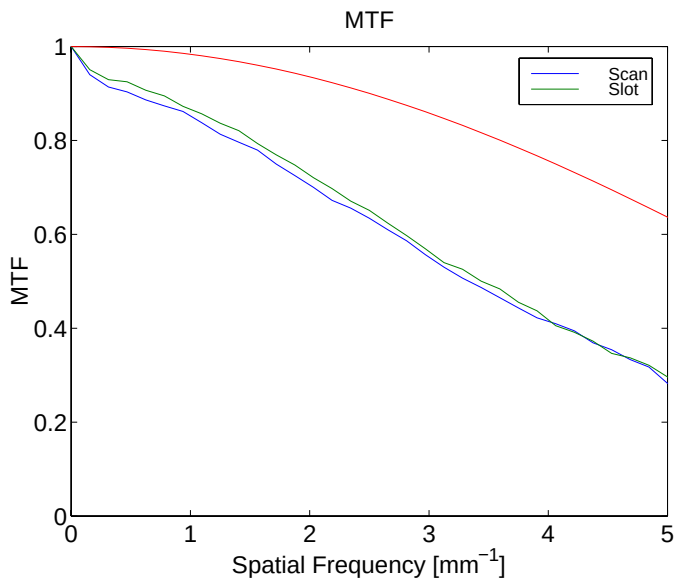


DQE of Fischer prototype system measured at 26 kVp *(left)* and at 40 kVp *(right).*

2.3.6.2 *GE Performance Characterization*

Modulation Transfer Function (MTF)

The MTF was measured using the IDMDG MTF tool, behind 4cm of Lucite, using a slanted edge to obtain the pre-sampled MTF [Yaffe 1998, Critten 1996, Shen 2000].



Detective Quantum Efficiency (DQE)

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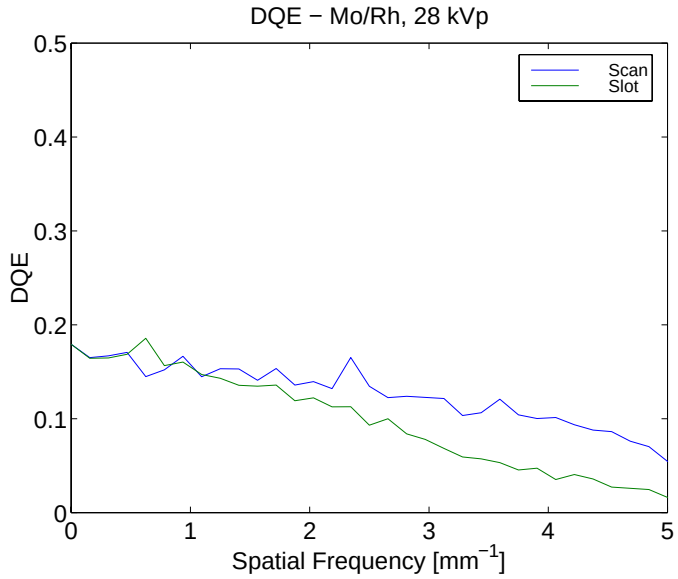
using a Radcal dosimeter *(from the OBSP kit).* The incident fluence was calculated using the mean energy from the measured spectrum and the exposure.

Images were made at various anode-filter combinations for the posted techniques for an "average" breast. The flat-field images were made with 4cm of Lucite, 5 each of bright and dark images per exposure. The images were corrected by performing a flat-field correction using all of the images, which was applied to one image per exposure. To correct for the noise under-estimate, a correction factor of N^2*/(1-2/n+2/N^2).* The incident fluence was calculated using the mean energy from the measured spectrum and the exposure.

Plots from Mo/Rh anode-filter combination at 28kVp, 110mAs. The mean energy for this spectrum is 17.5keV and the exposure was measured at 53.3mR.

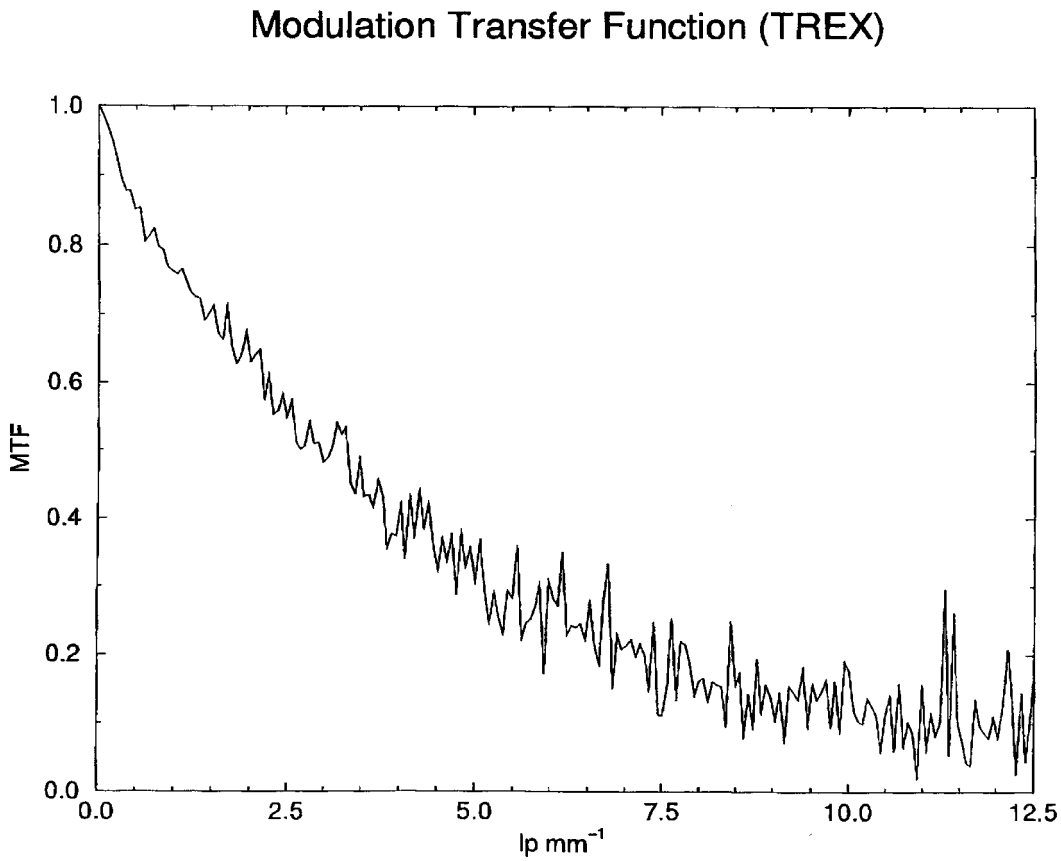


Plots from Rh/Rh anode-filter combination at 28kVp, 100mAs. The mean energy for this spectrum is 18.3keV and the exposure was measured at 57.1mR.

2.3.6.3 *Lorad Performance Characterization*

Modulation Transfer Function (MTF)

The MTF was measured using the IDMDG MTF tool, behind 4cm of Lucite, using a slanted edge to obtain the pre-sampled MTF [Yaffe 1998, Critten 1996, Shen 2000].



Detective Quantum Efficiency (DQE)

DQE was obtained using:

$$DQE(f) = \frac{S^2 \cdot MTF^2(f)}{\phi \cdot NPS(f)}$$

where S is the mean signal (in ADU) of the flat-field image, NPS is in units of ADUxmm^2, ϕ is the fluence in photons/mm^2. The fluence was calculated from the exposure and the mean energy of the incident x-rays.

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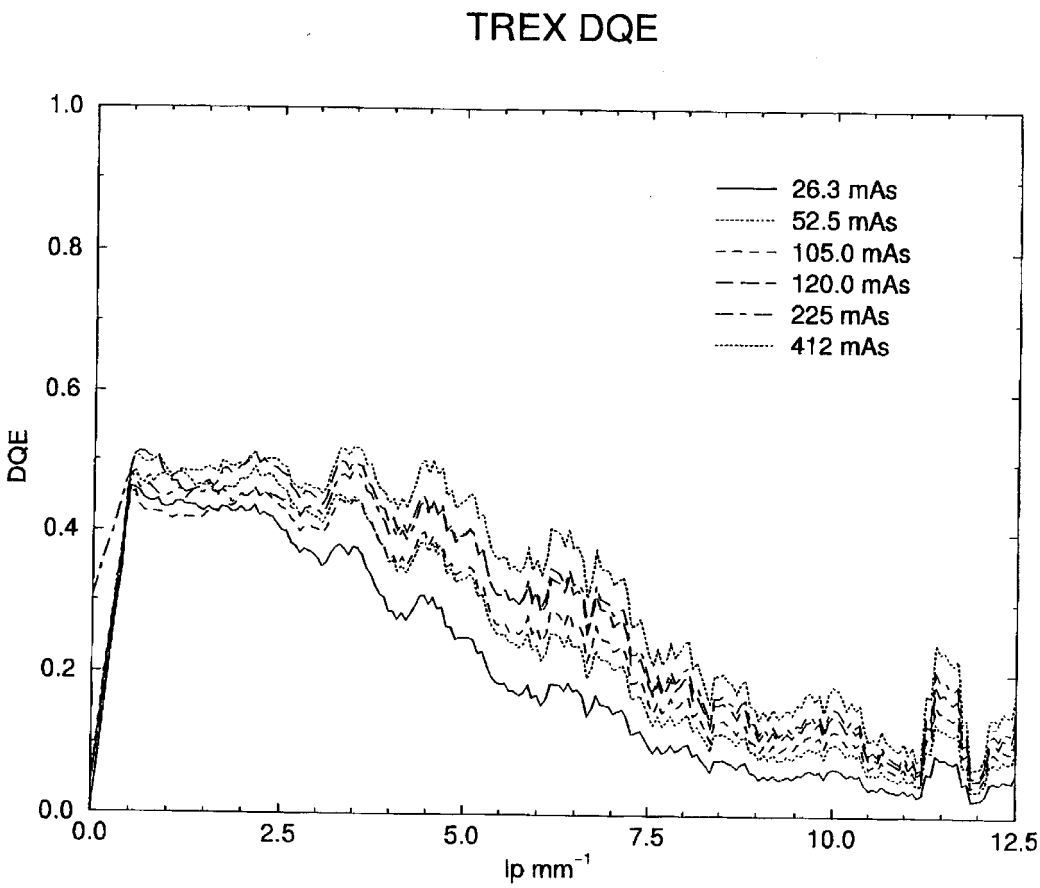
The clinical digital mammography system exhibited a zero spatial frequency DQE of 50% for 26 kVp and 40% for 40 kVp. For the higher x-ray energy, the x-ray absorption efficiency of the phosphor is lower, thereby reducing the DQE. However, all of these detectors exhibit DQE measurements that exceed or are equivalent to screen-film mammography.



2.4 Image Presentation

There are currently two ways digital mammography studies are presented: hardcopy *(laser-printed film)* and softcopy *(Cathode Ray Tube (CRT) displays)*. Each of these display types has its advantages and disadvantages for digital mammography.

2.4.1 *Hardcopy (Film)*

Laser printers for digital mammography are available from several vendors at this time. They support spatial resolutions comparable to screen-film mammography *(up to 4800x6400 pixel matrix size)*, and with the reproduced size capable of matching the acquisition resolutions of current scanners *(down to 41 micron spot size)*. The gray scale range is roughly similar to that of mammography film, with laser-printed films achieving maximum optical density *(OD)* of 3.5 to 4.0, while mammography films can achieve maximum OD's slightly over 4.0. Laser-printed films generally are not subject to the same level of processor variability or processor artifacts that are present with single-emulsion screen-film mammograms. Furthermore, laser-printed films allow radiologists to use the same reading protocols as they use currently in interpreting screen-film images. Films can be hung on a multi panel viewer with standardized layout, and a "hot light" and magnifying lens can be utilized readily. This takes advantage of the significant training and familiarity that radiologists have in interpreting screen-film mammograms.

The disadvantages of using laser-printed film are cost and the availability of only one presentation format per sheet of film. The costs include the time expended for printing and development as well as the personnel and supplies needed for these tasks.

Furthermore, if more than one processed version is needed to get the maximum amount of information from a mammogram, more than one version would have to be printed. This would be impractical, especially in a screening setting where speed and efficiency are essential to keep costs low. An additional disadvantage of film display is the loss of dynamic range inherent in displaying a 12 to 14 bit image at 8 bits [Feig].

2.4.2 *Softcopy*

Currently, only CRT technology supports the requirements of softcopy display for digital mammography. The best high quality CRT technology, 100-150ftL, 2048x2650 pixel matrix, is quite limited compared to film. The spatial resolution is less than one quarter of film resolution, and the luminance range is significantly lower. However, both of these factors can be mitigated. Full spatial resolution is possible through "roam and zoom" techniques but this must take place seamlessly so that reading on a monitor is similar to reading mammograms on film with a magnifying glass. Further, the luminance difference may not be that important. Two studies [Hemminger, H. Roehrig] have demonstrated that mammography feature detection performance does not degrade when softcopy display luminance ranges are used instead of mammography lightbox ranges. However, larger scale performance studies evaluating the effect of display characteristics on the detection and diagnosis of different mammographic features are required.

The advantage of softcopy is its flexibility. A large number of presentations of an image can be available instantaneously at the push of a button. This allows for the application of image processing specific to lesion type, or mammographic task *(screening vs. diagnosis)*. The digital image can be adjusted on-line to allow for immediate evaluation of questionable areas.

While softcopy presentation holds the greatest promise for realizing the full advantage of digital mammography, currently available commercial implementations are lacking. Current systems are not fast enough, and do not provide support for evaluation of the current examination along with previous images for comparison, nor do they allow for the ready rapid visualization of extra views frequently obtained in a diagnostic work-up. In addition, the user interfaces are awkward to use and they are not tuned to the specific tasks of screening and diagnostic readings.

At least two noncommercial digital mammography workstations that apparently overcome these limitations have been displayed at the Radiological Society of North America *(RSNA)* meetings in Chicago. [Hemminger 1998, Zhang]. Clinical testing of systems at UNC and UCSF is already underway, funded by two separate Department of Defense grants *(Edward Sickles, UCSF and Etta Pisano, UNC, Principal Investigators).*

2.5 Image Processing for Display

Image processing is critical for the success of digital mammography, as it is for all projection radiographic imaging systems. In addition, mammography requires specific processing to achieve images suitable for the different mammography reading purposes. Recent results of an IDMDG preference study suggest that different presentation formats are appropriate for different clinical tasks *(screening vs. diagnosis)* and for the diagnosis of different lesion types *(calcifications vs. masses)*. In addition, the type of image processing preferred by radiologists differed by machine-type *(Fischer vs. GE vs. Lorad)*.

The study utilized 28 digital mammograms obtained on Fischer, GE and Lorad devices. Most of the cases used had mammographic lesions that had undergone biopsy, and all had at least one mammographic finding that was presumed benign by virtue of stability since prior mammograms. Twelve radiologists reviewed eight different processed versions of these same cases and ranked the images relative to the accompanying screen-film mammograms for their ability to depict the features of the lesion that best revealed the known diagnosis. The algorithms studied were Manual Intensity Windowing *(MIW)*, Histogram-based Intensity Windowing *(HIW)*, Mixture Model Intensity Windowing *(MMIW)*, Contrast Limited Adaptive Histogram Equalization *(CLAHE)*, MUSICA *(Agfa®)*, Unsharp Masking *(UM)*, Peripheral Equalization *(PE)* and Lorad® processing. These choices were based partially on preliminary laboratory studies. [Puff 1992 and 1994, Pisano 1997A, 1997B, and 1998B] Of course, all potentially useful algorithms could not be included in this study.

Interestingly, the radiologists preferred different processing methods for the diagnosis of masses than for the diagnosis of calcifications, and the preferred method varied by machine type. In addition, this same study found that processing methods preferred for the purpose of screening differed from those chosen for lesion characterization or diagnosis. This implies that multiple presentations should be utilized, especially in the diagnostic situation. Thus, at least three different presentations may be desirable for the same case *(a screening presentation, and a presentation to evaluate calcifications and a presentation to evaluate masses)* [Pisano 1998C].

Given these results and those of others [Higashida, Cowen 1992, Oestmann, Kheddache], the diagnostic accuracy of digital mammography will depend not only on the acquisition device itself but also on the processing method utilized for image display. Further, if poor choices are made, diagnostic accuracy might be worse than for screen-film mammography. It is extremely important to determine what image processing methods would be appropriate both for screening and the diagnostic evaluation of calcifications and masses.

2.6 Industry-Sponsored Clinical Trials

On June 19, 1996, the FDA published "Information for Manufacturers Seeking Marketing Clearance of Digital Mammography Systems." This document is still available on the World Wide Web ***(http://www.fda.gov/cdrh/ode/diqmammo.html)***. It outlined a requirement that manufacturers conduct a clinical trial designed to show agreement between screen-film mammography and digital mammography if devices were to become FDA-approved through the 510*(k)* or Premarket Approval *(PMA)* mechanism. Manufacturers were instructed to discuss the proposed investigational plans with the FDA's Center for Devices and Radiological Health *(CDRH)*.

The FDA specifically indicated within their guidance document that the probability of a positive digital mammogram should be greater than 0.90 if the screen-film mammogram were positive and the probability of a negative digital mammogram should be greater than 0.95 if the screen-film mammogram were negative. In addition, the FDA estimated that 520 women *(260 with abnormal screen-film mammograms and 260 with normal screen-film mammograms)* would be needed in a trial to achieve such an estimate of agreement. There was no requirement that manufacturers determine truth about the presence or absence of cancer in the participant, only that the screen-film mammogram interpretation and the digital mammogram interpretations agreed.

All four manufacturers designed agreement studies, which were discussed extensively with the CDRH. Recruitment to clinical trials was begun shortly thereafter. The trials that were carried out were quite similar, as would be expected since the FDA provided a blueprint for the manufacturers to follow.

Specifically, the Fischer trial, led by Pisano, enrolled 570 women at four institutions *(UNC, Thomas Jefferson, Sally Jobe Clinic in Colorado and Brook Army Medical Center)*. The cohorts were women with BIRAD interpretation codes 3, 4 or 5 on the diagnostic mammograms and women with symptoms.

The GE trial, led by Hendrick, enrolled 652 women at four centers *(University of Colorado, University of Massachusetts, Massachusetts General Hospital and the University of Pennsylvania)*. The cohorts were women presenting for screening mammography and women presenting for diagnostic mammography.

The Lorad trial, led by Fajardo while she was at the University of Virginia, enrolled 520 women at two centers *(University of Virginia and Good Samaritan Hospital in New York)*. The cohorts were women with normal screening mammograms and women with abnormal screening mammograms. All studies utilized radiologist readers interpreting the screen-film and digital mammograms of the enrolled participants and measured agreement of these readings. Lorad submitted the data obtained using this protocol to the FDA in early December 1997.

Information on a Fuji agreement study protocol is not available. There are apparently three institutions designated to acquire cases with the cases to be read at an additional site. No further information about this protocol is available from the company or from the literature.

Unfortunately, the FDA's guidelines were flawed in that the level of agreement required for digital mammography with screen-film mammography was not attainable even with screen-film mammography compared to itself, because of intra- and inter-reader variability. [Howard, Elmore, Beam 1996]

This issue was discussed at a meeting of the Advisory Panel convened by the FDA on August 17, 1998. On February 8, 1999, the FDA revised their guidance document and notified the manufacturers that the clinical section was no longer valid. Letters were sent to all of the manufacturers, that have not been made public, that indicate that the digital mammography FDA approval trials must now be based on truth regarding breast cancer status and not direct agreement with screen-film mammography. That is to say, sensitivity and specificity, as measured by a methodology like Receiver Operating Characteristic *(ROC)* analysis, must now be reported.

All manufacturers subsequently negotiated with the FDA on protocol revisions so as to meet these new requirements. These new efforts have and will center on running reader studies utilizing sets of mammograms that contain multiple cases with biopsy-proven lesions. This might involve enrolling additional women or collecting additional cases from the existent databases at participating centers.

General Electric presented data to an FDA panel on December 16, 1999. PMA-approval

of the GE unit was granted on January 31, 2000. The other manufacturers are expected to submit data and receive FDA approval sometime before January 2001.

2.7 Federally-Funded Clinical Trials on Digital Mammography

There have been two federally funded clinical trials opened to date. One of the trials compares digital mammography to screen-film mammography for the diagnostic mammography population. The other trial compares General Electric digital mammography to screen-film mammography for the screening mammography population.

The diagnostic mammography trial, funded by the Office of Women's Health, was run under the auspices of the IDMDG *(Etta Pisano, University of North Carolina, PI)* and enrolled 210 women at 8 centers. Table 2 lists the centers involved in this study, the Principal Investigator at each site and the type of digital mammography unit used at that site. Two participant cohorts were enrolled, Group A and Group B.

Group A consisted of all consecutive women with mammographically dense breasts who presented to the participating mammography clinics for problem-solving mammography and who were scheduled to undergo either open or percutaneous large core needle breast biopsy within the 12 weeks after the eligibility mammogram. Women with palpable and/or nonpalpable lesions were included in this group.

Group B consisted of a random sample of women with mammographically dense breasts who presented to the participating mammography clinics for problem-solving mammography, who were not scheduled to undergo biopsy, and who were recommended for 1-year follow up.

Table 2
Office of Women's Health Clinical Trial

Institution	Machine Type	PI
University of Pennsylvania	GE	Emily Conant
Massachusetts General Hospital	GE	Dan Kopans
University of Toronto	Fischer	Rene Shumak
Mount Sinai Hospital	Fischer	Roberta Jong
Thomas Jefferson	Lorad	Stephen Feig
University of North Carolina	Fischer	Etta Pisano
Good Samaritan Hospital	Lorad	Melinda Staiger
University of Virginia	Lorad	Laurie Fajardo

Accrual to this trial has been completed. Eighteen radiologist readers interpreted images, either in screen-film format, manufacturer's printed digital format *(default)* or in digital processed format with Histogram-based Intensity Windowing *(HIW)* or Contrast Limited Adaptive Histogram Equalization *(CLAHE)* image processing. Readers scored all cases using a 6-point scale and ROC analysis was utilized. The results are currently under analysis.

This study will serve as a pilot study for another larger clinical trial funded by the Department of Defense *(Laurie Fajardo, JHU, PI)*. An additional 1075 women in essentially the same participant cohorts will be enrolled at 6 centers.
Table 3 shows the institutions and investigators involved and the type of digital mammography equipment that will be utilized at each site. A larger reader study of all

1275 cases will take place at the end of accrual.

Table 3
Department of Defense Center Clinical Trial

Institution	Machine Type	PI
Johns Hopkins University	Lorad	Laurie Fajardo
University of Pennsylvania	GE	Emily Conant
University of Toronto	Fischer	Rene Shumak
University of North Carolina	Fischer	Etta Pisano
Good Samaritan Hospital	Lorad	Melinda Staiger
University of California-LA	Lorad & GE	Lawrence Bassett

Both of these studies are somewhat limited by the fact that they rely on the presence of physical examination findings or an abnormal screen-film mammogram to select eligible participants. This may cause an underestimate of the diagnostic accuracy of digital mammography. An underestimate of the efficacy of digital mammography is possible because of the study design since some participants enter the study by virtue of the visibility of their breast lesions on screen-film mammography while no participants enter the study by virtue of the visibility of their breast lesions on digital mammography. Therefore, it would be difficult for digital mammography to perform better than screen-film mammography in such a population.

The only other federally funded clinical trial that is currently open is a screening study utilizing only General Electric digital mammography equipment, funded by the Department of Defense *(Edward Hendrick, UCHSC, PI)*. This study will ultimately enroll 15000 women over age 40 presenting for screening mammography at two centers, UC and the University of Massachusetts *(Carl D'Orsi, University of Massachusetts Medical Center (UMMC), co-PI)*. To date, approximately 4000 women have been enrolled *(personal communication, John Lewin, UCHSC, 2/26/99)*. The unique aspect of this study is that the work-up of lesions proceeds based on the findings of either digital or screen-film mammography. This is a significant strength of this study in that it allows for cancers to be detected by either modality.

Interim analysis of the data revealed that approximately equal numbers of cancers had been missed using each modality *(5 of 22 cancers missed by screen-film and 6 of 22 cancers missed by digital)*. In addition, digital mammography had a lower recall rate *(11.5% vs. 14.1%)* and a higher positive biopsy rate *(43.3% vs. 23.7%)* than screen-film mammography. [Lewin] All digital cases were read using softcopy display. It is possible that the reduced false positive rate for digital compared to screen-film mammography was because of this factor. That is to say, immediate manipulation of the image allowed for some on-line assessment of areas of concern that would ordinarily have required another participant visit and additional mammographic views.

Of course, the results reported to date are only preliminary and more precise estimates of sensitivity, specificity, and positive and negative predictive value of GE digital mammography over screen-film mammography for the screening population will be obtained at completion of the whole study.

2.8 Rationale for Proposed Research

The OWH study that will be completed shortly, along with the DOD study just underway, will evaluate the effect of digital vs. screen-film mammography in the

diagnostic mammography participant population. The second study, a full-fledged screening trial, has completed enrollment of approximately 5000 women utilizing the digital mammography unit of only one manufacturer, GE. Obviously, digital will have to prove its value in the screening setting as well as the diagnostic setting if it is to replace screen-film mammography.

We believe that a screening trial should include all available equipment from all manufacturers since that would allow a generic statement about the diagnostic accuracy of digital mammography vs. screen-film mammography. However, mixing together images acquired using the various digital mammography units into one study could potentially confound the results, especially if one or more of the systems perform significantly differently than the others. At a minimum, to detect machine-type differences in the outcome of a large screening study that included more than one machine type, one would have to include a large number of cases acquired using each piece of equipment. The numbers of cases per machine type would have to be determined by careful power calculations based on preliminary work and the available literature.

In order to minimize the differences that might be present between machines, a single large trial should be run that has rigorous quality control standards that all devices would have to meet. In this way, much like the MQSA sets standards for all different types of screen-film mammography systems, similar standards could be set and followed so that the machine differences would be reduced. This will allow statements regarding the benefits of digital mammography vs. screen-film mammography when both technologies meet high quality control standards.

Two other potential confounders for all clinical digital mammography trials are the display method *(softcopy vs. printed film)* and image processing algorithms applied to all images. Selecting the appropriate image processing for display of the digital mammograms is important and may significantly affect the outcome of all clinical trials involving digital mammography. Whatever is used should be standardized across all readers within any trial. Ideally, each manufacturer should make recommendations regarding how their own images should be printed or displayed on softcopy. In addition, the digital data should be stored for future reader studies in case another display algorithm is developed that might allow better performance.

Finally, for prior breast cancer screening trials, mortality from breast cancer has served as the most important outcome measure. This is neither possible nor realistic for digital mammography. The window of opportunity for performing such a study is quite narrow. Now that digital mammography is FDA approved, it will gradually become widely available. The longer the delay in opening a screening trial, the higher would be the probability that the results would be confounded by crossover of participants between the two systems and non-compliance. Surrogate end-points, such as those selected in the UCHSC/UMMC screening study, i.e. sensitivity and specificity, positive and negative predictive values, and ROC curve differences, seem practical and realistic for the currently proposed screening trials for digital mammography.
Finally, the issue of cost-effectiveness of this new technology compared to standard screen-film technology is of course an important issue. [Nields] Because of the software and hardware involved, digital mammography will likely cost more to provide than screen-film mammography. **At a minimum it must outperform the current technology**

if it is to be widely adopted. Digital mammography will not be an attractive alternative to screen-film mammography if it is only equivalent in diagnostic accuracy.

2.9 Proposed Research

This trial will enroll 49,500 women at at least 35 institutions. Given that approximately 6-7 women can be enrolled per day at each site, we expect the enrollment period to last for 18 months.

All women enrolled into the study will undergo both digital and screen-film mammography. The same mammography technologist will perform both examinations on an individual woman on the same day. All technologists performing studies for this protocol will be qualified to take mammograms under the U.S. Mammography Quality Standards Act *(MQSA).*

3.0 SPECIFIC AIMS

PRIMARY SPECIFIC AIM

3.1 To compare the diagnostic performance of digital mammography and screen-film mammography, as measured by the area under the ROC curve, sensitivity, specificity, and positive and negative predictive values in a prospectively enrolled screening cohort of asymptomatic women, across all digital mammography machine types.

SECONDARY SPECIFIC AIMS

3.2 To conduct four retrospective reader studies to determine the diagnostic accuracy of the digital mammograms obtained using each of the individual manufacturer's digital mammography units vs. screen-film mammography.

3.3 To assess the effects of participant characteristics, including age, lesion type, pathologic diagnosis, menopausal and hormonal status, breast density and family history on measures of diagnostic accuracy for digital mammography.

3.4 To assess the effects of technical parameters, including display type, machine type, and detector spatial and contrast resolution on measures of diagnostic accuracy for digital mammography.

3.5 To use collected accuracy, resource utilization and Quality-Adjusted Life Year *(QALY)* data to model the cost-effectiveness of digital mammography vs. screen-film mammography in a screening population.

3.6 To assess the effect of reduced false positive mammograms that are expected with digital mammography on the health-related quality of life and personal anxiety of women undergoing the screening mammography experience.

3.7 To conduct retrospective reader studies to assess the relation between the diagnostic performance of digital mammography and the rate of cancer in the set of cases that are utilized.

3.8 To conduct retrospective reader studies to determine the effect of softcopy vs. printed film display on the diagnostic performance of digital mammography.

3.9 To conduct a retrospective reader study to determine the effect of breast density on the diagnostic accuracy of digital mammography vs. screen-film mammography.

3.10 To determine the differences in image quality and breast radiation dose in digital and screen-film imaging among all participating study sites.

3.11 To assess temporal variations in image quality, breast radiation dose, and other quality control parameters at all participating study sites during the course of the screening trial.

4.0 PARTICIPANT SELECTION AND ACCRUAL

4.1 Inclusion Criteria

4.1.1 All consecutive women presenting for screening mammography at the participating institutions will be eligible.

4.1.2 Signed study-specific informed consent. See Appendix I.

4.2 Exclusion Criteria

4.2.1 All women who have presented with a complaint of a focal dominant lump or a bloody or clear nipple discharge.

4.2.2 All women who have breast implants.

4.2.3 Any woman who is pregnant or has reason to believe that she might be pregnant.

4.2.4 Participants who cannot, for any reason, undergo follow-up screen-film mammography at the participating institution or provide mammograms from another institution for review for one year after study entry.

4.2.5 All women with a history of breast cancer treated with lumpectomy. *Note: Women with a history of breast cancer treated with mastectomy who have now returned to a screening population will still be included in the study.*

4.3 Determining Participant Eligibility and Recruitment

At each institution the Research Associate *(RA)* will determine the eligibility of the women presenting for screening mammography by obtaining the names of all women scheduled for screening mammography for that day. This may be accomplished prospectively by checking the schedule of screening mammograms in advance. The RA may contact participants scheduled for their screening mammogram to determine if they are interested in being a part of this research project. Women who express an interest in participating will be scheduled to meet with the RA on site the day of their appointment. The RA will obtain study-specific informed consent, complete participant demographic information forms about the participant directly on the ACRIN website, or onto copies of the forms on a laptop computer that is not connected to the web site for sites without immediate internet access in the participant recruitment space. Each institution participating in the trial will be allowed to log on to the web based data collection module and download a registration form with a specific case number and pre-assigned treatment option. The system will generate random treatment assignments for these cases and balance the arm across the institution for the study prior to the download. For the first instance when there is no case registered for the institution a block of 12 case numbers will be generated. Subsequent to successful completion and submission of six cases, another block of six case numbers can be requested for further registration. *(See Section 4.4.)* The computer will assign a participant-specific study ID number. The digital mammogram will be labeled with that number only, without other identifiers. The screen-film mammogram will be labeled as per standard procedures for the site. All data forms for the reader interpretation study for that participant will contain the assigned study number, without other identifiers, to ensure participant confidentiality. In addition, for two weeks of accrual, a log of all eligible participants will be kept at each site so that the representativeness of the participant sample from each site can be determined. During those two weeks, minimal information regarding age and race will be collected for all patients not enrolled in the study. This log should be completed during two separate weeks of the study accrual period, once early in the accrual period and a second time toward the end of study accrual. The weeks for the collection of this data will be selected by the BDMC for each participating site.

4.4 Participant Entry Procedures

4.4.1 *Determining Eligibility*

Before a participant can be registered using the Online Registration System found on

the ACRIN website ***(www.acrin.org)***, the ACRIN clinical Research Associate must verify the participant's eligibility for this study and obtain study-specific informed consent. The RA must first complete the Eligibility Checklist *(Appendix III)* to verify that the participant has all study characteristics. The completed, signed, and dated checklist used at study entry must be retained in the participant's study file and will be evaluated during an institutional audit.

In the event that a participant has already been registered via online registration/laptop, when the RA determines that the participant is ineligible at the present time, does not wish to participate or, can not participate that day, the RA should urge the participant to return at a time the participant will be eligible. The RA should contact Data Management who will cancel the case. When the participant returns, she should be enrolled as if she were a new participant.

4.4.2 *Additional Work-Up*

For the DMIST study, it would be preferable for the radiologist reading the additional work-up images to be an ACRIN DMIST reader.

If a radiologist other than one of the five DMIST readers must read a protocol participant's work-up images, that person should complete the forms regarding the work-up images (including biopsy). The local site PI must provide contact information and Human Subject certificates for these individuals to ACRIN Headquarters.

In addition, it is the responsibility of the PI of each institution to educate the non-ACRIN Readers on the scales used on the forms that they will be completing.

If a participant goes to an outside, non-DMIST facility for work-up imaging, it is the responsibility of the local PI to obtain outside films for review and coding on the DMIST forms. If the study radiologists do not agree with the results of the work-up, or if they deem the work-up to be incomplete, the participant should be notified and offered additional work-up, as suggested by the local DMIST readers, at the DMIST facility where she was enrolled.

If a participant undergoes biopsy at an outside facility, appropriate slides should be obtained for central review by the DMIST pathologists. The participant has consented to this central review and so the local site PI should request that the appropriate reports and slides be sent to the DMIST site for submission to the central pathologist.

Please send email or fax information on non-DMIST radiologists to:

Jessie Ann Flaim-Spetsas
ACRIN/1101 Market Street, 14th Floor
Philadelphia, PA 19107
Fax: 215.717.0936
Email:jflaim@phila.acr.org

4.4.3 *IRB Approval and Informed Consent*

All institutions must have study-specific IRB approval. Eligible participants will be identified prospectively or on the day of the screening mammogram visit at participating institutions and will be approached by the RA to determine whether they are willing to participate in the study. The RA will explain the nature of the study and

indicate that there will be no direct medical benefit to the individual. Potential risks or discomforts from participating in the study will be explained. See the sample study-specific consent form in Appendix I. If the participant qualifies for the study, the RA must obtain the participant's consent to participate in this research. RA's must follow OHRP-approved consent procedures, as well as those set by the Institutional Review Board *(IRB)* at the institution. A copy of the IRB approval and the sample institutional study-specific consent form must be on file at ACR headquarters *(fax: 215-574-0300)* prior to obtaining case numbers or randomization.

4.4.4 *Using the Online Registration System*

Once a participant has consented, the RA will register her within two business days by logging onto the ACRIN web site and selecting the link for new participant registrations. The system triggers a program to verify that all regulatory requirements *(OHRP assurance, IRB approval)* have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the participant was found to be eligible on the basis of the checklist and the date the study-specific informed consent form was signed. Documentation that the checklist was completed must be kept as part of the participant's study file. The registration program also asks several demographic and medical history questions about the participant.

Once the system has verified that the participant is eligible and that the institution has met regulatory requirements, it assigns a participant-specific case number. The system then moves to a screen, which confirms that the participant has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the participant's record. The system creates a case file in the study's database at the DMC and generates a data submission calendar listing all data forms, images and reports and the dates on which they are due.

For sites without immediate access to the internet in their participant recruitment areas, prior to the first case registering, ACRIN will provide a block of 12 registration numbers with randomization in advance of each clinic day. Data at these sites will be entered into a laptop computer and uploaded to the ACRIN website at the end of the day. Additional study specific registration numbers will be provided in blocks of six to a site as each previously assigned number has been used and data for the participant assigned to that number has been uploaded to the ACRIN website.

4.4.5 *Data Security*

The registration system has built-in security features which encrypts all data for transmission in both directions preventing unauthorized access to confidential participant information. The web site is equipped with authentication and encryption power by using 128-bit SSL (secured socket layer) certificates. The Server ID included with the Site Trust service enables visitors to verify the site's authenticity and to communicate with it securely via SSL encryption, which protects confidential information from interception and hacking. 128-bit SSL enable the world's strongest SSL encryption with both domestic and export versions of Microsoft and Netscape browsers. Access to the system will be controlled by a sequence of identification codes and passwords.

4.4.6 *Unsuccessful Registrations*

If either the participant is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the participant. This screen can be printed.

In the unlikely event that the ACR web registration site is not accessible, participating sites may still register a participant by faxing the completed eligibility checklist to the

Data Management Center *(DMC)* at the ACR *(215-574-0300, ATTN: PARTICIPANT REGISTRATION)*. ACR staff will fax a response to the registering site with the confirmation of registration, randomization assignment, and participant case number as soon as possible.

4.4.7 *DMIST Registration Procedure in instances of Web Server Interruption*

ACRIN's first preference is to use the laptop application. Refer to section 4.4.4 for above for a more detailed description of these procedures, and to the Procedure Manual for additional instructions. ACRIN will provide training from the ACRIN RA trainer in the use of the laptop at the time each institution opens, via a conference call for institutions that were already open when this policy went into effect, and by telephone to those who need further assistance at any time during East Coast business hours.

If you have no case registration numbers available on your laptop, or your laptop is not functioning, and it is between 8:00 a.m. and 5:00 p.m. Eastern time, then you should proceed with telephoned registration.

- Call ACRIN's registration @ **215 574-3191** to inform them that the web is down and a fax will follow
- Complete the eligibility checklist (Appendix III in the protocol) and fax it with the following information to the Data Management Center @ **215- 574-0300, Attn: Participant Registration:**
  a. Your Name
  b. Phone Number
  c. Your Fax Number
  d. Your Institution Number
  e. Eligibility Form

Please be patient and allow Registration at least 15 minutes before you call back. If you are having trouble getting through, please call 1-800-574-5463 Ext 4183 or, 215-574-3183 and press "00". Ask for Jessie Ann Flaim or Boris Ginsburgs.

AT ANY TIME WHEN YOU USE EITHER PHONE NUMBER, YOU CAN PRESS "00" AND SPEAK WITH AN OPERATOR.

5.0 DATA COLLECTION AND MANAGEMENT

5.1 General

5.1.1 The ACRIN web address is *www.acrin.org.*

5.1.2 Data collection and management will be performed by the Biostatistics and Data Management Center *(BDMC)* of ACRIN under the direction of Dr. Constantine Gatsonis. The Biostatistics Center *(BC)* is located at Center for Statistical Sciences in Providence, RI, and the Data Management Center *(DMC)* is located at the American College of Radiology's Data Management Department in Philadelphia.

5.1.3 The BDMC uses screens on the ACRIN web site to register participants, collect participant data, and maintain calendars of data submissions for each participant. By using the World Wide Web, ACRIN has made participant registration, data entry, and updated calendar information available to clinical sites 24 hours a day.

5.2 Clinical Data Submission

5.2.1 As soon as a participant has been registered, the RA may download the participant's data submission calendar, which lists all forms and/or designated reports required by protocol, along with the date that each form is due at the DMC. These calendars will

be updated as the study proceeds to reflect data that has been received, reply deadlines for queries about unclear data, deadlines for follow-up reports of adverse events or changes in the protocol, which might change the data being collected or their timing. Updated calendars for each participant can be obtained 24 hours a day from the ACRIN website.

5.2.2 An investigator is obliged to submit data according to protocol as detailed on each participant's calendar as long as the participant is alive and the case status is designated as open or until the study is terminated. The case is closed when all data have been received and reviewed and no outstanding query exists for the case.

5.2.3 To submit data via the ACRIN website, the RA or investigator logs onto the web site, and supplies the pre-assigned user name and password. (Staff at institutions are not allowed to share passwords; all individuals should have their own.) Case report forms will be available on the web site through a series of links. The user selects the link to the appropriate form and enters data directly into the web-based form. As information is entered into the case report form, various logic checks will be performed. These logic checks look for missing data, data that is out of range, and data that is of the wrong form *(e.g. character data in a field requiring numeric responses)*. Such errors will be detected as soon as the user attempts to either submit the form or to move to the next page. They must be corrected before the form is transmitted to the DMC. The user will not be able to finalize form transmission to the DMC until all data entered passes these logic checks. Forms that are not completed in one sitting can still be submitted and completed at a later date. The data is transferred to the DMC and held.

5.2.4 Once a form is complete, the investigator presses the SUBMIT button on the participant calendar and the data is transferred into the clinical database. No further direct revision of the submitted data is allowed after this point. An email is generated and sent to the site listing all of the data completed and just submitted. Should a problem occur during transmission, this automated response supplies an explanation and instructions for resubmitting the data.

5.2.5 If a temporary problem prevents access to the Internet, investigators should wait until access is restored to submit data. Investigators should notify the DMC (215-574-3245) of the problem and an estimated time at which access is expected to be restored. If access will be unavailable for an extended period, sites must seek another Internet Service Provider *(ISP)*. On a short-term basis, the ACR can serve as an ISP.

5.2.6 *Data Collection Forms*

1) **The Eligibility Checklist *(Appendix III)*.** This form is to be completed by the RA at the clinical site before registration to confirm participant eligibility for the clinical trial. It must be kept in the participant's file.
2) **I1 Form**: The Patient Enrollment Form. This form is to be completed by the RA at the time of enrollment at the clinical site where a participant is enrolled. It includes information about participant and history.
3) **LX Form**: The Eligible Patient Not Enrolled Form. This form is to be completed during two selected weeks by the RA at the clinical site where a participant is eligible to be enrolled into the study but, for any reason other than not meeting eligibility requirements, she is NOT enrolled. The two weeks when this log form should be completed will be selected by the BDMC. One week will be early in the accrual period and the second week will be toward the end of study accrual.
4) **IA Form**: The Study Mammogram Interpretation Form-Screen Film. This form is to be completed by the radiologist who interprets the participant's screen film study mammogram, and gives the interpretation of that mammogram.

5) **ID Form**: The Study Mammogram Interpretation Form-Digital. This form is to be completed by the radiologist who interprets the participant's digital study mammogram and gives the interpretation of that mammogram.

6) **IM Form**: The Additional Work-Up/Prior Films Form. This form is to be completed by the radiologist who completes additional imaging work-up of enrolled participants based on findings seen on the **initial** study screen-film or digital mammogram. This form is also used to report any reinterpretation of initial study images that occur once prior films have been received. It includes recommendations for follow-up and additional imaging studies.

7) **BX Form**: The Biopsy Form. This form is to be completed by a radiologist at the clinical site for women enrolled in this clinical trial who undergo open surgical, core biopsy, or FNA at any time during the 15 months after enrollment in this study.

8) **PL Form**: The Pathology Interpretation Form. Part of this form is to be completed by the local RA, and then it is sent to the pathology consultant, who will record the interpretation of all surgical, core biopsy, and FNA specimens as determined by the pathology or cytology reports for all participants enrolled in this clinical trial.

9) **P4 Form**: Part of this form is to be completed by the local RA, and then it is sent to the pathology consultant to record her own interpretation of the available pathologic material on all participants who undergo FNA, core biopsy or open surgical biopsy during the year after enrollment in this clinical trial.

10) **PO Form**: This form is to be completed by a second pathology consultant to record his or her interpretation of the available pathologic material on all participants who require two opinions. These include all participants on whom there is substantial disagreement between the diagnosis recorded on the PL form, and on the P4 form.

11) **F1 Form**: This form is required for all participants except those who have been diagnosed with bilateral breast cancer within the first 12 months after enrollment. It is used to record the findings from a mammogram taken 10-15 months from the date of enrollment. This form is also used to record the findings of short term interval follow-up, if any, recommended on the basis of the initial screening images or on the basis of the 1-year follow-up exam (3, 6, 9, 15, 18, or 21 months from enrollment).

12) **TA Form**: The Technical Assessment Form. This form will capture technical factors relating to the screen film and digital mammograms. The TA form will be collected on the first 100 participants enrolled at each site for both digital and film screen mammogram acquisition. This sampling will be used to determine the need for subsequent sampling during course of accrual. It may also be required for an additional 50 cases during the second year of the study.

13) **CS Form:** Cover sheet for all Quality of Life forms *(QP, QL, QF)*. This form is to be submitted for all cases as outlined in Section 10.2.

14) **QP *(EQ5D and STAI Y-6)* Form:** Quality of Life and Anxiety Form *(pre-screen as per Section 10.2)*. See Section 10.0 for specifics.

15) **QL *(EQ-5D and STAI Y-6)* Form:** Quality of Life and Anxiety Form *(baseline as per Section 10.2)*. See Section 10.0 for specifics.

16) **QF *(EQ-SD, STAI Y-6, and PQ)* Form:** Quality of Life, Anxiety and resource Utilization Form *(12-month follow-up as per section 10.2)*. See Section 10.0 for specifics.

17) **IE Form:** This form is completed by the site radiologist who interprets the participant's short-term interim follow-up screen-film or digital mammogram, or if there are clinically significant changes since a prior study. This form will also be completed for BIRADS 3, 4, or 5 follow-up mammograms obtained 10 months or more after study entry. The completed form is submitted to the ACR.

18) **Confidential Patient Contact Form:** This form provides contact information to the local sites so that they may contact the participant to obtain follow-up information. It will be kept at the sites for use there. For participants selected for inclusion in the participant surveys, it will be copied and sent to the University of North Carolina where trained research assistants will use it to contact participants for the Quality of Life and Cost Effectiveness surveys.

19) **PR (Patient Non-Participation) Form:** The RA will use this form to provide information to the ACRIN Data Management department for non-participation.

20) **E2 (Breast Cancer Status Summary) Form**: This form is used to document the best source of information about a participant's breast cancer. It is to be completed in the following circumstances: Participant does not return for one-year mammogram; participant does not provide your institution with mammograms taken at an outside facility; and you are unable to obtain a mammography report of a mammogram taken at least 10 months after the date of enrollment. This form will be added to the participant calendar for all participants who are reported as lost/unknown on their 1 year F1 form. It ***may*** also be requested for participants known to be alive and reported as such on the F1 form, but for whom no screening mammography data is available.

21) **DE (Documentation of Effort) Form**: This form is to be completed for all participants who do not respond to initial requests to return for their 1 year follow-up mammogram. It is used to document all attempts to contact participants to schedule 1 year follow-up examinations. Refer to Appendix VI for more detailed information regarding the protocol for contacting participants for follow-up. For most cases for which it is required, the DE form will be kept as part of the participant's study record, but it will **not** be submitted to ACRIN. The DE form may be requested by Data Management for cases where the F1 form reports the case as lost or the E2 form reports breast cancer status as unknown. For other cases without follow-up mammography, the DE form will be part of the participant's study record, and will be subject to audit.

5.2.7 *Data Collection Table*

Form	**Due Date**
I1 Form – Initial Evaluation	Within 2 weeks of registration
LX Form – Eligible Pt. Not Enrolled	As defined in Section 4.3
IA Form – Study Mammography Interpretation Film –Screen ID Form – Digital Interpretation	Within 2 weeks of imaging (if prior images are referenced, can be submitted within 30 days of imaging, per MQSA guidelines)
IM Form – Additional Work-Up/ Prior Films	Within 12 weeks of recommendation for additional work-up
BX Form – Biopsy	Within 8 weeks of biopsy recommendation
PC Form – Pathology Transmittal	Within 8 weeks of biopsy
P1 Pathology Report	Submitted with PC Form

P4 Form – Core Pathology	Within 4 weeks of receipt of specimens
PL Form – Local Pathology Interpretation	Within 4 weeks of receipt of specimens
PO Form – Second Pathology Consultant	Within 4 weeks of receipt of specimens
F1 Form – Breast Cancer Status Follow-up	As defined in Section 8.0, (3, 6, and 9 months *(if recommended)* and 12 months)
IE Form – Follow-up Mammography Interpretation	As defined in Section 8.0, (3, 6, and 9 months *(if recommended)* and 12 months for BI-RADS 3, 4, or 5.)
QL Form – EQ5D and STAI Y-6 *(telephone baseline)*	As defined in Section 10.0
QF Form – EQ5D, STAI Y-6, and PQ *(telephone follow-up)*	As defined in Section 10.0
QP Form – EQ5D and STAI Y-6 *(participant self administered)*	As defined in Section 10.0
M1 – Screen film Mammogram*	Within 2 weeks of imaging date
D1 – Digital Mammogram*	Within 2 weeks of imaging date
MX Form – Reader Studies 1-4	Completed during reader studies
NX Form – Reader Study 5	Completed during reader studies
OX Form – Reader Study 6	Completed during reader studies
PX Form – Reader Study 7	Completed during reader studies
TA Form- Technical Assessment	Within 2 weeks of imaging. Collected on the first 100 participants enrolled at each site, and as needed thereafter
Confidential Patient Contact Form	At registration. Kept at local sites.
PR Form (Patient Non-Participation)	Submitted by RA upon participant's request for non-participation.
E2 Form – Breast Cancer Status Summary	After 18 months of enrollment (if the participant has not provided a screening mammogram and does not have one scheduled and the site is not able to obtain a mammography report taken at least 10 months after the date of enrollment into DMIST)
DE Form – Documentation of Effort	At the request of DMC

*Only initial mammogram will be collected. Follow-up films and/or mammograms will not be collected.

5.3 Image and Pathology Submission

5.3.1 ACRIN has software available that allows for electronic transmission to the DMC image archive of images that have been scrubbed of all participant identifiers. ACRIN will be contacting each site individually to determine their readiness and ability to work with this software. Please contact Rex Welsh *(215-574-3215)* for information about this software. Screen-films will be sent hardcopy via mail for subsequent entry to the image archive. A case specific study label will need to be applied to the film jacket prior to sending the films to the DMC. These labels will be provided by ACRIN. Digital images can be transmitted to the DMC via FTP or on DVD for subsequent entry to the image archive. ACRIN has a written policy to control entry of cases into this archive and to control

future access to these cases. Digital images stored on the DMC image archive can be routed to other sites involved using FTP for purposes of secondary interpretation. See Section 5.2.7 for the timeline for submission of the images to the DMC image archive. Mailed screen-film images or images on CD should be addressed and sent as follows:

Anita Murray
ACRIN Image Archive
ACRIN 6652 Images
American College of Radiology
1101 Market Street, Suite 1400
Philadelphia, PA 19107

5.3.2 The header records on image data, which often contains information identifying the participant by name, must be scrubbed and replaced with the unique study identifier before the image is transferred to the DMC.

5.3.3 Images Lost Due To Equipment Failure: DMIST will collect as much data as available on lost images. For example, if soft copy images are available for interpretation, and interpretation is complete, then the interpretation should be submitted.

5.3.4 All pathology specimens will be sent to one of two pathology-consulting sites. Each consulting pathologist will review the available FNA, core biopsy and open surgical biopsy material, and the report of the local pathologist. The consulting pathologist will record the interpretation of the local pathologist on form PL. The consulting pathologist's interpretation of the material will be recorded on form P4. If there is substantial disagreement between the local pathologist *(defined as a disagreement that changes the participant's breast cancer status)*, then the pathologic material will be sent to the second consultant for another interpretation *(recorded on form PO).* The true pathologic diagnosis will be considered that diagnosis that is agreed upon by two out of three interpreters. All specimens will be returned to the facility where the participant underwent biopsy after review by the central pathologists. Slides should be prepared according to the standard histology procedure *(i.e. hemotoxylin and eosin stained)*. Two glass sides *(usually 6-8 serial section cut)* and the tissue block should be sent to:

Shahla Masood, M.D.
ACRIN Breast Study 6652
University of Florida
655 West 8th Street
Jacksonville, FL 32209-6511
***(904)* 244-4387**
FAX # *(904)* 549-4060
Shahla.masood@jax.ufl.edu

If regulations at your institution will not allow you to send the entire tissue block, two unstained slides will be accepted in its place. All slides must be sent with the Pathology Transmittal Form *(PC),* as well as the PL and P4 forms. At the time of shipment, a copy of the PC form and the pathology report *(P1)* should also be faxed to ACRIN Data Management at 215-717-0936. Pathology specimens can be labeled with the ACRIN study and case number of the participant. The pathology report can have the participant identifiers replaced with the study and case number. Samples should be sent express mail.

5.3.5 If the central pathologists both disagree with the local pathologists so that the

participant's diagnosis is changed, then the radiologist and pathologist at the local site where the participant is enrolled will be informed *(form PO).* These individuals should contact the participant and the participant's referring physician about the discrepancy in opinion. The central pathologist will send a letter of this notification by certified mail to the local pathologist and local radiologist with a copy to Constantine Gatsonis, Etta Pisano and Jessie Flaim-Spetsas.

5.4 Electronic Data Management

5.4.1 Data received from the web-based forms is electronically stamped, with the date and time of receipt by the ACRIN server. The data is then entered into the database. A variable in the new record is set to "Unreviewed," until the data is reviewed at the DMC. A validation program is used to perform more extensive checks such as for accuracy and completeness. The logic checks performed on the data at this point are more comprehensive than those built into the web-based data entry screens. They include checking that answers are logical based on data entered earlier in the current form. This validation program produces a log of errors, which is sent to the research associate for resolution. This program is frequently updated to incorporate exceptions to rules so that subsequent, correctly entered data pass validity checks, minimizing the time the DMC research associate *(DMC RA)* at the DMC needs to spend resolving problems. Additional data review will take place once the data is transferred to the BC. The BC will run thorough cross-form validations, frequency distributions to look for unexpected patterns in data, and other summaries needed for study monitoring. Any errors found at the BC will be reported to the DMC RA for resolution.

5.4.2 If the program detects missing or problematic data, the DMC RA will send a Request for Information *(query letter)* to the investigator specifying the problem and requesting clarification. The DMC RA then updates the participant's data submission calendar with the due date for the investigator's response.

5.5 Missing and Delinquent Data Submission

In addition to providing the investigator a data collection calendar for each case, institutions are periodically prompted for timely submission of data through the use of a Forms Due Report. Distributed at intervals via the US mail system directly to both the RA and the investigator at each site, this report lists data items that are delinquent and those that will come due before the next report date. In addition to prompting clinicians to submit overdue data, the Forms Due Report helps to reconcile the DMC's case file with that of the investigator.

5.6 Data Quality Monitoring by the Biostatistics Center

5.6.1 The BC at Brown University will maintain a study database at its site for monitoring data quality and for performing interim analyses. The Data Management Center and the Biostatistics Center have recently been connected by a T1 line, which provides a private and secure means of transmitting data between the two locations. The availability of the T1 line allows ACRIN to avoid all public means of transmitting data. Both the DMC and the BC have firewalls in place to provide security once the data has been received by either host. The BC staff will draw data directly from the DMC's permanent database using a PowerBuilder utility that allows BC staff to log onto the DMC computer and select needed fields. This analysis database will be maintained in permanent SAS *(Statistical Analysis System software)* format on the BC's ACRIN server and updated on a scheduled basis, usually semi-monthly once the study is in its steady state. Any discrepancies and other data quality issues will be referred to DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.

5.6.2 A major goal of the monitoring of data in the BC is to assess compliance with the

protocol and to look for unforeseen trends that may be indicative of procedural differences among clinical sites. If patterns are discovered in the data, which appear to arise from causes specific to an institution, the BDMC will apprise the site of the problem and work with the site until the problem has been resolved. If the BDMC cannot find a solution, the problem will be brought to the Executive Committee for further discussion and resolution.

The BC, in conjunction with the DMC, will prepare frequent summaries of the accrued data to be presented to investigators. These summaries will report accrual rates *(overall and by sub-groups of interest to the investigators)*; assess the completeness and accuracy of the data; and discuss any trends that may impact the outcomes of the trial. These intermittent summaries will not include analyses of the study's endpoints.

No formal interim analyses with respect to endpoints, primary *(AUC)* or secondary are planned. This strategy will be discussed with the study Data Safety and Monitoring Committee *(DSMC)* at the beginning of the study, and might be modified as a result of that exchange.

At the beginning of the study, a list of important outcomes and a schedule for monitoring them will be established in consultation with the DSMC. The BDMC will monitor such outcomes on a regular basis and present the relevant information to the DSMC.

5.7 Institutional Audits

5.7.1 After the first 100 participants have been accrued at a participating site, the site may be contacted by an ACRIN auditor by telephone for an assessment interview, and the site will be eligible for an audit. Auditors will follow procedures established by the Clinical Trials Monitoring Branch and the Cancer Imaging Program of the NCI. Auditors will review on-site records against the submitted data forms, and they will record their findings on specially prepared questionnaires. IRB procedures, approvals, and consent forms will also be reviewed during the audit.

Major deficiencies will be forwarded to the appropriate oversight body within ACRIN.

In advance of the audit date, ACRIN will provide institutions with detailed instructions for preparing for audit, along with a list of up to 45 of the case numbers that have been selected. Five cases from the selection list will be reserved as surprise cases.

Cases to be audited will be randomly selected from three groups of participants:

1. Those diagnosed normal or definitely benign;
2. Those referred for additional imaging, but not for biopsy; and
3. Those referred for biopsy.
4.

Because the vast majority of cases fall into the first category and very few fall in the last, DMIST has chosen to select from these categories at different rates to ensure adequate representation from each. ACRIN will select 1% of cases from group 1, but no more than 20 and no fewer than 15; 50% of cases from group 2, but no more than 15 and no fewer than 10; and 100% of cases from group 3, but no more than 15.

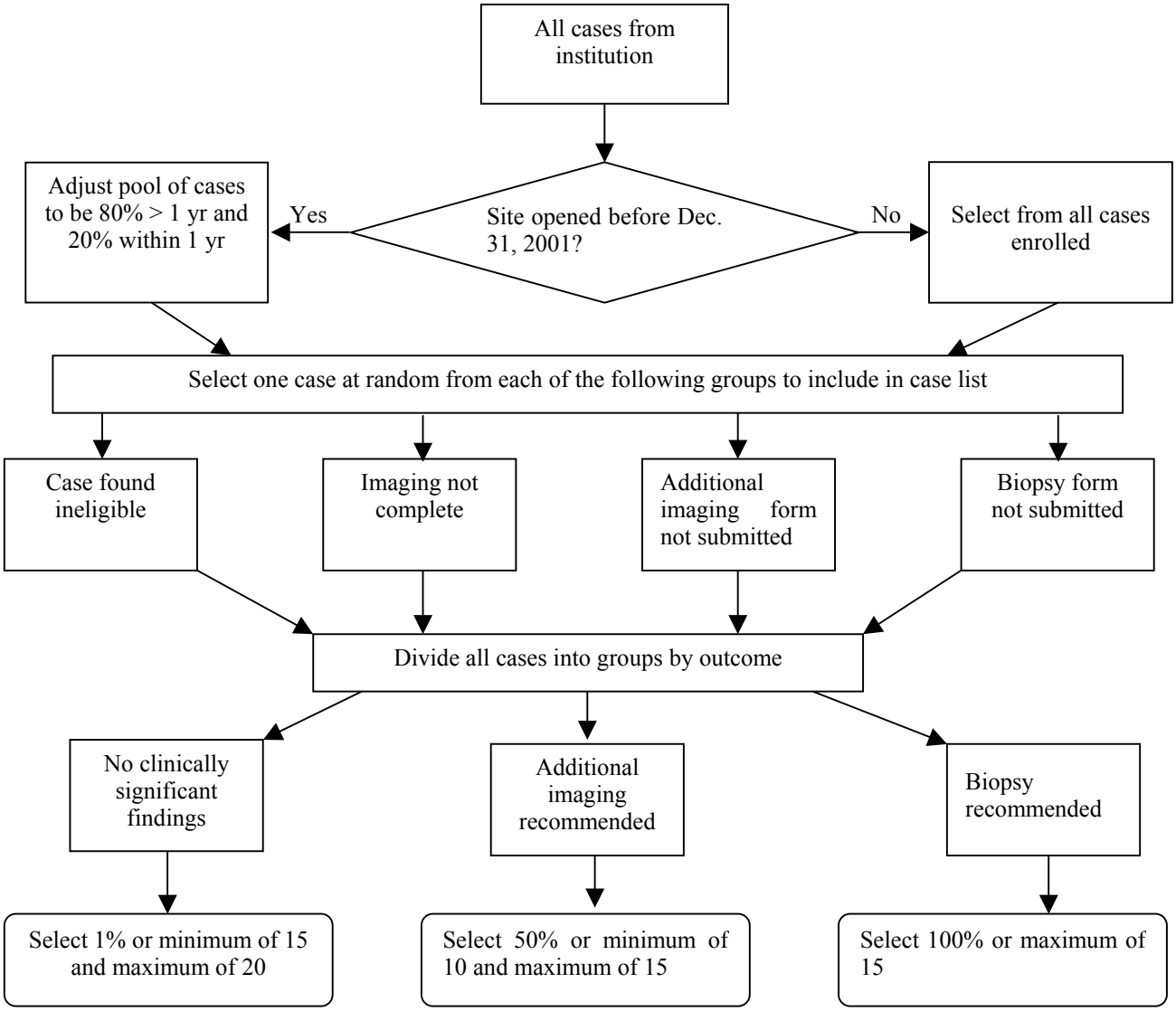
For the first audit for institutions opened by December 31, 2001, 80% of the cases selected will be from those enrolled a year or more before the audit, and 20% will be selected from cases enrolled within one year. This ensures that the auditors review follow-up data forms, as well as the forms required from the baseline visit. It also ensures that data from each year of the study will be audited over the course of the

study.

In addition to these selections, at least one case fitting each of the following descriptions will be included among cases audited (these are not mutually exclusive of the groups above): participants who were found to be ineligible, those who did not receive both a digital and a screen-film mammogram at study entry, those who were referred for additional imaging but who did not comply with this recommendation, and those who were referred for biopsy but who either did not comply or whose data regarding the biopsy have not yet been received. The schema below illustrates the audit case selection.

DMIST Audit Selections

Strata from Which Initial Audit Cases Selected



If the initial audit is acceptable, subsequent audits will be scheduled for 12 and 24 months after the initial audit date. If any of the audits are unacceptable, follow-up audits will be scheduled as per the ACRIN Audit Manual guidelines.

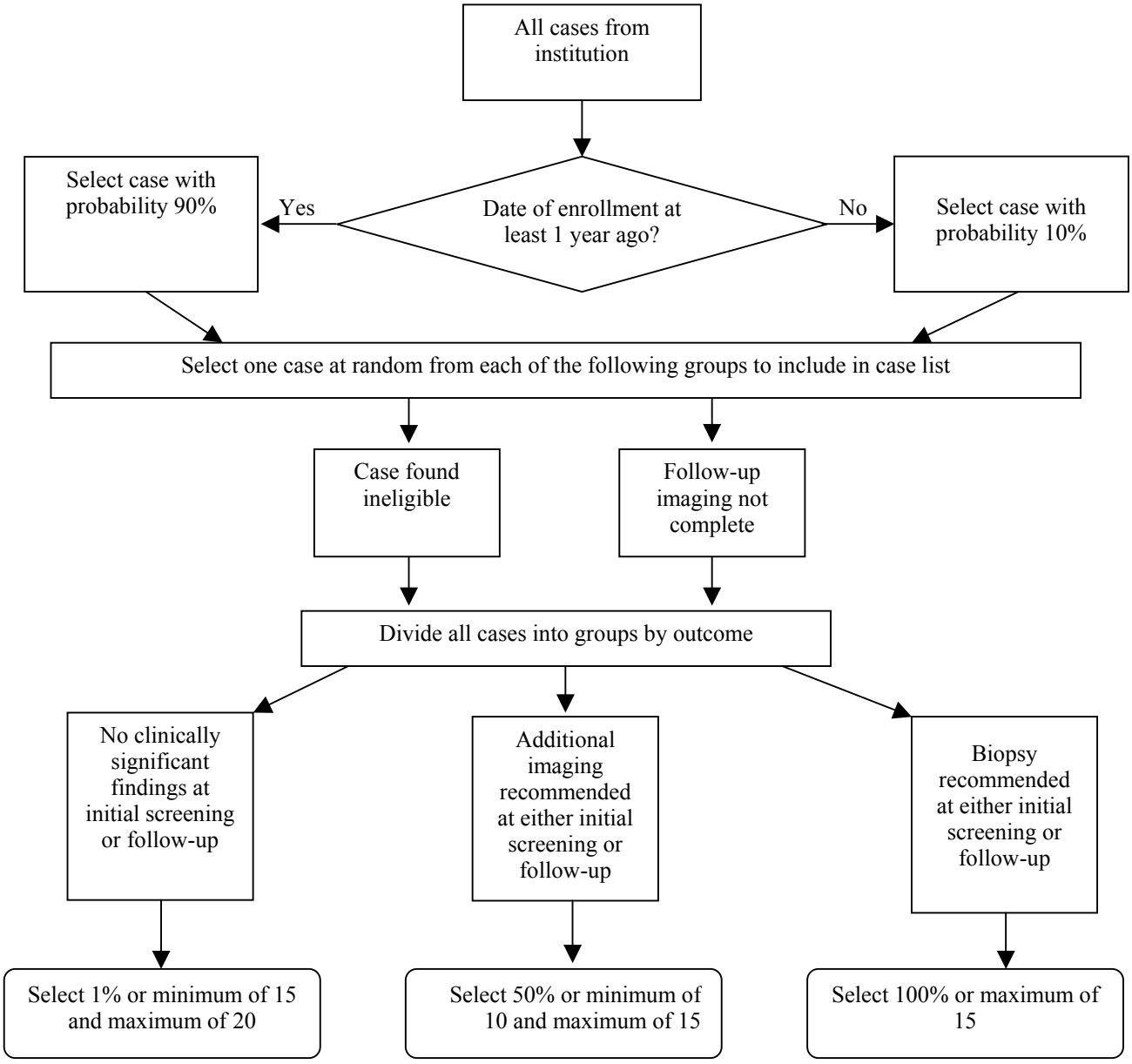
Selection of cases for follow-up audits

Selection of cases for follow-up audits will be completed according to the criteria outlined above for initial audits with the following exceptions:

- Cases previously audited and found acceptable will not be re-audited.
- Cases previously audited which required corrective action may be included in subsequent audits.
- 90% or more of the cases will be selected from among those who were enrolled 1 year or more from the date the list is generated so that forms for follow-up can be reviewed.
- At least 1 case for whom follow-up data has not been submitted on time, if any exist, will be included.

Documentation of Effort forms (DE) detailing steps taken to obtain the breast cancer status of the participant will be required for all cases for which 1-year follow-up information has not been collected by 18 months from enrollment. If one has been requested, a Breast Cancer Status form (E2) will also be required. The schema below illustrates the case selection for follow-up audits.

Strata from Which Follow-Up Audit Cases Selected



5.7.2 To aid sites in preparing for ACRIN audits and to assure the clinical RA maintains records accurately, the ACR Audit Department will offer regional audit educational training. The training sessions will cover all aspects of data collection as related to protocol-specific audit requirements, i.e. acceptable source documentation necessary to verify the accuracy of submitted data for audit purposes. ACRIN held training sessions at the October 2002 and the 2003 fall meetings.

5.7.3 Prior to enrollment of the first participant to the trial at a particular site, a site visit will be conducted by a data manager, a radiologist, and a physicist to determine that the site is in compliance with all protocol requirements. A particular site may not enroll participants to this trial until it has been visited and approved.

6.0 STUDY MAMMOGRAM ACQUISITION

All 49,500 women enrolled will undergo two-view mammograms *(both cranio-caudal and medio-lateral oblique views)* of both breasts, or of one breast if they have had prior mastectomy, using both the digital and screen-film systems.

The planned imaging protocol is to perform MLO and CC views on each woman using both screen-film and digital mammography equipment. The site's standard screen-film image receptor, processing, and AEC technique factor selection for each screen-film unit used for screening mammography unit will be used. The same technologist will perform digital mammography using the site's digital mammography system. Both film screen and digital images should be acquired on the same day unless equipment failure precludes same day imaging. In the case of digital equipment failure, digital images may still be acquired up to a maximum of 30 days after film screen imaging. Should this occur, interpretation of the film screen mammogram must be postponed to insure that the interpretations are completed within the required 7 day limit of each other. Digital acquisitions will be made using as close to the same positioning and degree of compression as for screen-film mammography and using the AEC system on the digital mammography unit, where available. AEC systems will be set up to deliver approximately the same dose with digital mammography as with screen-film mammography.

This will be done by finding the mean and standard deviation of mean glandular dose at specified breast thickness among screen-film mammography units at ACRIN sites and by maintaining digital doses to be within the mean screen-film dose plus one standard deviation. Doses for digital mammography may be lower than those for screen-film mammography where recommended by the manufacturer, such as for the Fischer Sensoscan digital unit, which by design obviates the need for a grid and therefore, permits lower breast doses.

The order of performance of digital and screen-film examinations will be randomly assigned. For large-breasted women, as many cranio-caudal and medio-lateral oblique views as are deemed necessary by the technologist to include each breast in its entirety will be performed. This is in accordance with standard clinical practice for the performance of screen-film mammography. All medio-lateral oblique and cranio-caudal mammograms obtained on the enrolled participants will be considered the study digital or screen-film mammogram.

7.0 DIGITAL AND SCREEN-FILM MAMMOGRAPHY INTERPRETATION

7.1 Most centers that perform screening mammography provide batch interpretation. That is to say, the radiologists do not interpret these studies immediately, but rather after they are prehung on a multiviewer at a later date and time. Many centers also employ double reading with more than one radiologist viewing and interpreting each case.

For this study, two different radiologists will interpret the mammograms, one for the study screen-film and the other for the digital mammograms of all participating women. Participants will be called back for additional work-up for any lesions that are seen that suggest the need for further work-up. Prior films on the participant can be used for comparison for the interpretation of both sets of images, unless they are not available. If prior films are referenced, they must be available for both digital and screen-film interpretations; in that case, the IA and ID forms may be submitted within 30 days of imaging, per MQSA guidelines.

A second radiologist reader at each site will read the digital mammograms. Again, participants will be called back for additional work-up for any lesions that are seen that suggest the need for further work-up. Prior films on the participant will be available for comparison.

The radiologists assigned to these two sets of interpretation tasks at each site should be balanced so that each reader interprets equal number of cases in each format. Ideally, no reader should read fewer than 200 film screen and 200 digital cases. All readers should be staff radiologists, and not fellows or residents.

All FUJI and Lorad Study mammogram initial reads will be done on hard copy. All Fischer study mammogram initial reads will be done in both hard copy and soft copy. All GE study mammogram initial reads will be done in soft copy. Hologic study mammogram initial reads may be done in either hard copy or soft copy.

The two radiologist readers will read independently and concurrently without consultation. The film and digital mammograms must be read within seven (7) days of one another. In addition, care will be taken at each site that there are no trainees who see both examinations on the same participant. Trainees are not allowed to view either version of the images until the primary reader of each has finished his or her interpretation and that interpretation has been entered into the data entry forms available on the internet. Further work-up will proceed based on findings made on both studies. Data on which downstream tests were caused by each examination will be collected on the interpretation form. The data entry system will not allow readers to change their readings once they are entered to reduce the likelihood of consultation affecting the study results.

If there is a positive digital mammogram, or, if there is a positive screen-film mammogram, or if both tests are positive, the participant will undergo further work-up. Both mammograms must be interpreted before any additional work-up is interpreted. (Work-up images may be taken, just not interpreted.) Work-up will proceed using either screen film or digital technology, according to standard clinical protocols at the involved sites. Digital mammography imaging for the work-up will only be acceptable if the digital unit to be used for this is FDA-approved.

A single breast-imaging expert radiologist will perform the additional work-up, as per usual clinical protocols at the involved sites. The recommendation at the end of work-up might include biopsy. The radiologist who performs the work-up images and makes the final decision about biopsy will have all images available to him or her. This radiologist might be the same one who read either the digital or screen-film mammograms, or might be a third radiologist.

Note should be made that there will not be conflicting data about participant recommendations AFTER work-up is completed since work-up will be accomplished by a single radiologist. There will be conflicting reports for the digital and screen-film mammograms, and that will be explained to the participant as part of the consent process. She will be informed that the two different mammograms may show different results and that she will undergo evaluation if EITHER test is abnormal. At this point, we have no reason to believe one test over the other, so disagreements between the two tests are expected as part of this study.

The usual method to decide whether a participant needs biopsy based on additional imaging, physical examination, etc., will be followed at each institution. At some institutions, biopsies are performed on participants only after two radiologists agree that a biopsy is needed. Whatever clinical procedures are in place at the enrolling institutions to determine whether a biopsy is needed will be followed under this protocol.

7.2 The digital and screen-film mammograms will be interpreted using two scales. The radiologists will be asked to score all of the findings on both the digital and screen-film mammogram using a malignancy scale, as follows:

1: The finding is definitely not malignant.
2: The finding is almost certainly not malignant.
3: The finding is probably not malignant.
4: The finding is possibly malignant.
5: The finding is probably malignant.
6: The finding is almost certainly malignant.
7: The finding is definitely malignant.

This scale will be the one utilized in primary ROC analysis.

The federally-mandated BIRADS scale for interpreting screening mammography will also be provided by the readers. Of course, all clinical interpretations provided to the participant's medical record will be in compliance with U.S. federal law, when applicable. The radiologists will also assign a numerical probability of malignancy for each mammogram. These scores will be assigned BEFORE any additional work-up is performed.

In addition, the 7-point scale and the BIRADS scale will also be provided by the radiologist interpreting the work-up of the participant, whenever such work-up occurs.

7.3 The second scale relates to the strength of the evidence for the need for call-back after the screening mammography, as follows:

1) There is NO evidence that the participant should be called back for diagnostic work-up.

2) There is SOME evidence of an abnormality but it is insufficient to justify that the participant should be called back for diagnostic work-up.

3) There is SUFFICIENT evidence to justify that the participant should be called back for diagnostic work-up.

4) There is STRONG evidence to justify that the participant should be called back for diagnostic work-up.

5) There is OVERWHELMING evidence to justify that the participant should be called
back for diagnostic work-up.

7.3.1 All study radiologists must meet the FDA requirements for reading digital mammograms. This will include 8 hours of CME credits in digital mammography, unless the radiologist had experience reading digital mammograms prior to April 28, 1999, as per FDA regulations promulgated under MQSA.

7.3.2 *Mammographic Findings for DMIST*

The only findings that MUST be recorded on DMIST participants are those that require further evaluation. There is no need to note benign findings that will not require work-up, either on the initial findings form (IA/ID) or, the supplemental findings forms (IM Additional Work-Up). Of course, these benign findings contribute to your scoring of the mammogram, including the BIRADS score.

7.4 Retrospective Formal Reader Studies

In accordance with Specific Aims 3.2, 3.7, 3.8 and 3.9, retrospective reader studies will be performed during year 3 of the protocol.

7.4.1 *Reader Studies 1-4: Comparison of the Diagnostic Accuracy of Each Individual Digital Mammography Unit vs. Screen-Film Mammography*

In this group of reader studies, four reading sets will be assembled and interpreted, one for each of the four mammography units involved in the study. Each set will consist of digital and screen-film studies on 50 cases with cancer and 75 cases without cancer, randomly selected among the participants who had their initial digital mammogram performed with the particular unit. For each mammography unit, 12 readers will be chosen at random from a pool of qualified radiologists and will interpret both screen-film and digital scans in random order. Scans for a specific case will be read 6 weeks apart to minimize case recall. The goal of the study is to compare the average diagnostic performance, as measured by AUC, of digital vs. screen-film mammography for each of the four mammography units in the study.

7.4.2 *Reader Study 5: Effect of Prevalence of Cancer on Reader Performance*

A question that continues to occur with ROC studies is the influence of enriching the case sample on the diagnostic accuracy obtained. While the ROC curve is invariant to prevalence when the diagnostic test is purely objective, prevalence may have an effect on diagnostic systems involving human observers. The issue to be decided is whether changing prevalence merely moves an observer's operating points along the same ROC curve, or whether changes in prevalence result in different ROC curves. The answer to this question has important implications for the generalizability of results from enriched case samples to settings with lower prevalences, especially screening settings. If we knew that prevalence did not affect the ROC curve, we could comfortably perform most studies with enriched case samples *(50%),* gaining statistical power and thereby saving much time and expense. If we knew that prevalence affected the ROC curve in a

predictable fashion, we could model that effect, allowing extrapolation to settings with different prevalences. The latter is similar to the low-dose extrapolation that occurs in, for example, teratology studies.

Finally, if we knew that prevalence affected the ROC curve, and that the manner in which it did so was not predictable, we would have stronger justification for large screening trials such as the main trial currently proposed.

The current trial presents a unique opportunity to assess this question. Unfortunately, it is not feasible to evaluate prevalences close to the expected prevalence in the screening setting *(5-6 cancers per 1000 screened women)*. However, we can make use of the rich data set to assess a wide range of prevalences that are feasible to study, thus making an important step toward resolving this recurring and crucial issue of study design.

In this study, three overlapping reading sets will be assembled, as follows:

10% prevalence: 30 cancers + 270 non-cancers
25% prevalence: 45 additional cancers *(total = 75)* + 225 of the 270 non-cancers above
50% prevalence: 75 additional cancers *(total = 150)* + 150 of the 225 non-cancers abv.
The 150 cancer cases will be randomly selected from the pool of cases diagnosed with cancer on the main study, and randomly allocated to prevalence groups *(10% only; 10% and 25%; all three levels).* If the cancer cases obtained in the prospective study vary notably in important characteristics, selection and allocation will take those characteristics into account. The 270 non-cancer cases will be randomly selected from the pool of cases with normal one-year follow-up, including cases that were called back and proved to not have cancer. If any demographic variables are found to affect diagnostic accuracy in the main study, a stratified random sample will be selected, to match the distribution of these variables in the selected cancer cases. Mammograms for each case will be displayed both as digital hard copy and as screen-film. If the results from Study 6 indicate superiority of digital soft copy, that will be used instead of digital hard copy.

A total of 30 readers will participate in this study. The readers will be randomly allocated to combinations of prevalence level and modality. If appropriate, randomization will be stratified on factors known to affect diagnostic accuracy *(as identified in the main study),* and soft-copy workstation. Thus, 5 readers will review 300 cases for each combination of prevalence level and display modality *(If soft-copy is used, there will be one reader per workstation, plus the fifth randomly assigned to one of the four workstations, where the latter randomization would be blocked to ensure balance across the six combinations of prevalence level and display modality).* Each reader will interpret cases independently of the other readers. Interpretations will be in the same format as those on the main study.
Readers will be given a vague description of the sample prevalence, e.g., " . . . a diagnostic setting with prevalence between 20% and 30%," to avoid confounding with the effect of determining the sample prevalence during the reading session.

The 15 readers assigned to interpret digital mammograms will be trained prior to their participation, using 25 digital mammograms *(12 cancer cases, 13 non-cancer cases)* and the forms and viewing conditions of the study. If soft-copy is used, training will occur using the workstation to which the reader has been assigned. Readers will be given

feedback regarding participant outcomes in the training set. Readers assigned to interpret screen-film mammograms will undergo similar training using 25 screen-film mammograms *(12 cancer cases, 13 non-cancer cases)*. Cases included in the training set will be identified from those remaining after selection of cases for the reader study.

7.4.3 *Reader Study 6: Effect of Softcopy and Printed Film Display on the Diagnostic Accuracy of Digital Mammography*

This study will compare the accuracies achieved by readers interpreting digital mammography in soft and hard copy displays. A total of 32 readers will participate in the study. Readers will be assigned at random to four groups of 8, and each group will receive training in reading scans from one of the four mammography units in the study.

A total of 400 cases will be used in the study, with equal numbers of cancer and non-cancer cases. Scans will be drawn at random from the sets of cancer and non-cancer cases of each of the four mammography units. Thus the final set of cases will include 50 cancers and 50 non-cancers for each mammography unit. Readers will not be informed of the actual case mix but will be made aware that the prevalence of cancer is considerably higher than in a screening setting. Thus, reader group I will interpret both soft and hard copy displays of all cases *(100)* for one of the mammography units. Reader group II will do the same for another of the four mammography units, and so on. Soft and hard copy displays of the same scan will be read at least 6 weeks apart, in order to minimize recall. The goal of the study is to compare the average diagnostic performance, as measured by AUC, achieved by soft copy display to that achieved by hard copy display.

7.4.4 *Reader Study 7: Comparison of the Diagnostic Accuracy of Digital and Screen film Mammography in Participants with Breasts of Varying Radiographic Density*

In this study, four reading sets will be assembled and interpreted. The sets will be constructed according to the standard BIRADS categories: fatty breasts, breasts with scattered fibroglandular tissue, breasts of heterogeneous density, and breasts with extremely dense tissue. Breast density will be determined for all participants entered into the trial as the BIRADS rating given to the participant's screen-film mammogram by the radiologist who interpreted that study. A total of 80 participants will be included at each breast density level. The number of cancer cases will be the total number of cancer cases at that density level, or 40 *(randomly selected from all cancer cases at that density level),* which ever is smaller. We expect that the risk of cancer for women with dense breasts is up to 6 times the risk of cancer for women with fatty breasts [Boyd]. Thus, the number of fatty breasts with cancer may be as low as 20, and is not expected to exceed 40; the number of dense breasts with cancer is expected to be at least 80.

The remaining non-cancer cases will be randomly selected within breast density level from the pool of cases with normal one-year follow-up, including cases that were called back and proved to not have cancer. If any demographic variables are found to affect diagnostic accuracy in the main study, a stratified random sample will be selected, matched to the distribution of these variables in selected cancer cases. Mammograms for each case will be displayed both as digital hard copy and as screen-film. If the results from Study 6 indicate superiority of digital soft copy, that will be used instead of digital hard copy.

A total of 16 readers will participate in this study. The readers will be randomly allocated to either digital or screen-film, and will interpret all four reading sets within that modality. If appropriate, randomization will be stratified on factors known to

affect diagnostic accuracy *(as identified in the main study)*, and soft-copy workstation. Thus, 8 readers *(two per workstation, if soft-copy is used)* will review 80 cases at each of 4 breast density levels for each modality. Each reader will interpret cases independently of the other readers. Interpretations will be in the same format as those on the main study.

The eight readers assigned to interpret digital mammograms will be trained prior to their participation, using 25 digital mammograms *(12 cancer cases, 13 non-cancer cases, balanced across breast density levels)* and the forms and viewing conditions of the study. If soft-copy is used, training will occur using the workstation to which the reader has been assigned. Readers will be given feedback regarding participant outcomes in the training set. Readers assigned to interpret screen-film mammograms will undergo similar training using 25 screen-film mammograms *(12 cancer cases, 13 non-cancer cases, balanced across breast density levels)*. Cases included in the training set will be identified from those remaining after selection of cases for the reader study.

7.4.5 *Training for Reader Studies*

The method of training involves each reader's interpreting 25 digital mammograms, and then being given the same participant's screen-film mammogram and information about each participant's breast cancer status, including which lesions, if any, underwent biopsy, and the pathologic evaluation of the biopsied lesions. This allows the readers to become familiar with the appearance of lesions on digital mammograms, compared with the same lesion as seen on a screen-film mammogram. The radiologist completes the study forms that he or she will be using during the reader study for each case viewed for training purposes.

In addition, if the display method involves the use of a system new to the radiologist, the images will be displayed using that system during training. Also, different readers will be used for each reader study.

8.0 FOLLOW-UP OF STUDY PARTICIPANTS' MAMMOGRAMS

All women who participate in this study will be considered registered and participating in this study for up to 3 years after their date of entry. Women will undergo whatever additional views and ultrasound are suggested by the interpretation of either the screen film or digital mammogram using either the standard screen film or digital technology as per usual clinical protocols at the involved sites. Percutaneous and open surgical breast biopsies will proceed as per standard clinical protocols. All participants will also be asked to sign an informed consent giving permission to be contacted by phone or by mail for up to 20 years. Participants will be asked about their current health status, recent mammograms, and any clinical breast exams that may have been performed.

8.1 Determination of Truth Regarding Breast Cancer Status

If the participant undergoes breast biopsy at any time during the first 15 months after her initial study mammograms, she will inform personnel where she entered the study so that the pathology report on that biopsy will be provided. All biopsies that are recommended because of the study mammogram will be included in this group. The PI radiologist at each site will provide documentation of the location of any biopsy performed on a participant registered to this study by completing the BX form.

All women will be encouraged through the study newsletter to undergo mammography one year after their entry mammogram at the site where they were enrolled. The follow-

up mammography will be either a screen film or digital mammogram as per usual clinical protocols at the involved sites. At that time, information will be obtained about prior breast biopsies that have occurred since the previously recorded visit.

Breast cancer status will be recorded on form F1 for all study participants each time there is a short-term interim or one year follow-up screen film or digital mammogram, or if there are changes since a prior study. In addition to form F1, form IE will be completed for all participants returning for short-term interim follow-up mammograms. Form IE will also be completed for all one-year follow-up mammograms with a BI-RADS classification of 3, 4, or 5. Form IE will NOT be completed for negative one-year follow-up mammograms. BI-RADS classification *0 – needs additional imaging* will not be allowed on follow-up mammography exam forms. If additional imaging is necessary on follow-up exams, forms F1 and IE should not be submitted until after the additional imaging has been completed. If, after additional imaging has been completed, the BI-RADs classification is 3, 4, or 5, forms F1 and IE should be completed. If the BI-RADS classification is 1 or 2, only the F1 form should be completed. Mammograms taken 10 to 15 months from the date of enrollment will be accepted as the one-year follow-up mammogram.

Truth about breast cancer status will be determined by ascertaining the presence of malignancy at 3, 6, and 9 months *(if recommended)*, and 12 months after the study mammogram. Study personnel will encourage participants to have a follow-up mammogram, even if the participant is unable to be imaged within the 10-15 month window. They will also obtain pathology specimens and results from any biopsies performed as a result of initial or follow-up imaging. Every enrolled woman who does not return for follow-up mammography will be contacted by study personnel at each site to determine whether she has been diagnosed with breast cancer and, if so, on what date. This will involve mail and phone contacts up to 3 years from the time of their enrollment into the study. Data from participant contacts will be recorded on the Breast Cancer Status Form (E2). For women who do not respond to these contacts, a search of their medical chart, state tumor registries, and/or the National Death Index (NDI) will be conducted. An E2 Form will be used to record these data as well.

8.2 Quality Control Protocol and Acceptance Testing

This is described in detail in the "ACCEPTANCE TESTS AND QUALITY CONTROL PROCEDURES FOR FULL-BREAST DIGITAL MAMMOGRAPHY," provided to the sites as a separate document.

The primary purpose of the QC program is to ensure that, once accepted, adequate quality is maintained throughout the course of the study, consistently from site to site. It is NOT intended as a mechanism to collect data to modify exposure, imaging, and display parameters.

If QC testing reveals that a particular system at a particular site is deficient *(falls out of control)*, the site's technologist or medical physicist will initiate corrective actions to bring that system back into compliance with study standards. Those corrective actions will be communicated to the Study QC Committee, which will be co-chaired by Drs. Yaffe and Hendrick.

Problems with technique factors that cause deficient image quality or excessive breast dose will be identified upon acceptance testing into the study, and at that time, corrective

actions will be taken by the Study QC Committee in collaboration with the site's radiologist and medical physicist.

If a site has a proposal to modify technique factors *(e.g., to lower breast dose)* during the course of the study, those modifications and their reasons would be submitted to the Study QC Committee and given due consideration before changes are made. This would typically include testing on the site's unit or an identical unit using phantoms to see if the desired changes occur without and adverse effect on image quality or dose.

In addition, there will be a program of continuous quality improvement by constant feedback by each site's technologist and radiologists concerning image quality for both screen-film and digital mammography.

Issues of concern are brought to the attention of the site's medical physicist for immediate correction and corrective actions will be communicated to the Study QC Committee.

If a manufacturer has a proposal for a change in image acquisition, processing, or display during the course of the study, the proposed changes will be evaluated by the Study QC Committee and, if needed, the Study Radiologist's Advisory Committee to determine if the changes lead to improvements in image quality or interpretation quality. Only after approval by the appropriate study committee would those changes be implemented at study sites. The site radiologists and physicists will be advised of these study policies prior to initiation of the study.

In fact, the imaging systems, exposure/imaging protocol, display method and image processing and technical specifications are not under the control of the investigators, but rather are determined by the manufacturers of the digital mammography equipment. It is NOT the goal of the researchers to optimize any of these parameters and then study some sort of ideal digital mammography system. Rather, the goal of this study is to compare digital mammography, as it exists in clinical practice, with screen-film mammography, as it exists in clinical practice. Both types of systems may not be optimized, but the systems that exist in clinics are those that will be used on participants. Studying real systems that will be manufactured and sold and used on participants allow the study's results to apply to the real world of clinical practice and will allow us to make statements about clinically available systems.

9.0 COST-EFFECTIVENESS ASSESSMENT

9.1 Rationale

Cost containment pressures have fueled interest in assessing the economic value of new technologies. A formal cost-effectiveness evaluation will estimate the net change in direct medical costs associated with digital screening mammography compared with screen-film screening mammography over a 12-month time period. If the net change in cost is *positive (i.e., costs are increased)*, it is important to consider the increased cost relative to the increased effectiveness. Measurement of effectiveness would ideally include long-term changes in quality-adjusted life expectancy.
However, long-term outcomes will not be observed in the course of the proposed 12-month study.

9.2 Study Plan

The cost-effectiveness of digital versus screen-film mammography will be addressed in

two phases. First, cost-effectiveness analysis will be based on observed test outcomes *(i.e., true positive, false positive, true negative, false negative),* associated direct medical costs, and quality-adjusted life years *(QALYs)* as estimated based on EQ-5D *(see Section 10.1.2)*. Second, if appropriate *(i.e., pending results of phase one)* a modeling phase that addresses the long-term cost-effectiveness of digital versus screen-film mammography will be undertaken. The latter phase of the analysis would address the cost-effectiveness of screening programs on cost per additional QALY saved.

9.3 Resource Utilization Data

The observed cost and effectiveness endpoints for the proposed 12-month study period are the direct medical costs and human costs associated with medical care resulting from a positive screening mammogram *(digital or film).* "Positive" or "abnormal" screening mammograms are any exams for which the woman was asked to return for additional views, ultrasound, biopsy, surgical consult, breast MRI, or short-interval follow-up mammograms. Detailed resource utilization associated with follow-up tests for a sub sample of 1200 women *(600 women who have abnormal digital or screen film screening mammograms and 600 women with normal screening mammograms)* will be collected both at each institution and *(for women with abnormal screening mammograms)* through a follow-up Patient Questionnaire *(PQ see Section 10.1.1)*. Utilization of the following services after the screening mammogram will be collected for all women:

1) extra mammographic views
2) Ultrasound
3) Short-term interval follow-up mammogram *(3-6 months)*
4) Physical examination by referring physician
5) Surgical Consultation
6) Percutaneous biopsy with sonographic or stereotactic guidance
7) Needle-localized open surgical biopsy
8) Breast MRI
9) Other _____

The PQ questions women regarding use of health care services for breast cancer related concerns and includes several questions documenting the time costs associated with follow-up medical tests and consultations to resolve the breast cancer concerns in the year following the screening mammography. Responses to these questions will provide a basis for estimating the personal time costs associated with various test outcomes.

10.0 PARTICIPANT HEALTH-RELATED QUALITY OF LIFE ASSESSMENT

10.1 Rationale

The main result of this trial with respect to outcomes affecting quality of life will be determination of the differential rate at which falsely positive screening exams occur with digital versus film/screen imaging and the impact of false positive screening exams on the quality of life of women with this screening result. The 12-month time-frame precludes observation of longer term effects such as effects on future screening compliance noted in other studies. Because multiple diagnostic pathways complicate the follow-up of positive screening results, we have elected to make the first assessment of women with positive results shortly after the positive screening mammogram. This point should fall near the most anxiety-sensitive time point for women with a positive screening mammogram. An additional assessment will be made at 12 months following the original screening mammogram. The measurement at the initial assessment and the change at 12 months in women with a positive screening mammogram will be compared with the corresponding quantities measured on a sample of women with negative

screening mammograms.

Outcomes measurement will consist of three parts, an existing generic quality of life measurement instrument *(the EuroQol EQ-5D),* which will be modified to include a subjective assessment of current health as excellent, very good, good, fair, or poor, and a rating scale for current health, a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory *(STAI Y-6)* [Marteau 1992], and a patient questionnaire *(PQ).* The PQ will only be administered at the 12-month follow-up. For the purpose of this study, a false positive mammogram is defined as a study that is interpreted as abnormal when the participant does NOT have breast cancer.

The Quality of Life, Anxiety and Resource Utilization instruments are implemented as forms QP, QL, and QF *(see Section 10.2)*. In the next sections, individual components of these forms are described.

10.1.1 *Patient Questionnaire*

The PQ, a retrospective telephone-administered instrument which will be administered at the 12-month follow-up among the random sample of women who also answer the health-related quality of life and anxiety questionnaires *(see Section 10.1.2 for description of sampling scheme)*, will characterize use of medical services related to breast follow-up, if any, and time burden and anxiety caused by follow-up exams and procedures.

10.1.2 *Quality of Life Instrument*

The instrument we will use is the EuroQol EQ-5D [Kind]. This instrument consists of 5 questions, one each about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each question has three possible answers categorizing degree of problem with the particular aspect of health. Along with the EQ-5D, women will assess their overall health as excellent, very good, good, fair or poor and will complete a rating scale for current health. The latter provides a direct valuation of each women's current health.

The EQ-5D will be used to estimate the time course of health related overall quality of life in the year following the screening mammogram [Kind]. We will measure generic health-related quality of life at two points in time in a stratified random sample of 600 women whose screening study led to additional follow up *(of 6000 expected).* Stratification will be by age group as follows: age less than 50 years, 50 - 59, 60-70, above 70. The same questionnaire will be administered at the same time points to a random sample of 600 women with negative screening exams.

EQ-5D will be administered once shortly after the screening mammogram and then at the time of the 12-month follow-up. Six minutes direct interview time and 24 min. administrative time each is budgeted for the first administration as a standalone interview; the incremental time added to the 12-month follow-up interview is 2 minutes.

The first data point is meant to sample quality of life at a point after additional follow up views for a suspicious screening mammogram, but before the time a biopsy would be performed. The second data point is to sample quality of life at a long-run point of time usually 6 months after the last of the women have received negative results *(those who had 6 month follow-up mammograms)*. To assess whether the baseline health-related quality of life and anxiety for women varies prior to the screening event, we

will *also* administer both surveys prior to any mammograms for the first 42 women enrolled in the study at each site.

10.1.3 *Participant Anxiety Instrument*

The same participants will also undergo evaluation with a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory *(STAI Y-6)*. [Marteau 1992] This will allow a direct measure of participant anxiety with a previously validated instrument.

10.2 Summary of Measurements

Form Cohort	QP Before screening mammogram *(participant self-administered)*	QL Baseline post-screening mammogram *(telephone-interview)*	QF At 12 month follow-up *(telephone-interview)*
First 42 women enrolled/site	EQ-5D STAI Y-6		
600 women with neg. screening results		EQ-5D STAI Y-6	EQ-5D STAI Y-6 PQ
600 women with either digital or regular mammogram positive		EQ-5D STAI Y-6	EQ-5D STAI Y-6 PQ

10.3 The aggregate impact of a falsely positive screening exam is a function of four quantities, Q_n, Q_p, f_c , and f_d. Q_n is the quality of life with a negative screening exam, and Q_p the quality with a falsely positive screening exam; f_c is the probability of a false positive in a population screened with conventional screen film mammography and f_d is the same probability in a population screened with digital mammography. The decremental impact on quality of life of a false positive compared to a negative exam result is (Q_n-Q_p) and the change in frequency with which this happens when digital mammography is substituted for conventional film/screen mammography is (f_c - f_d). The impact of the change from conventional to digital mammography is then (f_c - f_d) (Q_n-Q_p). In fact the $Q_.$ should be calculated as a difference in quality-adjusted time.

As discussed in the quality of life measurement section, we will need to approximate these quantities over time from two point-in-time measurements of health-related quality of life using the EQ-5D; the first point is soon after the negative or positive result is communicated to the screenee and the second point is at a 12-month follow-up. We will assume the immediate impact on quality of life *(QoL)* is indicated by the difference in mean EQ-5D scores for women with negative results versus women with falsely positive results and that this difference in QoL lasts until the average time that the falsely positive result is reversed by subsequent information *(e.g., a follow-up mammogram, or a biopsy)*. If the mean 12-month follow-up QoL measurements for these same women are different, we will presume the difference in these QoLs has

lasted from the average time of the true negative information to the 12-month follow-up. These two quality-adjusted times will be added together to get one year of quality adjusted time for women with an initial negative result (Q_n) and another quality adjusted time for women with a false positive result (Q_p) – so each of these quantities is computed from QoL data summarized over the trial. The two frequencies, *f*., are derived from the reader studies of conventional and digital mammography.

The product of the two differences will be reported in units of QALY, quality-adjusted life years. *(See MR Gold et al., Cost-effectiveness in health and medicine, Oxford University Press, 1996, Chapter 4, for commentary on QALY methodology.*

This book was sponsored by ODPHP/DHHS to be the definitive statement on cost-effectiveness methods for the Public Health Service.)

Thus, although the impact of a false positive result is not directly *observable* in this study where all screenees have both types of imaging study, the impact is directly *calculable* from data produced by the study.

11.0 STATISTICAL CONSIDERATIONS

REMOVED FROM WEB VERSION

12.0 ADVERSE EVENT REPORTING

12.1 Definition of Adverse Event

An **Adverse Event (AE)** is any untoward medical occurrence in a participant that does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

12.2 Definition of Serious Adverse Effect

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:

- Results in death or is life-threatening (at the time of the event) or
- Requires inpatient hospitalization or prolongation of an existing hospitalization or
- Results in persistent or significant disability or incapacity

12.3 Adverse Event Grading

Grade is used to denote the severity of the adverse event. An AE is graded using the following categories (provided the term does NOT appear in the current version of the Common Toxicity Criteria v.3.0 [CTCAE]):

0 – Within normal limits
1 – Mild
2 – Moderate
3 – Severe
4 – Life-threatening or disabling
5 – Fatal

(For terms listed in the CTCAE, the grade is still recorded as 1, 2, 3, 4, or 5; however, the definition of the various grades will be specific to the term being used.)

12.4 Expected Adverse Events from Mammography

Bruising
Discomfort

Skin tear

12.5 Expected Adverse Events from Contrast Agent (gadolinium)

Nausea
Headache
Hives
Temporary low blood pressure
Allergic reaction

12.6 Expected Adverse Events from Biopsy

Minor discomfort
Bleeding
Infection
Bruising
Collection of air or gas in the chest cavity (pneumothorox)
Anesthesia-related problems

12.7 Reporting of Adverse Events

Prompt reporting of adverse events is the responsibility of each investigator, clinical research associate, and nurse engaged in clinical research. Please refer to the ACRIN Adverse Event Reporting Manual for specific details about what to report and when. Anyone uncertain about whether a particular adverse event should be reported should contact the ACRIN headquarters at 215-574-3150 for assistance. Any event that is judged to be NOT related to the treatment or procedure should NOT be reported as an adverse event. However, an adverse event report should be submitted if there is a reasonable suspicion of the medical treatment or imaging procedure effect.

12.8 When to Report

12.8.1 You must use expedited event reporting to within 10 working days for all Grade 5 events occurring within 30 days of the study intervention, regardless of attribution and regardless of whether the event was expected or unexpected. You must use expedited event reporting within 10 working days for Grade 4 unexpected events occurring within 30 days of the study intervention, regardless of attribution. These reports should be sent to ACRIN, NCI's Biomedical Imaging Program (BIP), and the local Institutional Review Board (IRB).

12.8.2 All fatal (Grade 5) adverse events should also be reported by telephone to NCI and ACRIN within 24 hours of the event.

12.8.3 Expedited adverse event reporting is NOT required for expected events of grades 1-4 or unexpected-indirect adverse events of any grade.

12.8.4 All expedited reports should be reported within ten (10) working days of knowledge of the event. All fatal adverse events should also be reported by telephone to the NCI and to ACRIN within 24 hours of knowledge of the event.

12.9 How to Report

12.9.1 An expedited adverse event report requires submission to the NCI-BIP and ACRIN using the paper templates "Adverse Event Expedited Report—Single Agent" or "Adverse Event Expedited Report—Multiple Agents," available on the CTEP home page, http://ctep.info.nih.gov. Protocols involving only imaging procedures must be submitted using a paper version. Investigators following those protocols should omit the Course Information section and the Protocol Agent section, even though the template indicates those as mandatory. (Do not try to send the form via the web site; it will not accept a form without those fields filled in.)

12.9.2 Completed expedited reports should be sent to:

NCI
Barbara A. Galen, MSN, CRNP, Program Director
Re: Adverse Event Report
Biomedical Imaging Program
6130 Executive Blvd., MSC 7412
Bethesda, MD 20892-7412

To make a telephone report, contact NCI at (301) 496-9531, available 24 hours a day (recorder after hours from 5 PM to 9 AM ET).

12.9.3 A copy of all expedited adverse event reports should be sent to **ACRIN** by fax at **(215)-717-0936.** All fatal adverse events should be reported by telephone within 24-hours of the event. To make a telephone report to ACRIN, call **(215)-717-2763**, available 24 hours a day (recorder after hours from 5 PM to 8 AM ET).

12.9.4 All expedited adverse event reports should be sent to your local Institutional Review Board (IRB). Adverse events not requiring expedited reporting are normally reported to your local IRB in an annual report.

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APPENDIX I: SAMPLE CONSENT FOR RESEARCH STUDY

ACRIN 6652

STUDY TITLE: DIGITAL VS. SCREEN-FILM MAMMOGRAPHY

This is a clinical trial (a type of research study). Clinical trials include only participants who choose to take part. Please take your time to make your decision.

You are being asked to be in this study because you are scheduled for a standard screening mammogram today.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to figure out whether a new type of breast x-ray machine is as good or better at finding breast cancer as the traditional type of breast x-ray machine. You are being asked to take part in a study to evaluate a new, experimental type of mammography called digital mammography. This uses electronics instead of film to record your mammogram. This study will try to determine if this new technology will be able to detect breast cancers more accurately compared to the current standard, film mammography.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 49,500 women will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

If you agree to take part in this study you will receive:

Before Mammograms:

Some women will be asked to complete two brief questionnaires.

All women will be asked to give some background information about themselves.

At Time of Enrollment:

A digital mammogram will be taken. This will be four views altogether, two per breast.

A standard screen-film mammogram will be taken. This will also be four views altogether, two per breast. You are scheduled to undergo this type of mammogram whether or not you decide to participate in this research project.

For some women, especially those with large breasts, additional digital and film mammograms might have to be taken to assure that all portions of both breasts are included.

The digital mammography examination will seem nearly identical to the standard film mammography examination. A certified radiologic technologist will conduct both examinations. Each examination will be interpreted by a board-certified radiologist with special expertise in mammography. The digital exam and the standard film exam will each typically consist of two images of each breast. Additional images may be obtained during the exam.

You and your doctor will be informed if a suspicious finding appears on either the digital examination or the standard film examination. This may require additional follow-up including exams, biopsies, or other tests. Two different mammograms may show different results and you will undergo evaluation if EITHER test is abnormal.

If you undergo a biopsy, this tissue will be sent to the hospital's pathology department for testing. You are being asked for permission to use the remainder of the tissue samples for tests related to this protocol. Since this tissue was removed at the time of biopsy, your permission to use this tissue will not lead to any additional procedures or expense. This tissue will be sent to a central office for review and research investigation associated with this protocol and after that review is completed, it will be returned to your hospital's pathology department.

The first 42 women at each site will also be asked to fill in a short survey that includes some general questions about their quality of life.

Within a few days after Mammograms:

Some participants will be contacted by telephone to answer some survey questions. One of the surveys is titled EuroQol EQ-5D. This questionnaire will ask general questions about your quality of life. In the same telephone call, a second short questionnaire about any anxiety you may be experiencing will be given; it is called the "STAI Y-6". Together these two questionnaires will take approximately 10 minutes to complete. These surveys will be administered only to a sampling of participants. The sample will include some participants who will have additional follow-up tests done and some participants who will not have additional follow-up tests.

One Year After Mammograms:

A standard screen-film mammogram, as would be performed as part of our routine health care. If you don't schedule this at the appropriate time, you might be contacted by study personnel to remind you to undergo the mammogram, or to obtain a copy of the mammogram if it has been taken at another facility.

Quality of Life Questionnaire titled EuroQol EQ-5D, the STAI Y-6 questionnaire about anxiety and the patient questionnaire (PQ) about Quality of Life will be administered via telephone to the same women who were selected to answer the survey questions within a few days of their mammogram.

The PQ questionnaire asks you how you felt about any follow-up tests used for a positive screening tests and time burden and anxiety caused by follow-up exams and procedures.

These questionnaires will be administered over the phone by an ACRIN representative at a central location.

HOW LONG WILL I BE IN THE STUDY?

Undergoing the digital mammogram itself and answering questions about yourself as part of the study will take approximately 30 minutes of your time today. You will need to return for follow-up mammography in one year. In addition, you may also be contacted during a 2-3 year period to see if you have had normal mammograms and clinical breast examinations. This information will be used for research purposes only.

The researcher may decide to take you off this study if you cannot for any reason return for follow-up mammography in one year at your institution or provide follow–up mammogram films from another institution.

If you are pregnant or have reason to believe you might be pregnant, you should not participate in this research study, either now or at follow-up.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

Each of your breasts will be compressed during the digital mammography exam, just as they are during a standard film mammography exam. This compression can cause bruising, discomfort, or tearing of the skin. In addition, as with your film mammography examination, your breast will receive a small amount of radiation. The effective radiation dose from the digital mammography will be between 150 and 200 millirads per view. You will receive two views to each breast so the total amount of radiation will be 300 to 400 millirads to each breast. This is about the same radiation dose that you will receive with the current, high quality screen-film mammography that you have done on this study. Having the digital mammography in addition to the standard screen-film mammography will give an additional 300-400 millirads to each breast. The radiation exposure during a mammographic examination has an overall possible risk of one in a million of causing a cancer. There is also the risk that the digital study will falsely indicate an abnormality that could cause extra procedures to be done, and cause unnecessary anxiety.

By enrolling in this study, you agree to allow us to check your state Central Cancer Registry to see if you were diagnosed with breast cancer during the two or three years following your examination. This will help determine if there may have been a cancer, which was not visible on either standard film mammography or digital mammography. For the same reason, we may also attempt to contact you during this two to three year period to see if you have had normal mammograms and clinical breast examinations. This information will be used for research purposes only.

Additional studies may be done using the data and images we collect as part of this research project.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to participate in this study, there may or may not be direct medical benefit to you. There is a possibility that this new technology may be more sensitive in detecting early breast cancer. If you have breast cancer that is not evident by physical exam or regular mammography, this test may detect it. Early detection of breast cancer generally corresponds with an improved prognosis. If any abnormalities are observed from the digital systems that were not seen on the conventional mammograms, that information will be provided to your physician.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study and just have the standard screen-film mammography.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the American College of Radiology Imaging Network *(ACRIN).* All data sent to ACRIN over the web will be coded so that other people cannot read it. Personal identifiers will be removed from your data by ACRIN and replaced with a unique study number before it is sent to the Bio-Statistics Center for analysis.

Your mammograms will be permanently kept on file at ACRIN and used for future research. Your mammograms can be obtained at your request for use within two business days. ACRIN requests that you return the films for research purposes after they have been used.

Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration *(FDA),* the National Cancer Institute *(NCI),* qualified representatives of applicable mammography manufacturers, and other groups or organizations that have a role in this study.

WHAT ARE THE COSTS?

There will be no cost to you for the digital mammogram. Your screen-film mammogram is part of your routine health care and will be paid for in whatever manner you normally pay for such expenses. It is possible that the research digital mammogram might lead to further evaluation of one or both of your breasts, even a breast biopsy. All other costs that may occur as a result of your participation in this study will be paid for by you or your insurance provider.

In the case of injury or illness resulting from this study, emergency medical treatment is

available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. You or your insurance company will be charged for continuing medical care and/or hospitalization. You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

For additional information about your health, you may contact:

_____ _____
Name Telephone Number

For information about this study, you may contact:

_____ _____
Name Telephone Number

For information about your rights as a research subject, you may contact:
(OHRP suggests that this person not be the investigator or anyone else directly involved with the research)

_____ _____
Name Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at: **1–800–4–CANCER (1–800–422–6237)** or **TTY: 1–800–332–8615.**

Visit the NCI's Web sites for comprehensive clinical trials information **http://cancertrials.nci.nih.gov** or for accurate cancer information including PDQ **http://cancernet.nci.nih.gov.**

Visit the American College of Radiology Imaging Network's website at www.acrin.org

SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol *(full study plan)*.

_____ _____

Participant Signature *(or legal Representative)* Date

ACRIN 6652
ADDITIONAL CONSENT

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE: DIGITAL VS. SCREEN-FILM MAMMOGRAPHY
LONG TERM CONTACT

We are asking for your permission to contact you by mail and/or telephone for up to 20 years. The mailings or telephone calls will be done about once every year. An ACRIN representative will contact you for information. You will be asked about your health, recent mammograms and any clinical breast exams that you have had. This information will be used for research purposes only and it will be added to the information obtained from the study.

SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol *(full study plan)*.

_____ _____
Participant Signature *(or legal Representative)* Date

APPENDIX II

AJCC BREAST STAGING
Breast, 5th Edition

DEFINITION OF TNM

Primary Tumor (T)

Definitions for classifying the primary tumor *(T)* are the same for clinical and for pathologic classification. The telescoping method of classification can be applied. If the measurement is made by physical examination, the examiner will use the major headings *(T1, T2, or T3)*. If other measurements, such as mammographic or pathologic, are used, the examiner can use the telescoped subsets of T1.

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ*: intraductal carcinoma, lobular carcinoma *in situ*, or Paget's disease of the nipple with no tumor.
T1 Tumor 2 cm or less in greatest dimension
T1mic Microinvasion 0.1 cm or less in greatest dimension

T1a Tumor more than 0.1 but not more than 0.5 cm in greatest dimension
T1b Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
T1c Tumor more than 1 cm but not more than 2 cm in greatest dimension

T2 Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3 Tumor more than 5 cm in greatest dimension
T4 Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below.
T4a Extension to chest wall
T4b Edema *(including peau d' orange)* or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
T4c Both *(T4a and T4b)*
T4d Inflammatory carcinoma

Note: Paget's disease associated with a tumor is classified according to the size of the tumor.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed *(e.g., previously removed)*
N0 No regional lymph node metastasis
N1 Metastasis to movable ipsilateral lymph node*(s)*
N2 Metastasis to ipsilateral axillary lymph node*(s)* fixed to one another or to other structures
N3 Metastasis to ipsilateral internal mammary lymph node*(s)*

Pathologic Classification (pN)

pNX Regional lymph nodes cannot be assessed *(e.g., previously removed, or not removed for pathologic study)*

pN0 No regional lymph node metastasis
pN1 Metastasis to movable ipsilateral axillary lymph node*(s)*
- pN1a Only micrometastasis *(none larger than 0.2 cm)*
- pN1b Metastasis to lymph node*(s)*, any larger than 0.2 cm
  - pN1bi Metastasis in one to three lymph nodes, any more than 0.2 cm and all less than 2 cm in greatest dimension
  - pN1bii Metastasis to four or more lymph nodes, any more than 0.2 cm and all less than 2 cm in greatest dimension
  - pN1biii Extension of tumor beyond the capsule of a lymph node metastasis less than 2 cm in greatest dimension
  - pN1biv Metastasis to a lymph node 2 cm or more in greatest dimension
- pN2 Metastasis to ipsilateral axillary lymph nodes that are fixed to one another or to other structures
- pN3 Metastasis to ipsilateral internal mammary lymph node*(s)*

Distant Metastasis (M)

MX Presence of distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis *(includes metastasis to ipsilateral supraclavicular lymph node[(s)])*

STAGE GROUPING

Stage 0	Tis	N0	M0
Stage I	T1*	N0	M0
Stage IIA	T0	N1	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

* Note: T1 includes T1mic
** Note: The prognosis of participants with N1a is similar to that of participants with pN0.

APPENDIX III

Institution #

ACRIN 6652 **ELIGIBILITY CHECKLIST *(S)***

Case # _____ *(page 1 of 2)*

_____(N) 1. Is this patient enrolled in other digital mammography trials where the film screen mammogram would NOT be able to be provided for the study?

_____ 2. Year of first baseline mammogram.

_____(Y) 3. Is the patient scheduled for screening mammography?

_____(N) 4. Does the patient have a focal dominant lump?

_____(N) 5. Does the patient have a bloody or clear discharge?

_____(N) 6. Does the patient have breast implants?

_____(N) 7. Is the patient pregnant, nursing, or does she have any reason to believe she may be pregnant?

_____(Y) 8. Does the patient understand and agree to the follow-up requirements as outlined in Section 8.0 of the protocol?

_____(N) 9. Does the patient have a history of breast cancer treated with lumpectomy?

_____(N/Y) 10. Does the patient have a history of breast cancer treated with mastectomy?

_____ 11. Month/Year of last mammogram (mm/yyyy)

_____(N/Y) 12. Has the patient signed the 20-year consent?

APPENDIX III

Institution #

ACRIN 6652 **ELIGIBILITY CHECKLIST *(S)***

Case # ____ *(page 2 of 2)*

The following questions will be asked at Study Registration:

_____ 1. Name of institutional person registering this case?

_____(Y) 2. Has the Eligibility Checklist *(above)* been completed?

_____(Y) 3. Is the patient eligible for this study?

_____ 4. Date the study-specific Consent Form was signed? *(must be prior to study entry)*

_____ 5. Patient's Name or Initials (last, first)

_____ 6. Verifying Physician

_____ 7. Date of Birth (mm/dd/yyyy)

_____ 8. Race

_____ 9. Patient's Country of Residence

_____ 10. Zip Code *(US residents only)*

_____ 11. Patient's Insurance Status

_____ 12. Will any component of the patient's care be given at a military or VA facility?

_____ 13. Date of Protocol Imaging

_____ 14. Date of Randomization

Completed by _____ Date _____

APPENDIX IV

Participating Institutions

Beth Israel Deaconess Medical Center
Department of Radiology
330 Brookline Avenue
Boston, MA 02215

Memorial Sloan-Kettering
Guttman Diagnostic Center
55 Fifth Avenue, 12th Floor
New York, NY 10003

LaGrange Memorial Hospital
5101 S. Willow Springs Road
LaGrange, IL 60525

University of North Carolina
Department of Radiology
Campus Box 7510
Chapel Hill, NC 27599-7510

University of California Davis
Department of Radiology
4860 Y Street, Suite 3100
Sacramento, CA 95817

University of California Los Angeles
Department of Radiological Sciences
200 UCLA Medical Plaza, Rm 165-47
Los Angeles, CA 90095-6952

University of Washington
Roosevelt Clinic
4245 Roosevelt Way NE
Seattle, WA 98195-7115

Northwestern University
Department of Radiology
Lynn Sage Breast Screening Center
676 N. St. Clair, Suite 1950
Chicago, IL 60611

Washington Radiology Associates, PC
2141 K Street, NW
Suite 900
Washington, DC 20037

Shore Memorial Hospital
1 E. New York Avenue
Somers Point, NJ 08244

University of Cincinnati Hospital
234 Goodman St.
Cincinnati, OH 45219

University of Iowa
Department of Radiology
200 Hawkins Dr.
Iowa City, IA 52242

University of Texas Southwestern
Medical Center at Dallas
Breast Imaging Center
2201 Inwood Road
Dallas, TX 75390

Washington University in St. Louis
School of Medicine
Barnes-Jewish Hospital
Breast Health Center
Center for Advanced Medicine, 5th floor
4921 Parkview Place
St. Louis, MO 63110

Mt. Sinai Medical Center
One Gustave L. Levy Place
New York, NY 10029-6374

Monmouth Medical Center
The Jacqueline M. Wilentz
Comprehensive Breast Center
300 2nd Ave.
Long Branch, NJ 07740

University of Virginia Medical Ctr.
Department of Radiology
1215 Lee St.
Charlottesville, VA

University of Colorado Hospital
Campus Box F724
1635 N. Ursula
Denver, CO 80010

The Emory Clinic
1365-B Clifton Road NE, Suite 1300
Atlanta, GA 30322

University of Pennsylvania
Department of Radiology
3400 Spruce Street
Philadelphia, PA 19104-4283

Sunnybrook & Women's College HSC
2075 Bayview Avenue
Toronto, Ontario, Canada M4N 3M5

Columbia Presbyterian Medical Center
Breast Imaging Center
Herbert Irving Pavilion, 10th Floor
161 Fort Washington Avenue
New York, NY 10032

Thomas Jefferson University
Mammography Screening Center
909 Walnut St.
Philadelphia, PA 19107

Johns Hopkins University
Mammography and Breast Imaging, Rm. 4155
Johns Hopkings Outpatient Center
601 North Caroline Avenue
Baltimore, MD 21287

William Beaumont Hospital
3577 W. 13 Mile Rd.
Royal Oak, MI 48073

Massachusetts General Hospital
Department of Radiology
55 Fruit St.
Boston, MA 02114

Allegheny Cancer Center
320 E. North Ave.
Pittsburgh, PA 15212

The Elizabeth Wende Breast Clinic
170 Sawgrass Drive
Rochester, NY 14620

H. Lee Moffitt Cancer Center
12902 Magnolia Drive
Tampa, FL 33612

Brown University
Rhode Island Hospital
Diagnostic Imaging Research
593 Eddy Street
Providence, RI 02903

Lahey Clinic
41 Mall Rd.
Burlington, MA 01805

APPENDIX V

DMIST Source Documentation

Registration

- On line immediate registration up to 24 hours from the time of consent is not a deficiency.
- Off line registration over two business days is considered a major deficiency.

Regulatory binders must have:

- All source documentation for initial IRB approval
- All annual re-approval letters from IRB within 365 days from the last approval
- All Protocol Amendments, checked for IRB approval, verifying version date, and amendments
- 310 Form, IRB letter or IRB meeting minutes approving Protocol participation
- Current version of the informed consent

Approved IRB consent form must be sent to ACRIN Headquarters to be kept on file by the ACRIN Regulatory Department.

- If the incorrect IRB approval is sent to headquarters, a regulatory staff member will notify site that an incorrect approval was obtained (i.e., expedited instead of full) and inform the site to resubmit to their IRB. A general list of regulations will not be sent to the sites.

Consent Form

- This form must be signed and dated by participants and contain all other signatures requested by the local IRB.
- If the site consent form requires the PI's signature, a letter from the IRB must state a time frame within which the PI must sign. If no time frame is specified, all consents should be signed by the PI within two weeks of the participant's signature.
- Informed consent will be checked to verify that the witness and participant have signed on the same date.
- Twenty year consent form if agreed to and signed/dated by participant.

Randomization Sequence

- Randomization sequence will be verified by documentation containing the technologist's printed name, signature, and the date.

Supplemental instructions for audit documentation.

Sites will maintain electronic copies of submitted data and any supporting source documentation within the participant's research file. The site Research Associate will print the documents required by the auditor's upon notification of the audit date.

Superscript detail descriptions for the following source documentation:

1 Print selected pages of the forms.
2 Good Clinical Practice (GCP) standards should be followed when recording data. All data documentation provided by the participant is expected to be reviewed by the Research Associate and the participant. In the event a discrepancy is noted upon review of documents completed by the participant, the initials of the participant and the RA in addition to the date must be noted next to the revised item.
3 The utility for digitized signatures will be available at all sites for use when data is entered directly into the web application.

ACRIN will provide the RAs and PIs at the institutions the capability to store verifiable signatures that are entered by the participants in a digital format. This capability can be accomplished by means of software application developed by the HQ. These digital signatures will be associated with specific forms completed by an RA and can then be saved into the local machine. The document with the digital signature is viewable and can be printed at a later stage. The digital signature can be captured via the web by various input devices such as Mouse, Pen Pad, etc. This technique of capturing signature is designed to improve the functionality of the Web by providing more flexible and adaptable information identification.

Form	Source Documentation
A0 Form Registration/ Eligibility and Randomization **Registration Confirmation**[1] i.e. Randomization sequence confirmation screen	• Eligibility Checklist **signed and dated** by Research Associate (printed copy of Appendix III) **OR** • If information is entered directly on-line, the confirmation email must be **printed**, **signed and dated** by the RA **OR** • A printed **copy of the A0 signed and dated** by the RA with verification of information origination, i.e. participant interview, mailed in form. • Participant registration confirmation[1]**.** • Randomization form **signed and dated** by the Technologist
I1 Form – Initial Evaluation	• UNC Worksheet[2] (completed by participant) o **Signed and dated** by the participant **OR** • Site specific worksheet[2] (completed by participant) o **Signed and dated** by the participant **OR** • I1 Form[1] o Direct entry of information obtained directly from participant through interview ▪ Participant's **digitized signature**[3] **and date** ▪ Documented notation stating the source of information and the method, e.g., participant interview ▪ RA's **digitized signature** [3] **and date** o I1 Form (completed by participant) ▪ Signed and dated by the participant **OR** • Mammography Department Questionnaire[2] in addition to any of the above OR in place of the above if ALL pertinent information is collected on the questionnaire. (completed and signed by participant)

Form	Source Documentation
IA Form – Study Mammography Interpretation Film-Screen	• UNC Worksheet (completed by Radiologist) o **Signed and dated*** by the Radiologist OR • Site-specific worksheet (completed by Radiologist) o **Signed and dated*** by the Radiologist OR • IA Form[1] o Direct entry of information obtained directly from the study images, o Radiologist's **digitized signature[3] and date*** OR o Printed IA Form - **signed and dated** by the Radiologist* OR • Clinical mammography report, clearly stating the reader of the film screen, the date of the film screen, the date of the interpretation, and the BI-RADS score ***Date of the signature on worksheet or IA form is within 2 weeks of study interpretation (if prior images are referenced, form can be signed and submitted within 30 days of imaging, per MQSA guidelines).**
ID Form Digital Interpretation	• UNC Worksheet (completed by Radiologist) o **Signed and dated*** by the Radiologist **OR** • Site-specific worksheet (completed by Radiologist) o **Signed and dated*** by the Radiologist **OR** • ID Form[1] o Direct entry of information obtained directly from the study images o Radiologist's **digitized signature[3] and date*** **OR** o Printed ID Form—**signed and dated** by the Radiologist* **OR** • Clinical mammography report, clearly stating the reader of the digital imaging, the date of digital imaging, the date of the interpretation, and the BI-RADS score ***Date of the signature on worksheet or ID form is within 2 weeks of study interpretation (if prior images are referenced, form can be signed and submitted within 30 days of imaging, per MQSA guidelines).**

Form	Source Documentation

IM Form –
Additional Work-up/
Prior Films
	• UNC Worksheet (completed by Radiologist)
	  o **Signed and dated*** by the Radiologist
	OR
	• Site-specific worksheet (completed by Radiologist)
	  o **Signed and dated*** by the Radiologist
	OR
	• IM Form[1]
	  o Direct entry of information obtained directly from the study images
	  o Radiologist's **digitized signature[2] and date**
	OR
	  o Printed IM Form—**signed and dated** by the Radiologist*
	AND
	• All applicable clinical reports, e.g., Biopsy, surgical, imaging reports.
	
	***Date of the signature** on worksheet or IM form is **within 2 weeks of study interpretation**.

BX Form –Biopsy Procedure	• Copy of Biopsy procedure report in Participant Research file.
P1 Pathology Report	• Copy of pathology report in Participant Research file.

F1 Form
Breast Cancer Status
Follow-up (3, 6, and 9 months, if recommended, and at 12 months for **all** participants)
	• Site-specific Worksheet
	  o **Signed and dated** by the RA
	OR
	• F1 Form[1]
	  o Direct entry of information obtained directly from participant through interview
	  ▪ RA's **digitized signature[2] and date**
	  ▪ Documented notation stating the source of information and the method, e.g., participant interview
	OR
	  o F1 form, printed, verified for accuracy, signed by RA and dated day form is printed
	AND
	• Imaging reports, pathology reports, operative reports and progress notes as applicable.
	
	(One year follow-up mammography to be completed within 10-15 months of the initial imaging.)

Form	Source Documentation
IE Form – Follow-up Mammography Interpretation (at 3, 6, and 9 months, if recommended; at 1 year only if participant has BI-RADS 3, 4, or 5 at 1-year follow-up)	• UNC Worksheet (completed by Radiologist) o **Signed and date**d* by the Radiologist **OR** • Site-specific worksheet (completed by Radiologist) o **Signed and dated*** by the Radiologist **OR** • IE Form o Direct entry of information obtained directly from the study images o Radiologist's **digitized signature[2] and date** **OR** o Printed IE Form—**signed and dated** by the Radiologist* **AND** • Clinical Mammography Report is required in addition to the IE Form, worksheet and site-specific worksheet. ***Date of the signature** on worksheet or IE form **is within 2 weeks of study interpretation.**
PR (Patient Non-Participation) Form	• Copy of PR form in Participant Research file, **signed and dated**, by RA. All applicable notes in and/or e-mails should be filed in the participant's study chart. • RA must clearly document the reason a participant refuses to continue in the study e.g., technical difficulties, scheduling conflicts, withdrawn consent, etc.
DE Form: Documentation of Effort	• Completed, signed, and dated by the RA
E2 Form: Breast Cancer Status Summary	• Completed, signed, and dated by the RA **AND** • Clinical reports, imaging reports, pathology reports, surgical reports, progress notes, etc., as applicable

APPENDIX VI

ACRIN 6652
DMIST Annual Follow-up

These guidelines are based on follow-up procedures at UNC. All follow-up strategies must follow the guidelines of the local IRB.

Forms must be submitted for each participant enrolled in the DMIST approximately 1 year after the date of the enrollment. The purpose of these forms is to determine if the participant has been diagnosed with breast cancer since the prior mammogram or has had any breast health problems since her enrollment in DMIST. Each participant, except those diagnosed with bilateral breast cancer within 15 months of enrollment, must have an F1 form completed. The RA will complete the F1 form. Any participant who is a BI-RADS 3, 4, or 5 requires that an IE form be completed by a DMIST radiologist in addition to an F1 being completed.

Procedure

Prior to calling the participant, check to see if a radiology report for an annual mammogram is present. If it is present, print out the report, complete an F1, and, if necessary, have reading radiologist complete an IE. Submit forms and file all forms in participant case file. Enter participant into DMIST follow-up database. A participant call record does NOT need to be completed.

If no radiology report is present, check to determine if participant is scheduled to return for annual mammogram. Make note of appointment date on a participant call record and file in follow-up log book. Follow above procedures once report is available.

If no appointment is scheduled the participant must be contacted.

Participant Contact Schedule

The participant must be contacted 12 months after her enrollment in DMIST. Please note the date the participant was enrolled in DMIST on the call record and the DE form. An attempt to contact the participant must be made at least once every 2 weeks for up to three months. If no contact is made during the three consecutive months, a final attempt to reach the participant must be made 18 months after her enrollment in DMIST. If the participant's phone is not working, the participant's doctor and/or contact person must be contacted in order to obtain accurate contact information. A busy number does not qualify as a contact, and another attempt to contact the participant must be made that month. Please follow the participant's instructions as noted on the Confidential Contact Form when contacting the participant at work or leaving a message. Do NOT leave a message for participants who do not specifically express permission to do so. All calls must be noted on a call record.

If the participant schedules an appointment, note the date of the appointment on the participant call record. When the appointment passes and a clinical report is available, complete the above procedures.

If the participant has had a mammogram at another facility, an attempt must be made to obtain the films and/or the clinical report from this mammogram.

If a participant is contacted, but she refuses to return for an annual mammogram, please obtain necessary information.

If contact is made with the participant but no appointment has been scheduled at 18 months past participant enrollment in DMIST, the RA may obtain information from the participant. If the participant is not willing to schedule a mammogram at that time, the RA should request that DMIST be notified of the results the next time she does have a mammogram. This information must be documented on the record and the DE form. However, the participant should be encouraged to return at that time, even though her imaging would occur outside the 10-15 month window.

If no contact is made with the participant after six months (18 months after enrolment in DMIST), submit the F1. Contact date is the last date your institution had contact with the participant (at screening/additional work-up/or if any other phone calls made in the interim). The RA must check with the State Tumor Board Registry to determine participant has not been diagnosed with breast cancer.

Attempts must be made to collect information about the participant's breast cancer status. E2 and DE forms are used for this purpose for women with no follow-up mammogram. The Documentation of Effort (DE) form is used to record all attempts to contact the participant to schedule her follow-up mammogram, as well as steps taken to determine her breast cancer status. E2 and DE forms are not required for any participants for whom you have a BI-RADS score from a mammogram taken 10 months or more from enrollment.

The E2 form will be submitted on paper to Data Management where the data will be entered into the main database. Data Management will add E2 forms to participants' calendars for every participant whose F1 form reports her as lost. Documentation of Effort (DE) forms will be required for all of these cases, but will only be submitted to Data Management if requested. The DE form should be kept as part of the participant's study record and is subject to audit.

** 6652 DE and E2 forms are posted on the ACRIN web site (www.acrin.org).