Table of Contents

1. Statistical Analysis Plan (SAP)

EA1141: Comparison of Abbreviated Breast MRI and Digital Breast Tomosynthesis in Breast Cancer Screening in Women with Dense Breasts

Statistical Analysis Plan (SAP)
(10/10/2019)

Study Chair:	Christopher Comstock, MD
Study Co-chairs:	Christiane Kuhl, MD
	Gillian Newstead, MD
Protocol Statistician:	Constantine Gatsonis, PhD
Protocol Epidemiologist:	Ilana Gareen, PhD
Data Manager:	Melissa Tepper, MS
Project Manager:	Sharon Mallett, MS

Prepared by Bradley S. Snyder, MS

ECOG-ACRIN Biostatistics Center
Center for Statistical Sciences
Brown University Box G-S121-7
121 South Main Street
Providence, RI 02912
tel: 401-863-9181

Table of Contents

I. Introduction

This Statistical Analysis Plan (SAP) for EA1141 is based on the protocol version dated February 26, 2018 (amendment 4), and describes details on statistics and analyses to be reported in the primary paper, which will include the primary aim, secondary aim #1(a), and secondary aim #2. ***Other secondary aims are not included in this SAP, and will be addressed in separate publications in the future as data become available***. A complete list of study objectives can be found in section III of this document.

II. General Principles

The analysis and statistical reporting will be conducted by the ECOG-ACRIN Biostatistics Center Office located at Brown University. All analyses will be performed using SAS version 9.4, or R version 3.4.4, or higher.

III. Study Objectives

The primary objective of EA1141 was to compare the rate of detection of invasive cancers between the initial abbreviated breast MRI (year 0 AB-MR) and the initial digital breast tomosynthesis (year 0 DBT).

Secondary objectives include:

- #1: To compare the positive predictive value of biopsy, call back rates, and short-term follow up rates after AB-MR and DBT on both (a) the initial (year 0) screening, and (b) 1 year follow up (year 1) studies.
- #2: To estimate and compare the sensitivity and specificity of AB-MR and DBT, using the 1 year follow up to define a reference standard.
- #3: To compare patient-reported short-term quality of life related to diagnostic testing with AB-MR and DBT using the Testing Morbidities Index.
- #4: To compare willingness to return for testing with AB-MR vs DBT within the recommended screening interval, and to explore factors associated with willingness to return for screening.
- #5: To compare the tumor biology of invasive cancers and DCIS detected on AB-MR and DBT.
- #6: To estimate the incident cancer rate during the 3 years following the year 1 AB-MR/DBT when patients return to standard screening.

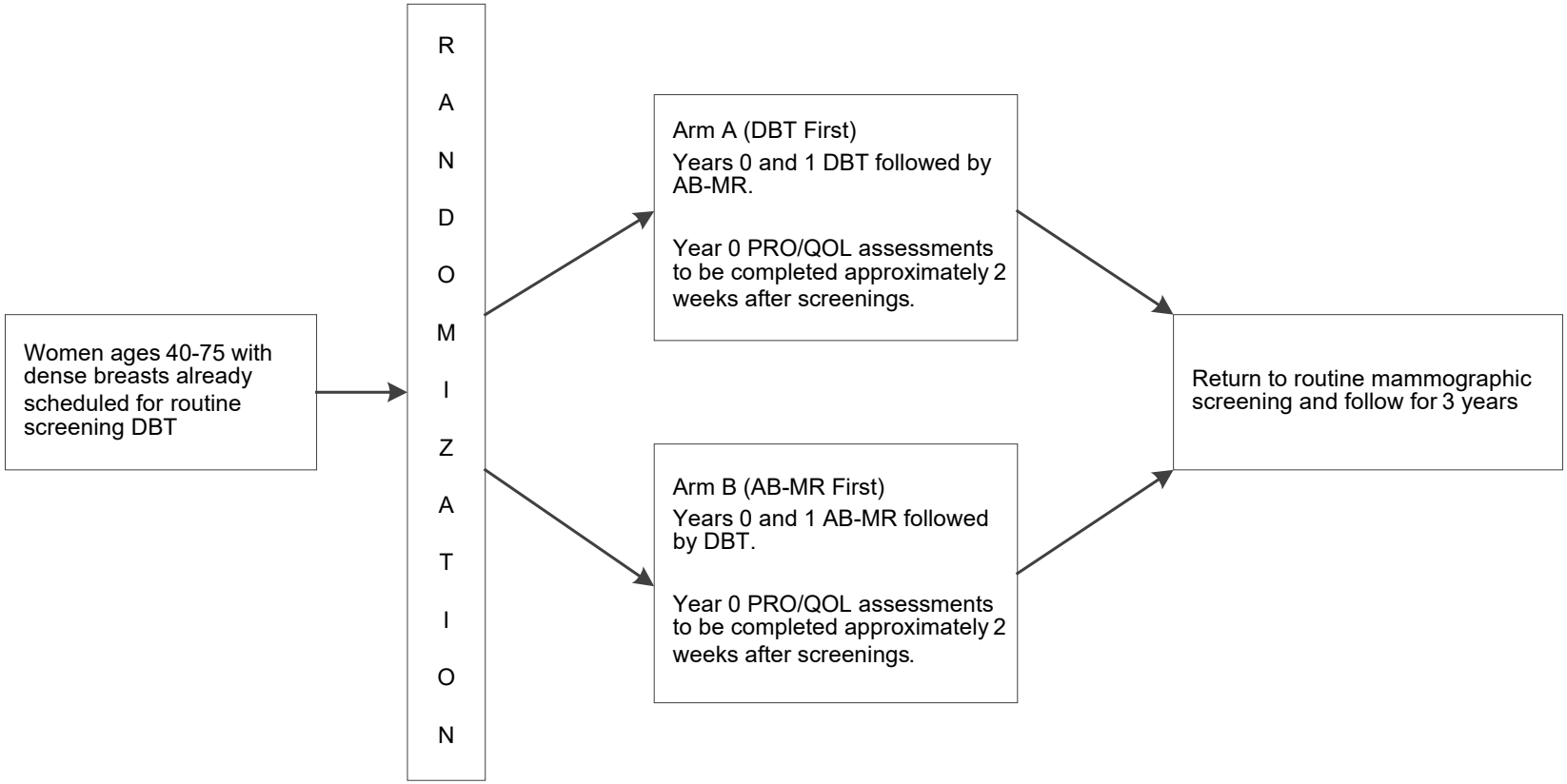
IV. Study Population and Design

Participants must be women of age 40 to 75 years with mammographically dense breasts [ACR BI-RADS lexicon categories c or d (heterogeneous or extreme fibroglandular tissue) on their most recent prior screening] who are scheduled for routine screening DBT; must be asymptomatic for breast disease; must be able to undergo breast MRI with contrast enhancement; and, must agree to not undergo screening ultrasound of the breast for the duration of the one-year study imaging period. Participants must not be pregnant or breast-feeding; must not have previously had a breast MRI or molecular breast imaging (MBI, MIBI); must not have undergone a screening breast ultrasound within 12 months prior to randomization; must have no known breast cancer (DCIS or invasive cancer); must not be currently undergoing treatment for breast cancer; must not be planning surgery for a high risk lesion; must not be taking chemoprevention for breast cancer; and, must not be suspected of being at high-risk for breast cancer as defined by the ACS breast MR screening recommendations (lifetime risk of 20-25%). A complete listing of all study inclusion and exclusion criteria can be found in section 3 of the study protocol.

All patients will undergo both DBT and AB-MR within 30 days following registration. Generally, the DBT and AB-MR will be performed on the same day and interpreted by two different radiologists, each blinded to the other modality. However, DBT and AB-MR can be performed within 24 hours of each other, as long as each radiologist remains blinded to the results of the other modality. Patients will be randomized to the order of which study is performed first. If DBT is the first test, any additional imaging (spot compression/magnification view and/or ultrasound) recommended from the screening DBT views should be completed and a final recommendation recorded on the DBT imaging data forms by the interpreting radiologist prior to the AB-MR. If AB-MR is performed first, the results should be recorded on the AB-MR imaging data forms prior to DBT. No biopsy should be performed until both the DBT and AB-MR have been completed. All suspicious findings on either the DBT or AB-MR should be biopsied regardless of the recommendation of the other modality. If the same suspicious lesion is detected on both DBT and AB-MR, the interpreting radiologists will determine the best modality for biopsy guidance. High risk lesions on core biopsy, such as ADH and LCIS, will be managed as per local site standard practice. All women will undergo DBT and AB-MR at 1 year in the same order as the baseline (year 0) DBT and AB-MR, and will be followed for 3 years after the year 1 AB-MR/DBT when patients return to standard screening.

In addition, patients will be recruited at the time of randomization into the patient reported outcomes portion of the study, and will be asked to complete forms approximately 2 weeks after the baseline (year 0) screening.

The study schema is as follows:



Accrual Goal= 1450

1. Suspicious lesions detected on one or both of the modalities at the Year 0 or 1 time points will be biopsied as per local standard practice.
2. Tissue collection and analysis for all cancers detected.

V. Sample Size Considerations

We are not aware of previous studies comparing AB-MR to DBT. Our choice of plausible values for the additional yield of AB-MR at the baseline (year 0) screen was based on a recent comparative study of MRI to FFDM, which reported an additional yield of about 12/1000 *invasive* cancers in a population of women at average risk [1,2]. We conservatively assumed that the difference in yield between AB-MR and DBT would be smaller, and computed the sample size required to detect a difference as low as 9/1000. The following table presents computations of the required sample size to ensure power 90% using a two-sided McNemar's test of level 0.05, and for a range of values of the difference in detection rates and total rates of discordant pairs. Based on these computations, we selected a sample size of 1363 cases with complete data from both tests and pathology. This sample size is needed to ensure power 90% for a difference in the rates of invasive cancer detection of 9/1000 when the discordant pair rate is in the middle of the range. Assuming that adequate information to evaluate the primary endpoint will not be available on up to 6% of cases, a sample size of **1450** will provide power 90% to compare the diagnostic yield in invasive cancer between the two modalities. Women that complete either only the AB-MR or only the DBT, but not both studies at baseline (year 0), will not be included in the analysis.

Power	Sample size	Difference in invasive cancer rates (AB-MR –DBT)	Proportion of discordant cases
0.90	1191	0.009	0.010
0.90	**1363**	**0.009**	**0.011**
0.90	1552	0.009	0.012
0.90	1057	0.010	0.011
0.90	1197	0.010	0.012
0.90	949	0.011	0.012

VI. Changes from the Original Protocol

The original protocol (dated April 18, 2016) has undergone 4 amendments:

Amendment 1 (dated November 15, 2016) amended the inclusion/exclusion criteria to exclude patients with prior molecular breast imaging (MBI, MIBI); mandated a pregnancy test be done within 2 weeks prior to randomization in women suspected of being pregnant, or unsure of their pregnancy status; and clarified blood sample submissions.

Amendment 2 (dated January 26, 2017) corrected a typographical error in the inclusion/exclusion criteria, specifically clarifying that patients must have mammographically dense breasts (ACR BI-RADS lexicon categories c or d) on their most recent prior screening.

Amendment 3 (dated July 25, 2017) loosened protocol criteria to allow the AB-MR and DBT screening exams to be done up to 24 hours apart, as long as the exams were still performed in the indicated randomized order; defined an allowable window for year 1 screening (no less than 11 months to no more than 13 months from baseline (year 0) screening); mandated and clarified that patients were to have follow-up contact through a phone call at 6 months (+/- 1 month) after the baseline screening, and immediately prior to the year 1 screening, and every 6 months (+/-1 month) thereafter for 3 years post year 1 screening; further clarified optional fast scanning for AB-MR for participating sites; and further clarified that the mandated pregnancy test for women uncertain of pregnancy status would be per local site standard of practice.

Amendment 4 (dated February 26, 2018) updated CTSU and Medidata RAVE language, updated the CTCAE version, clarified language regarding submission to TRIAD, and clarified language regarding tissue collection and follow-up contact.

VII. Analysis Sets

This section defines patient subsets which will be referred to throughout the remainder of the document.

Enrolled Set: All subjects registered to the trial, regardless of eligibility.

Analysis Set: All *eligible* subjects with both the baseline (year 0) AB-MR and the baseline (year 0) DBT completed. In particular, the following patients are excluded:

- Ineligible patients (i.e. patients documented to have failed the protocol inclusion/exclusion criteria)
- Patients which did not complete either the baseline (year 0) AB-MR or the baseline (year 0) DBT, or both.

A study flowchart showing the derivation of the analysis set, as well as patient exclusions, will be prepared.

VIII. Eligibility

Documented ineligibility will be tabulated, along with the reasons for failed inclusion/exclusion criteria. In addition, the number of eligibility waivers, and reasons for waiver, will be summarized, if applicable.

IX. Analysis Definitions

The primary endpoint is the invasive cancer detection rate based on the baseline (year 0) screening for each modality. Secondary endpoints to be reported in the manuscript will be assessed for the baseline screening. For each modality we will estimate and compare, (a) sensitivity, (b) specificity, (c) positive predictive value (PPV) of biopsy, and (d) additional imaging recommendation rate. Exploratory, pre-specified endpoints will include (a) the overall (invasive and DCIS) cancer detection rate, (b) interval cancer rate, (c) lesion-level estimated PPV of biopsy, (d) local stage of cancers detected, and (e) characteristics of cancers based on histopathological and immuno-histochemical information. Definitions of these endpoints are provided below.

A. Primary and Secondary Endpoints

i. Invasive cancer detection rate: For both modalities, invasive cancer detection will be defined at the patient-level. For DBT, the numerator will consist of the number of patients with at least one lesion scored as BI-RADS 3, 4 or 5 on the *Tomosynthesis YR-0 Lesions form,* with subsequent pathology for that lesion verifying invasive disease on either the *Needle Biopsy Pathology form* or the *Surgical Biopsy Pathology form*; the denominator will consist of the number of patients screened. Similarly, for AB-MR, the numerator will consist of the number of patients with at least one lesion scored as BI-RADS 3, 4 or 5 on the *MRI YR-0 Lesions form,* with subsequent pathology for that lesion verifying invasive disease on either the *Needle Biopsy Pathology form* or the *Surgical Biopsy Pathology form*; the denominator will consist of the number of patients screened.

ii. Sensitivity/specificity: Per protocol, institutions were to conduct patient follow-up at 6 months (+/- 1 month) and 12 months (+/- 1 month, but prior to year 1 screening), consisting both of patient contact (by telephone) to ask regarding breast cancer status, as well as record assessment at the local institution. These data were captured on the *Follow-up Patient Questions* form and the *RA Follow-up Records Assessment* form. The reference standard will be defined as follows. Subjects with breast cancer (invasive or DCIS) detected on the year 0 screening, or with breast cancer (invasive or DCIS) reported at any time from the year 0 to the

year 1 screening based on follow-up data, will be considered reference standard positive. Patients with no breast cancer reported up to the time of the year 1 screening will be considered reference standard negative. However, subjects which are not imaged at year 1, and which have <11 months of patient follow-up (<330 days) post year 0 screening will be considered to have incomplete reference standard.

Patient-level estimates of sensitivity and specificity will then be reported as follows. Sensitivity will be estimated as the fraction of reference standard positive subjects for whom the imaging modality result is positive (BI-RADS 3-5), and where the location of the positive imaging finding is matched to the location of the cancer indicated by the reference standard. Specificity will be estimated as the fraction of reference standard negative subjects for whom the imaging modality result was negative (BI-RADS 1-2).

iii. PPV of biopsy.

For DBT, PPV of biopsy will be defined and reported at the patient-level.

a. The numerator will consist of the number of patients with DCIS or invasive disease (reported on either the *Needle Biopsy Pathology form* or the *Surgical Biopsy Pathology form*) resulting from a DBT finding recommended for biopsy. The denominator will consist of the number of patients recommended for biopsy which received a biopsy. Patients recommended for biopsy will consist of those patients with at least one lesion rated BI-RADS 4 or 5 on the *Tomosynthesis YR-0 Lesions* form, with biopsy recommended on the *Final Management – Tomo Lesions* form (either "Stereotactic-guided core biopsy", "Ultrasound-guided core biopsy", "MR-guided core biopsy", or "Surgical biopsy").

In a similar manner, for AB-MR, PPV of biopsy will be defined and reported at the patient-level.

b. The numerator will consist of the number of patients with DCIS or invasive disease (reported on either the *Needle Biopsy Pathology form* or the *Surgical Biopsy Pathology form*) resulting from an AB-MR finding recommended for biopsy. The denominator will consist of the number of patients recommended for biopsy which received a biopsy. Patients recommended for biopsy will consist of those patients with at least one lesion rated BI-RADS 4 or 5 on the *MRI YR-0 Lesions* form, with biopsy recommended on the *Final Management – MRI Lesions* form (either "Stereotactic-guided core biopsy", "Ultrasound-guided core biopsy", "MR-guided core biopsy", or "Surgical biopsy").

iv. Additional imaging recommendation rate: This metric will combine the call-back rate and the short term followup (STFU) rate, both defined below. As the concept of a call back does not apply for AB-MR, we will define the additional imaging recommendation rate at the patient-level for purposes of comparison between the modalities. For DBT, the additional imaging recommendation rate will consist of a recommendation of either a call back or STFU. For AB-MR, the additional imaging recommendation rate will consist of a recommendation of STFU.

a. Call back rate: For DBT, call back will be defined at the patient-level. A call back consists of a Yes response to either, or both, of the following questions on the *Tomosynthesis YR-0 Interpretation form*:

- "Were additional diagnostic views performed to evaluate a possible finding on the screening views?"
- "Was targeted Ultrasound performed to evaluate a finding on DBT?"

To calculate the call back rate for DBT, the numerator will consist of the number of patients with a call back and the denominator will consist of the number of patients screened. For AB-

MR, the definition of call back does not apply; accordingly, call back rate will not be estimated for AB-MR.

b. Short-term follow up rate: For both modalities, short-term follow up (STFU) will be defined at the patient-level. For DBT, STFU consists of at least one lesion rated BI-RADS 3 on the *Tomosynthesis YR-0 Lesions form*; for MRI, STFU consists of at least one lesion rated BI-RADS 3 on the *MRI YR-0 Lesions form*. To calculate the STFU rate, for each modality, the numerator will consist of the number of patients with STFU and the denominator will consist of the number of patients screened.

B. Exploratory Endpoints

i. Overall cancer detection rate: This metric will be defined identically to the invasive cancer detection rate, except that both DCIS and invasive cancers will contribute to the count.

ii. Interval cancer rate: Any cancer (invasive or DCIS) which was not detected on the baseline (year 0) screening, or from associated STFU from the baseline (year 0) screening, but which was reported based on subsequent patient follow-up prior to the year 1 screening will be defined as an interval cancer.

iii. PPV of biopsy at the lesion-level:
For DBT, PPV of biopsy will be defined and reported at the lesion-level.

a. Test-positive (T+) will be defined as a lesion rated BI-RADS 4 or 5 on the *Tomosynthesis YR-0 Lesions form,* with biopsy recommended on the *Final Management – Tomo Lesions form* (either "Stereotactic-guided core biopsy", "Ultrasound-guided core biopsy", "MR-guided core biopsy", or "Surgical biopsy"), and with biopsy performed. Disease-positive (D+) will be defined as a lesion recommended for biopsy with pathology of DCIS or invasive disease as reported on either the *Needle Biopsy Pathology form* or the *Surgical Biopsy Pathology form*. PPV of biopsy for DBT will then be calculated as the ratio of disease-positive lesions to test-positive lesions, i.e. as the conditional probability P(D+/T+).

In a similar manner, for AB-MR, PPV of biopsy will be defined and reported at the lesion-level.

b. Test-positive (T+) will be defined as a lesion rated BI-RADS 4 or 5 on the *MRI YR-0 Lesions form,* with biopsy recommended on the *Final Management – MRI Lesions form* (either "Stereotactic-guided core biopsy", "Ultrasound-guided core biopsy", "MR-guided core biopsy", or "Surgical biopsy"), and with biopsy performed. Disease-positive (D+) will be defined as a lesion recommended for biopsy with pathology of DCIS or invasive disease as reported on either the *Needle Biopsy Pathology form* or the *Surgical Biopsy Pathology form*. PPV of biopsy for AB-MR will then be calculated as the ratio of disease-positive lesions to test-positive lesions, i.e. as the conditional probability P(D+/T+).

X. Demographics and Risk Score Summary

Demographics and baseline characteristics will be summarized for the Enrolled Set and the Analysis Set, both overall and by randomization arm. Data will be presented in side-by-side columns to allow for the assessment of any potential selection bias.

Enrolled Set and Analysis Set (side-by-side)

- Demographics
  - Age
  - Race
  - Ethnicity
- Randomization arm
- Breast density
- Family history of breast cancer
- Family history of ovarian cancer
- Prior benign breast biopsies
- Breast Cancer Screening Consortium (BCSC) 5-year and 10-year risk scores [3].
  (NOTE: BCSC scoring was not specified in the protocol, but will be added for completeness to help describe the study cohort).

XI. Statistical Analysis

A. Statistical Analysis of the Primary Endpoint

Refer to section IX for the definition of the invasive cancer detection rate. The total number of invasive cancers detected, as well as the number of patients in whom invasive cancer was detected, will be reported for each modality.

The invasive cancer detection rate at the patient-level, along with corresponding 95% confidence interval calculated using the Wilson method, will be reported for each modality. A 95% confidence interval for the difference in invasive cancer detection rates will also be reported using the Wald interval with Bonett-Price Laplace adjustment [4]. The comparison of the invasive cancer detection rate between DBT and AB-MR will be conducted using a two-sided exact McNemar's test to account for the paired design.

B. Statistical Analysis of Secondary Endpoints

Refer to section IX for the definition of these various screening metrics.

The comparison of the sensitivity and specificity of AB-MR and DBT will be conducted at the patient-level using a two-sided exact McNemar's test to account for the paired design, with 95% confidence intervals for the sensitivity and specificity of each modality calculated using the Wilson method.

The comparison of PPV of biopsy between DBT and AB-MR will be reported at the patient-level. Generalized estimating equation (GEE) regression will be used as suggested by Leisenring et al [5], with the p-value reported from the resulting score test. The 95% confidence interval for PPV of biopsy for each modality will be derived from the GEE model using the appropriate estimable contrasts with robust standard error.

The comparison of the additional imaging recommendation rate at the patient-level between AB-MR and DBT will use a two-sided exact McNemar's test to account for the paired design, with 95% confidence interval for each modality calculated using the Wilson method.

C. Statistical Analysis of Exploratory Endpoints

Refer to section IX for the definition of these exploratory screening metrics.

The overall cancer detection rate, will be estimated at the patient-level, with 95% confidence interval for each modality calculated using the Wilson method. The comparison of the overall cancer detection rate between DBT and AB-MR will be conducted using a two-sided exact McNemar's test to account for the paired design.

The interval cancer rate, along with corresponding 95% confidence interval using the Wilson method, will be reported.

The PPV of biopsy at the lesion-level will also be compared between DBT and AB-MR. Again, generalized estimating equation (GEE) regression will be used as suggested by Leisenring et al [5], with the p-value reported from the resulting score test. The 95% confidence interval for PPV of biopsy for each modality will be derived from the GEE model using the appropriate estimable contrasts with robust standard error.

The local stage and histopathological and immuno-histochemical information of each detected cancer will be reported, along with appropriate summaries.

D. Adjustment for Multiplicity of Comparisons

A post hoc, non-protocol-specified Bonferroni adjustment will be used to adjust for multiplicity of inference, including the primary endpoint and the four secondary endpoints, for a total of 5 comparisons, as follows:

1. Comparison of invasive cancer detection rate (*primary aim*)
2. Comparison of sensitivity (*secondary aim*)
3. Comparison of specificity (*secondary aim*)
4. Comparison of PPV of biopsy (*secondary aim*)
5. Comparison of additional imaging recommendation rate (*secondary aim*)

Accordingly, we will use an adjusted alpha level of 0.05/5=0.01 when reporting these 5 comparisons. The analyses of exploratory endpoints will not be adjusted for multiplicity.

XII. References

1. Kuhl CK, Schrading S, Strobel K, Schild HH, Hilgers RD, Bieling HB. Abbreviated breast magnetic resonance imaging (MRI): first postcontrast subtracted images and maximum-intensity projection-a novel approach to breast cancer screening with MRI. J Clin Oncol. 2014; 32(22):2304-10.

2. Schrading S KC. MRI screening of women at average risk of breast cancer. J Clin Oncol. 2013; 31:(suppl 26; abstr 1).

3. Tice JA, Miglioretti DL, Li CS, Vachon CM, Gard CC, Kerlikowske K. Breast density and benign breast disease: risk assessment to identify women at high risk of breast cancer. J Clin Oncol. 2015; 33(28):3137-43.

4. Fagerland MW, Lydersen S, Laake P. Recommended tests and confidence intervals for paired binomial proportions. Statist. Med. 2014; 33:2850-75.

5. Leisenring W, Alonzo T, Pepe MS. Comparisons of predictive values of binary medical diagnostic tests for paired designs. Biometrics. 2000; 56(2):345–51.

2. Study Protocol

Comparison of Abbreviated Breast MRI and Digital Breast Tomosynthesis in Breast Cancer Screening in Women with Dense Breasts

STUDY CHAIR:	Christopher Comstock, M.D.
STUDY STATISTICIAN:	Constantine Gatsonis, Ph.D.
STUDY CO-CHAIR:	Christiane Kuhl, M.D.
STUDY CO-CHAIR:	Gillian Newstead, M.D.
STUDY EPIDEMIOLOGIST:	Ilana Gareen, Ph.D.
BREAST COMMITTEE CHAIR:	Kathy Miller, M.D.
BREAST COMMITTEE IMAGING CHAIR:	Christopher Comstock, M.D.

Version Date: February 26, 2018

STUDY PARTICIPANTS	***ACTIVATION DATE***
	September 2, 2016
	Addendum #1 – 2/17
	Addendum #2 – 5/17
ALLIANCE / Alliance for Clinical Trials in Oncology	Addendum #3 – 9/17
NRG / NRG Oncology	Addendum #4
SWOG / SWOG	

Table of Contents

STUDY CHAIR

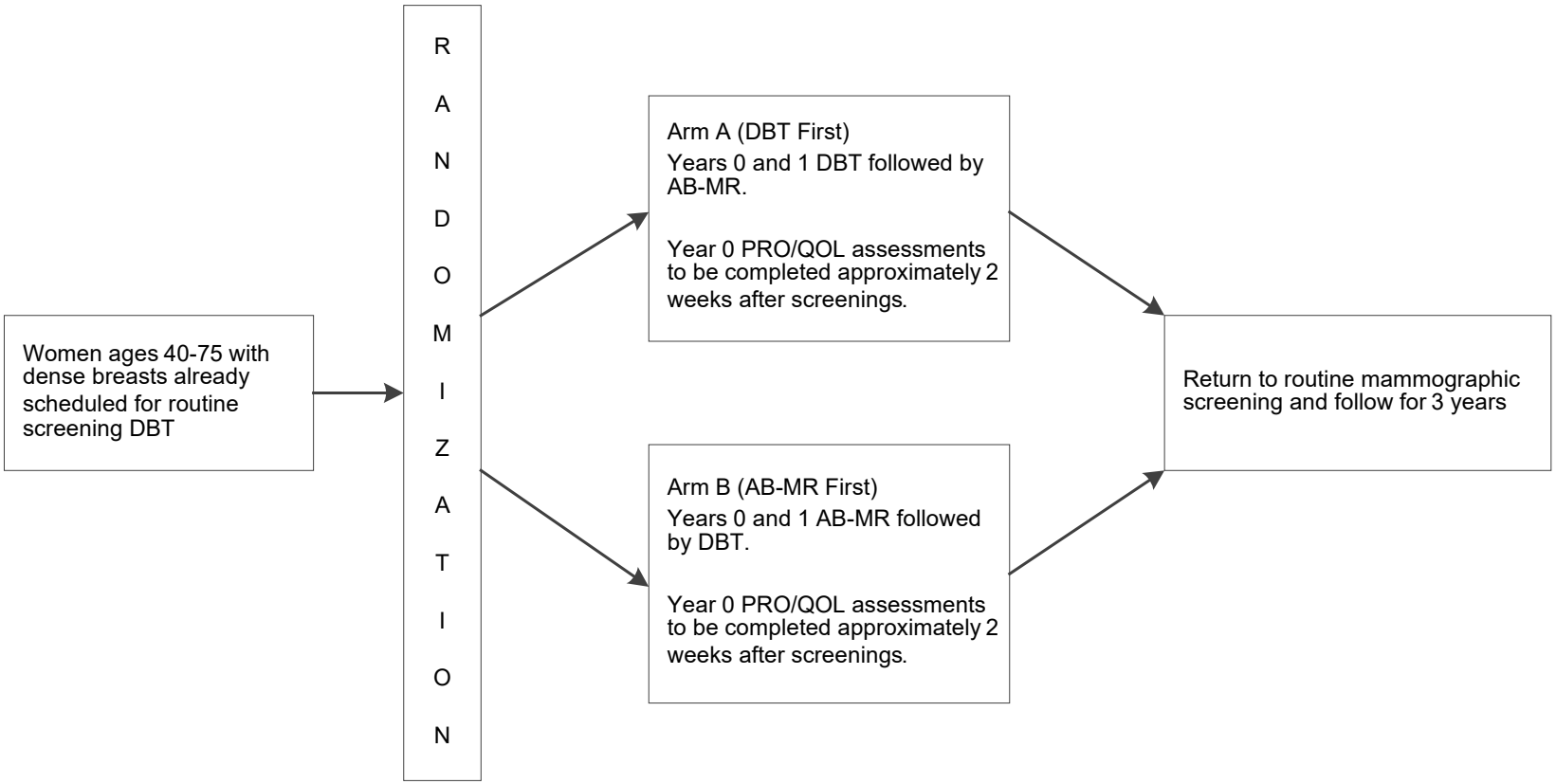
Christopher Comstock, M.D.,
Memorial Sloan-Kettering Cancer Center,
300 E. 66th St RM 733
New York, NY 10065
Phone: (646) 888-4500
Fax: (646) 888-4515
Email: comstocc@mskcc.org

Rev. 2/17
Rev. 9/17

CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

Schema



Accrual Goal= 1450

1. Suspicious lesions detected on one or both of the modalities at the Year 0 or 1 time points will be biopsied as per local standard practice.
2. Tissue collection and analysis for all cancers detected.

1. Introduction

1.1 Rationale for Proposed Phase II Study

Due to breast density notification legislation in many states, standard of practice breast cancer screening for many women with dense breasts now includes annual mammographic screening supplemented by whole breast ultrasound. In addition to concerns over the added costs and potential overdiagnosis of this approach, whole breast ultrasound suffers from high unnecessary biopsy and short-term follow up rates with only a mild increase in sensitivity.[1] ***The purpose of this study is to evaluate a low-cost abbreviated breast MRI (AB-MR) protocol as a supplemental screening method to mammographic screening in women with dense breasts.*** In addition, the study will assess the interval cancer rate and compare the types and biologies of cancers detected on mammography to those found on MRI. If AB-MR proves to detect significantly more high-grade cancers than mammography while reducing interval cancers, future studies may be indicated to evaluate AB-MR as a stand-alone screening modality to replace mammography.

1.2 Current Breast Cancer Screening

Film mammography has been shown in multiple clinical trials to reduce mortality from breast cancer.[2-4] Sixty-seven percent of women 40 and older in the U.S. reported having a mammogram within the past 2 years. However, screening mammography has remained relatively unchanged for over 50 years and has been criticized for high false positive rates and possible overdiagnosis.[5,6]The sensitivity of mammography is related to breast density. Although registry data has reported the sensitivity of digital mammography in women with dense breasts to be as high as 83.6%, with a specificity of 88.7%, a prospective multicenter trial reported the sensitivity to be as low as 38% with a specificity of 97%.[7-9] Digital breast tomosynthesis (DBT) is a newly FDA-approved 3-dimensional mammographic technique that is rapidly becoming the standard in many practices. Early trials have shown that DBT increases breast cancer detection compared to standard full field digital mammography (FFDM) with fewer call-backs and false positive biopsy recommendations.[10-13] In a recent study by Friedewald et al of 454,850 examinations, the use of DBT plus FFDM versus FFDM alone increased the cancer detection rate from 4.2/1000 to 5.4/1000.[13] Of the cancers detected on DBT, 75% were invasive and 25% were DCIS.

Due to the shortcomings of mammographic screening, particularly in women with dense breasts, multiple states have enacted legislation mandating that the patient and referring physician be notified when the mammographic pattern of fibroglandular tissue (FGT) is dense, and that additional screening should be considered. It is estimated that more than 50% of women fall into the dense breast category, with 40% having heterogeneously dense breasts and 10% having extremely dense.[14] These breast density notification laws have led to a proliferation of supplemental screening methods in women with dense breasts. Ultrasound has become the primary supplemental imaging modality to screen women with dense breasts that are at average and intermediate risk for breast cancer. Multiple studies have consistently shown that screening breast ultrasound will detect an additional 3 to 4 cancers occult on FFDM per 1000

women screened that are predominantly invasive carcinomas.[1,15] Although DBT is slightly more sensitive than FFDM for breast cancer detection, the data suggests that screening breast ultrasound will detect additional mammographically occult cancers even in women having DBT.

Therefore, the current standard screening practice for women with dense breasts is combined screening with annual DBT and whole breast screening ultrasound. However, screening breast ultrasound has a number of limitations including time, cost, and a low PPV of approximately 8%, leading to a significant number of unnecessary biopsies and a much higher rate of recommendation for short-term interval follow up.[1,15-16] The combined cost of DBT ($290) with ultrasound ($390) and the additional call-backs, unnecessary biopsies, and short-term follow-up studies represent a significant economic burden on health care costs. [17] A recent study by Sprague et al estimated the cost per QALY gained by combined screening with mammography and ultrasound was $320,000.[16] In addition, this approach likely contributes to overdiagnosis and overtreatment.

1.3 Abbreviated breast MRI (AB-MR)

Breast MRI is the most sensitive breast cancer screening test. MRI detects a significant number of additional breast cancers in intermediate to high risk women with dense breasts who have had combined screening with FFDM and whole breast ultrasound.[18,19] In the ACRIN 6666 trial, breast MRI was performed in 612 women who had undergone 3 negative annual screening rounds with FFDM and whole breast screening ultrasound.[18] The additional cancer yield of screening MRI in these women was 14.7/1000. Biopsy was recommended in 43/612 (7%) women, yielding malignancy in 8 (19%).Of the 8 cancers detected, 6 (75%) were invasive and 2 (25%) were ductal carcinoma in situ (DCIS).

MRI has also been shown to be more sensitive than WBUS in screening women at average to intermediate risk with dense breasts. In one study that included 427 asymptomatic women at mild to moderately increased risk for breast cancer and dense breasts with a negative FFDM and WBUS, screening MRI resulted in an additional cancer yield of 18.2/1000.[20] There were 7 invasive cancers (64%) and 4 cases (36%) of DCIS. The invasive cancers detected were small T1, node negative cancers, and both the invasive cancers and DCIS were predominantly high-grade tumors—what is generally considered “biologically significant” disease. Ultrasound in the 11 patients diagnosed with breast cancer was negative.

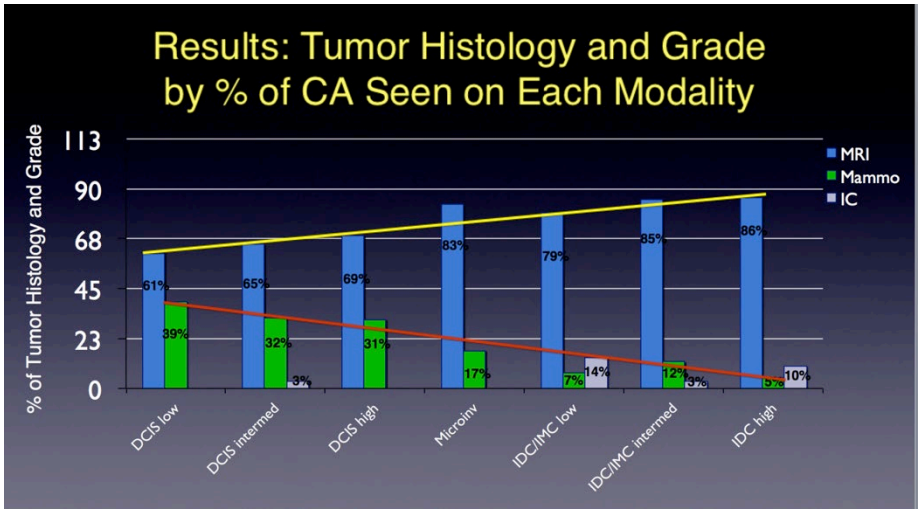
The sensitivity of breast MRI is also substantially higher than FFDM in women at average breast cancer risk. In one study that included 1387 women who underwent 1705 annual screening breast MRIs, the additional cancer yield of MRI in average risk women was 11/1000.[21] A total of 18 cancers were detected, including 11 invasive cancers (61%) with a mean size of 11 mm and 7 cases (39%) of DCIS. Nine (82%) of the 11 invasive cancers and 6 (86%) of the 7 cases of DCIS were either intermediate or high grade disease. The PPV of biopsy in this study was 33% (18/54), which is comparable to the accepted rate for mammography and significantly higher than that of ultrasound.

Despite its high diagnostic accuracy among breast cancer screening tests, the cost of MRI has precluded its use as a screening test for all women with dense breasts. One alternative is AB-MR, which uses a scan time of less than 10

minutes (compared with 25-40 minute time for non-abbreviated breast MRI) and reduces its cost to one that is comparable to WBUS. **Combined screening with DBT and AB-MR may be the best method to screen women with dense breasts.**

Early studies of screening MRI interpreting an abbreviated protocol have shown equivalent sensitivity to full MRI with only a slight decrease in specificity. [20, 22-24] Kuhl et al compared the sensitivity and specificity of an abbreviated and full protocol, and reported a sensitivity of 100% and specificity 94% using the abbreviated protocol, which included only one pre- and one post-contrast acquisition and their derived images. Given the vastly superior sensitivity and specificity of MRI compared to whole-breast ultrasound (WBUS), AB-MR may be the optimal, cost-efficient supplemental screening modality to DBT in women with dense breasts.

Screening AB-MR has the potential to detect many cancers that are missed on screening mammography and ultrasound, leading to earlier treatment and potentially reduced mortality. At the same time, AB-MR maintains a high positive predictive value (PPV) and preferentially selects for biologically significant tumors, thereby potentially reducing overdiagnosis and overtreatment[figure 1,19,25]. This proposed study will evaluate the additional invasive cancer yield of AB-MR to digital breast tomosynthesis (DBT) and the 1 year interval cancer rate. In addition, the study will provide an assessment of breast cancer incidence during a 3 year interval following AB-MR. Multihance will be used as the contrast agent. The high relaxivity of Multihance may improve sensitivity since the AB-MR protocol includes only early phase post-contrast imaging.



1.4 Patient-Reported Outcomes (PRO)

1.4.1 Background and Rationale for QOL Study

Consensus recommendations for high-quality decisions regarding the choice to participate in breast cancer screening need to ask for and incorporate patient values and preference. We plan to ask patients to provide information on their experiences with AB-MRI and DBT, as well as their willingness to return for each test, and their preference for examiner gender. Information may be used to compare the tests,

as well as to determine how best to develop informed consent and patient education to enhance patient adherence.

1.4.2 QOL Study Design

For a detailed description of the patient reported outcomes (PRO) data collection process, please refer to Section 8.3. In brief, the questionnaire will be administered to women approximately 2 weeks after the Year 0 (baseline) DBT and AB-MR to assess their aniticipated and actual pain/discomfort, fear/anxiety, and embarrassment before and during each test, as well as their willingness to repeat each test.

1.4.3 Rationale for Quality of Life Measure Selection

We plan to use the Testing Morbidities Index (TMI) to evaluate short-term test-related quality of life. The TMI is a validated instrument that assesses seven attributes: pain or discomfort before and during testing, fear or anxiety before and during testing, embarrassment during testing, and physical and mental function after testing. The TMI measures short-term functional health on a preference-based or psychometric scale, and previous studies have shown early evidence of content, construct, and discriminative validity of the TMI. [26–29] The measure is unique because it was specifically designed to evaluate patient responses to diagnostic testing.

1.5 Significance of the Study

Ongoing breast density notification legislation has led to a dramatic change in breast cancer screening practices nationally. A significant number of women with dense breasts are undergoing annual mammographic screening supplemented by WBUS. However, screening ultrasound has been shown to only minimally increase breast cancer detection, and interval cancer rates remain significantly high. In addition, due to the poor performance of screening ultrasound, the proliferation of its use has led to a dramatic increase in cost, unnecessary biopsies, and increases in short-term follow up studies. Breast MRI has the ability to detect as many as 150% more cancers compared to screening ultrasound while maintaining a high PPV and preferentially detecting biologically significant disease. AB-MR imaging is a new, fast, low cost method of performing breast MRI and has the potential to be a superior alternative to screening breast ultrasound. In addition, **the detection of biologically significant tumors at a smaller size and earlier stage will lead to an overall reduction in surgical and adjuvant therapies and their associated morbidities.** This study, comparing AB-MR to DBT and evaluating its value as a supplemental screening modality, represents an advanced imaging, high-impact, phase II trial with the potential to change the standard of care and improve clinical outcomes for breast cancer patients. The results of this study may change how intermediate risk women with dense breasts are screened for breast cancer. This study may also provide exploratory data on AB-MR as a potential standalone replacement to screening mammography which could be performed every 2-3 years rather than annually. Patients will be followed for three years after the AB-MR to compare the impact of AB-MR on the historical expected incident cancer rate of screening mammography. Compared to annual screening with mammography and

ultrasound, this approach could substantially reduce the false positives, costs, and overdiagnosis of biologically insignificant tumors associated with current breast cancer screening.

2. Objectives

2.1 Primary Endpoints

2.1.1 To compare the rates of detection of invasive cancers between the initial AB-MR and DBT.

2.2 Secondary Endpoints

2.2.1 To compare the positive predictive value (PPV) of biopsies, call back rates, and short-term follow up rates after AB-MR and DBT on both the initial and 1 year follow up studies.

2.2.2 To estimate and compare the sensitivity and specificity of AB-MR and DBT, using the 1 year follow up to define a reference standard.

2.2.3 To compare patient-reported short-term quality of life related to diagnostic testing with AB-MR and DBT using the Testing Morbidities Index.

2.2.4 To compare willingness to return for testing with AB-MRI vs DBT within the recommended screening interval and explore factors associated with willingness to return for screening.

2.2.5 To compare the tumor biologies of invasive cancers and DCIS detected on AB-MR and DBT.

2.2.6 To estimate the incident cancer rate during 3 years following the year-1 AB-MR/DBT when patients return to standard screening.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to randomization by the treating physician.

3.1 Eligibility Criteria

Rev. 2/17

_____ **3.1.1** Patients must be women ages 40 to 75 years and scheduled for routine screening DBT.

_____ **3.1.2** Women must not be pregnant or breast-feeding as gadolinium enhanced MRI and screening DBT are contra-indicated.

All females of childbearing potential who are uncertain if they could be pregnant or may be pregnant or as per local site standard of practice in women undergoing DBT and MRI must have a blood test or urine study within 2 weeks prior to randomization to rule out pregnancy.

A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

_____ **3.1.3** Women of childbearing potential must be strongly advised to use an accepted and effective method of contraception or to abstain from sexual intercourse for the following year until the Year 1 AB-MR and DBT studies are performed.

Rev. 5/17

_____ **3.1.4** Patient's breast density must be known; patients must have mammographically dense breasts, ACR BI-RADS lexicon categories c or d (heterogeneous or extreme fibroglandular tissue) on their most-recent prior screening.

_____ **3.1.5** Patient must be asymptomatic for breast disease and undergoing routine screening.

_____ **3.1.6** Patient must have no known breast cancer (DCIS or invasive cancer), not currently undergoing treatment for breast cancer, or planning surgery for a high risk lesion (ADH, ALH, LCIS, papilloma, radial scar).

_____ **3.1.7** Patient must not be taking chemoprevention for breast cancer.

_____ **3.1.8** Patient must not have undergone screening breast ultrasound within 12 months prior to randomization

Rev. 9/17

_____ **3.1.9** Patient must not have previously had a breast MRI.

_____ **3.1.10** Patient must not have previously had molecular breast imaging (MBI, MIBI)

_____ **3.1.11** Patient must agree to not undergo screening ultrasound (of breast) for the duration of the 1 year study period as screening ultrasound adds no benefit in women undergoing breast MRI

_____ **3.1.12** Patient must not be suspected of being at high-risk for breast cancer, as defined by the ACS breast MR screening recommendations (lifetime risk of ≥ 20-25%). See Appendix I.

_____ **3.1.13** Patient must be able to undergo breast MRI with contrast enhancement. Patients unable to undergo breast MRI with contrast enhancement for any reason are ineligible.

3.1.13.1 *No history of untreatable claustrophobia;*

3.1.13.2 *No presence of non MR compatible metallic objects or metallic objects that, in the opinion of the radiologist, would make MRI a contraindication.*

3.1.13.3 *No history of sickle cell disease*

3.1.13.4 *No contraindication to intravenous contrast administration;*

3.1.13.5 *No known allergy-like reaction to gadolinium or moderate or severe allergic reactions to one or more allergens as defined by the American College of Radiology (ACR); patient may be eligible if willing to undergo pre-treatment as defined by the institution's policy and/or ACR guidance (see http://www.acr.org/quality-safety/resources/contrast-manual for reaction definition and premedication guidance);*

3.1.13.6 *No known or suspected renal impairment. Requirements for GFR prior to MRI as determined by local site standard practice.*

3.1.13.7 *Weight less than or equal to the MRI table limit;*

3.1.13.8 *No women who have had prior contrast enhanced mammography (CESM or CEDM).*

3.1.13.9 *No women who have breast prosthetic implants (silicone or saline).*

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

4. Randomization Procedures

Rev. 2/17

Rev. 9/17

Rev. Add4

CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>.For questions, please contact the RCR ***Help Desk*** by email at <RCRHelpDesk@nih.gov>.

CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data

to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the EA1141 protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the ECOG-ACRINlink to expand, then select trial protocol #EA1141
- Click on LPO Documents, Click on the Site Registration Documents link

Requirements For EA1141 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- MRI Qualification (through the ACR Imaging Core Laboratory)
  - ACR breast MRI accreditation.
  - AB-MR reader training certification.

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Required Protocol Specific Regulatory Documents

1. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

2. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:
   - Indicate all sites approved for the protocol under an assurance number.
   - OHRP assurance number of reviewing IRB
   - OHRP IRB Registration Number of reviewing IRB
   - Full protocol title and number
   - Version Date
   - Type of review (full board vs. expedited)
   - Date of review.
   - Signature of IRB official

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website:

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

NOTE: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Patient Enrollment

Patients must not start protocol trial procedures prior to randomization.

Imaging should start within thirty (30) working days after randomization.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at <https://ctepcore.nci.nih.gov/iam>) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Registration Demographics

The following information will be collected at registration:

4.1.1 Protocol Number

4.1.2 Investigator Identification

4.1.2.1 *Institution and affiliate name*

4.1.2.2 *Investigator's name*

4.1.3 Patient Identification

4.1.3.1 *Patient's initials (first and last)*

4.1.3.2 *Patient's Hospital ID and/or Social Security number*

4.1.3.3 *Patient demographics*

- Gender
- Birth date (mm/yyyy)
- Race
- Ethnicity
- Nine-digit ZIP code
- Method of payment
- Country of residence

4.2 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.

4.3 Additional Requirements

4.3.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.3.2 Biological specimens are to be submitted as indicated in Section 10.

4.3.3 Patient Reported Outcomes (PROs) must be reported using the ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO). See Section 8.2

Rev. Add4

4.3.4 Clinical data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

Rev. 2/17

Rev. Add4

4.3.5 Digital Imaging Data Submission Using TRIAD

All on-study imaging studies, including additional spot views and ultrasounds, are to be submitted to the TRIAD database.

TRIAD is ACR's proprietary image exchange application that will be used as the sole method of data transfer to the ACR Clinical Research Center Core Laboratory for this trial. TRIAD can be installed on one or several computers of choice within the institutional "firewall" and on the institutional network; internet access is required. The TRIAD application can then be configured as a DICOM destination on either scanner(s) and/or PACS system for direct network transfer of study related images into the TRIAD directory. When properly configured, the TRIAD software de-identifies, encrypts, and performs a lossless compression of the images before they are transferred to the ACR Imaging Core Laboratory image archive in Philadelphia.

Rev. 2/17

Rev. Add4

4.3.5.1 *TRIAD Access Requirements*

Site radiology staff who will submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. and be registered as an AP, NPIVR or IVR. Please refer to CTEP Registration Procedures of the protocol for instructions on how to request a CTEP-IAM account and complete registration in RCR.

To submit images, the site user must be on the site's affiliate rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role. RAs are able to submit standard of care imaging through the same method.

Rev. 2/17

4.3.5.2 *TRIAD Installations*

When a user applies for a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link https://triadinstall.acr.org/triadclient/

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org or call 703-390-9858

4.4 Instructions for Patients Who Do Not Complete Imaging Tests

If neither of the baseline imaging tests are completed, no further data will be collected and the patient will be excluded from the study. If a patient completes only one of the baseline imaging tests, initial imaging data and 1 year follow-up data are still required to be collected and must be submitted through Medidata Rave according to the schedule in the EA1141 Forms Completion Guidelines. However, DBT and AB-MR screening at year 1 are not required, and no further follow-up data beyond 1 year will be collected.

All other patients are required to collect and submit all requested data through Medidata Rave according to the schedule in the EA1141 Forms Completion Guidelines.

5. Imaging Administration

5.1 Imaging Schedule

Rev. 2/17
Rev. 9/17
Rev. Add4

All patients will undergo both DBT and AB-MR within 30 days following randomization. The DBT and AB-MR will be performed on the same day and interpreted by two different radiologists, each blinded to the other modality. Although it is optimal to perform the DBT and AB-MR on the same day, sites may perform the DBT and AB-MR within 24 hours of each other as long as the radiologists remain blinded to the results of the other modality. Patients will be randomized to the order of which study is performed first. If DBT is the first test, any additional imaging (spot compression/magnification view and or ultrasound) recommended from the screening DBT views should be completed and a final recommendation recorded on the DBT imaging data forms by the interpreting radiologist prior to the AB-MR. If AB-MR is performed first, the results should be recorded on the AB-MR imaging data forms prior to DBT. No biopsy should be performed until both the DBT and AB-MR have been completed. All suspicious findings on either the DBT or AB-MR should be biopsied regardless of the recommendation of the other modality. If the same suspicious lesion is detected on both DBT and AB-MR, the interpreting radiologists will determine the best modality for biopsy guidance. High risk lesions, such as ADH and LCIS, on core biopsy will be managed as per local site standard practice.

The specifications for performance and interpretative guidelines of the AB-MR and DBT will follow methods outlined below;

- Breast density will be assessed by the radiologist interpreting the DBT, based on the standard BI-RADS classifications.
- Recommendations for findings on DBT will be based on ACR guidelines. Recommendation for findings on AB-MR will be based on the Society of Breast MRI interpretative guidelines.
- The interpreting radiologist may refer to mammograms or ultrasounds from previous years while interpreting the DBT or AB-MR. The radiologist must only be blinded to the other imaging study performed that same day as part of the study protocol.
- Tissue collection and analysis for all cancer, including both invasive cancer and DCIS.
- All women will undergo DBT and AB-MR at 1 year in the same order as the baseline DBT and AB-MR. The year 1 follow up imaging must be completed no less than 11 months from baseline imaging and no more than 13 months from baseline imaging
- Patients will have follow-up contact through a follow-up visit, email, or phone call 6 months (+/- 1 month) after the year 0 imaging and immediately prior to the year 1 imaging. Patients diagnosed with breast cancer in the interval between the year 0 and year 1 imaging studies will have no subsequent follow up and will not undergo the year 1 study imaging.
- Patients will be asked, but not required, to forgo WBUS during the study period as this may confound the data and as WBUS has already been shown in multiple trials to have no added benefit after negative breast MRI.

Rev. 9/17

5.1.1 ARM A (DBT first)

Patients randomized to Arm A of this study will undergo DBT followed by AB-MR. Although it is optimal to perform the DBT and AB-MR on the same day, sites may perform the DBT and AB-MR within 24 hours of each other as long as the radiologists remain blinded to the results of the other modality, and any work up needed from the DBT (spot compression/magnification views and or ultrasound) is completed prior to the AB-MR.

5.1.2 ARM B (AB-MR first)

Patients randomized to Arm B of this study will undergo AB-MR followed by DBT. Although it is optimal to perform the DBT and AB-MR on the same day, sites may perform the DBT and AB-MR within 24 hours of each other as long as the radiologists remain blinded to the results of the other modality.

5.2 Imaging

5.2.1 Magnetic Resonance Imaging

5.2.1.1 *Site Qualification*

Prior to patient enrollment, all participating scanners must be ACR Accredited for Breast MRI.

All interpreting physicians must have completed the Society of Breast MRI for AB-MR interpretation training.

Rev. 5/17

5.2.1.2 *Magnetic Resonance Imaging (MRI) Procedures*

Rev. 9/17

MRI will be performed within 30 days after patient randomization. The bilateral breast MRI should be acquired on a 1.5T or 3.0T MRI scanner with a dedicated breast radiofrequency coil. The patient should be scanned in prone position.

AB-MR is defined as a breast MRI fulfilling the following requirements:

Total scan time of less than 10 min (including localizer)

A localization scan

1 pre- and 1 post-contrast gradient echo (GRE) axial acquisition; The center of K-space should be between 60 and 90 seconds post contrast administration. Fat suppression is recommended if it is usual site practice.

In-plane resolution of 1 mm or less

Slice thickness of 3 mm or less

For advanced imaging sites, optional fast temporal scanning at 3 phases between 0-30 seconds after contrast injection as long as the center of K-space of the post-contrast GRE remains between 60 and 90 seconds.

For sites approved to perform the optional advanced imaging, fast temporal scanning to include phases of approximately 3.5sec for 3T magnets and 7sec for 1.5T magnets starting with the contrast injection until 30 seconds after completion of the contrast injection. Optional fast scanning may only be performed if the center of K-space of the post-contrast GRE remains between 60 and 90 seconds.

Axial T2 weighted sequence with in-plane resolution matching the GRE sequences and 3 mm or less slice thickness

Sequence	Slice Thickness	Gap	Maximum In Plane Pixel Dimension for Phase and Frequency
Axial GRE	≤ 3 mm	0 mm	≤ 1 mm

Contrast Medium: An intravenous catheter will be inserted in the arm or hand prior to the start of imaging. For the contrast-enhanced study following the T2-weighted, Multihance (no substitutions allowed) gadolinium contrast agent will be administered intravenously using a power injector at a dose of 0.1 mmol/kg body weight and rate of 2 ml/second, followed by a 20 ml saline flush.
MRI Findings: The Society of Breast MRI interpretation guidelines for AB-MR will be followed by the interpreting radiologist at each site. Site radiologist will use the study specific forms to document MRI results. Each breast MRI will be reported using the standard BIRADS guidelines

Rev. 2/17

5.2.2 Digital Breast Tomosynthesis (DBT) Procedure:

DBT will be performed within 30 days after patient randomization. DBT technique will be defined as per local site standard of care, which may include the following: tomosynthesis views in the CC or MLO views or both views with either a 2D full field digital mammogram or synthetic 2D views.

DBT Findings:

DBT interpretation will be performed by radiologists at each site using the standard of care American College of Radiology BI-RADS lexicon. Work-up of suspicious findings may include spot compression or magnification views, as well as targeted ultrasound. Each DBT will be reported using the standard BI-RADS guidelines.

BI-RADS® Category	Overall Final Assessment
1	Negative
2	Benign Finding(s)

3	Probably Benign Finding – Short-Interval Follow-Up Suggested
4	Suspicious Abnormality – Biopsy Should Be Considered
5	Highly Suggestive of Malignancy – Appropriate Action Should Be Taken
6	Known Biopsy-Proven Malignancy – Appropriate Action Should Be Taken

5.2.3 Central Imaging Quality Control and Collection

All breast imaging will be transferred and stored at the ACR Imaging Core Laboratory for quality control review.

For this protocol, the following images will be collected and submitted to the ACR Core Laboratory via TRIAD:

- All clinical imaging exams performed as part of standard of care;
- AB-MR and DBT performed as part of study protocol
- Any other imaging scans performed as part of the study, including ultrasounds and biopsy imaging.
- Please refer to Section 4.3.5 for detailed TRIAD access and installation instructions.

5.3 Adverse Event Reporting Requirements

5.3.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

- **Routine reporting:** Adverse events are reported in a routine manner at scheduled times during a trial using Medidata Rave.
- **Expedited reporting:** In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

5.3.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of a drug/procedure in humans, whether or not considered drug/procedure related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product/procedure, whether or not considered related to the medicinal product.

- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment/procedures, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to treatment/procedures.
Unlikely	The AE is *doubtfully related* to treatment/procedures.
Possible	The AE *may be related* to treatment/procedures.
Probable	The AE is *likely related* to treatment/procedures.
Definite	The AE is *clearly related* to treatment/procedures.

- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Expectedness:** Expected events are those that have been previously identified as resulting from administration of the agent/procedure. An adverse event is considered unexpected, for expedited reporting purposes, when either the type of event or the severity of the event is NOT listed in the protocol or drug package insert.

5.3.3 Reporting Procedure

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). The CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (617-632-3610)
- the FDA (1-800-FDA-1088)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the FDA (800-332-0178) in the same timeframe.

CTEP Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please

contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.3.4 Determination of Reporting Requirements

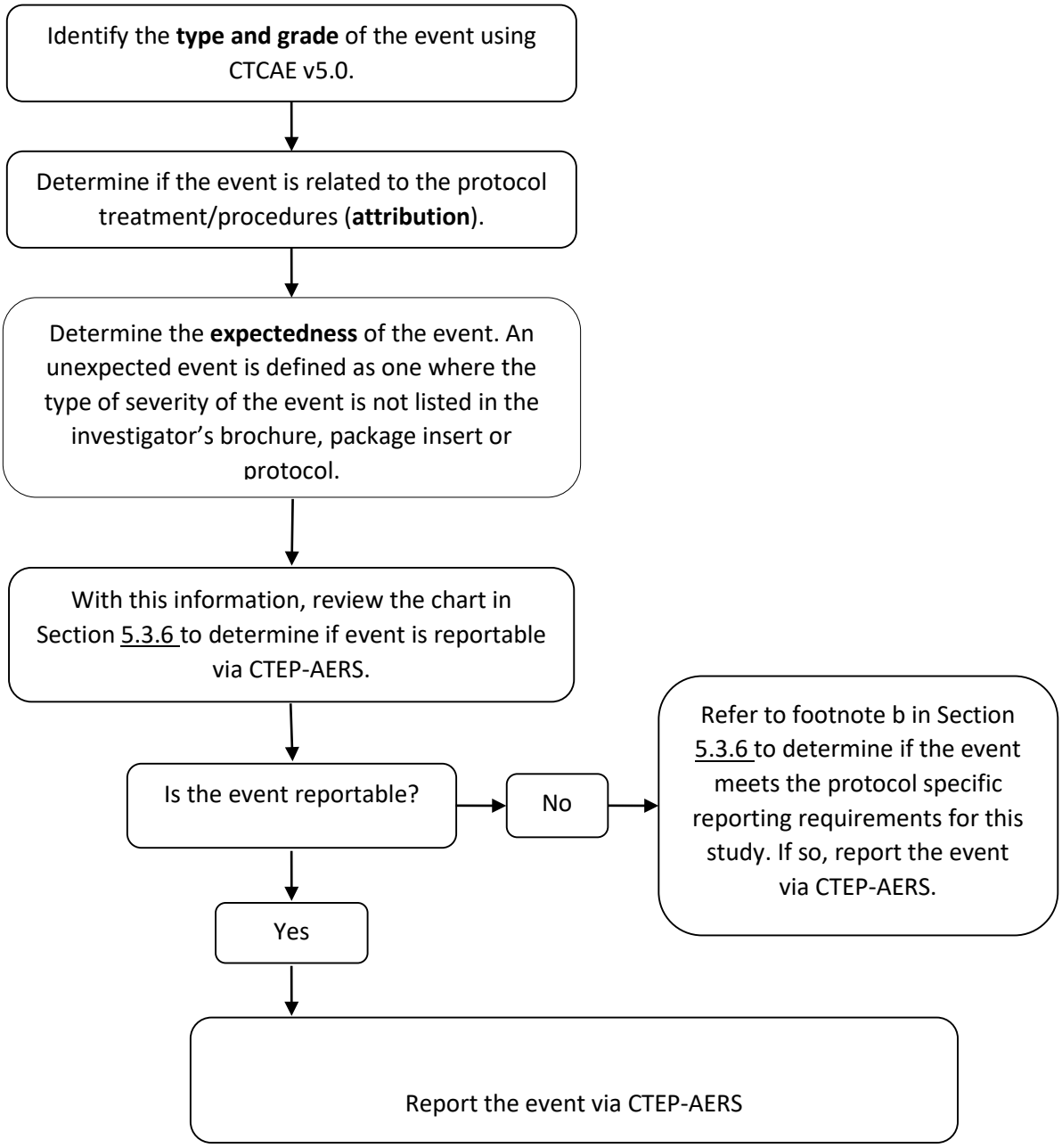
Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- the relationship to the study treatment/procedures (attribution)
- the expectedness of the adverse event

Using these factors, the instructions and tables in the following sections have been customized for protocol EA1141and outline the specific expedited adverse event reporting requirements for study EA1141.

Rev. Add4

5.3.5 Steps to determine if an event is to be reported in an expedited manner:



Rev. Add4

5.3.6 Expedited Reporting Requirements for protocol EA1141

Expedited reporting requirements for adverse events experienced by patients on protocol EA1141					
Attribution	**Grade 4**		**Grade 5[a]**		**ECOG-ACRIN and Protocol-Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely			7 calendar days	7 calendar days	See footnote (b) for special requirements.
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

a A death occurring while on study or within 30 days of the last dose of treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

NOTE: Any death that occurs > 30 days after the last dose of treatment/procedures and is attributed possibly, probably, or definitely to the treatment/procedures must be reported within 7 calendar days of learning of the event.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment/procedures that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported via CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

Kidney Adverse Events: Any grade 4 kidney adverse event must be reported via CTEP-AERS within 7 calendar days of learning of the event, regardless of attribution.

Nephrogenic Systemic Fibrosis (NSF) or Nephrogenic Fibrosing Dermopathy (NFD): Any occurrence of Nephrogenic Systemic Fibrosis (NSF) or Nephrogenic Fibrosing Dermopathy (NFD) must be reported via CTEP-AERS within 7 calendar days of learning of the event, regardless of attribution.

5.3.7 Other recipients of adverse event reports and supplemental data

Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.4 Expected Adverse Events

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

5.4.1 MRI

- Anxiety/stress;
- Claustrophobia;
- Discomfort;
- Rare, but Serious: Injury associated with foreign bodies and the MR magnet; this is most likely to occur should the institution fail to ask or should a participant fail to inform the site of contraindications to MR use (e.g., presence of metallic or surgical implants or metal pieces in the body).

5.4.2 Contrast injection/IV Needle Placement

- Hematoma at the injection site
- Phlebitis;
- Bleeding;
- Infection;
- Bruising;
- Minor discomfort;
- Headache;
- Nausea;
- Vomiting;
- Hives;
- Temporary low blood pressure;
- Allergic-type reaction;
- Rare, but Serious: Kidney impairment, details follow.

Rare but severe adverse events occur in approximately 15/100,000 persons administered intravenous gadolinium. There is a risk of death in 1/100,000 persons.

Precautions should be exercised for patients with severely impaired renal function or hemolytic anemia. The very unlikely possibility of a reaction, including anaphylactic-like or cardiovascular reactions, should be considered, especially for patients with a known sensitivity to gadolinium or history of asthma.

Nephrogenic Systemic Fibrosis (NSF) or Nephrogenic Fibrosing Dermopathy (NFD), kidney disorders, may occur in patients with

moderate to end-stage kidney disease (glomerular filtration rate < 30 mL/min/1.73m^2) and in patients with renal dysfunction due to the hepatorenal syndrome or in the perioperative liver transplantation period after they have had a MRI scan with gadolinium-based MR contrast agents.

NSF causes fibrosis of the skin and connective tissues throughout the body. Patients develop skin thickening that may prevent bending and extending joints, resulting in decreased mobility of joints. NSF usually starts in the lower extremities. Fibrosis can also develop in the diaphragm, muscles in the thigh and lower abdomen, and lung vessels.

Reference: FDA/Center for Drug Evaluation and Research. May 23, 2007 Available at: http://www.fda.gov/cder/drug/infopage/gcca/qa_200705.htm.

5.4.3 DBT

- Bruising
- Skin abrasion

5.5 Supportive Care

5.5.1 All supportive measures consistent with optimal patient care will be given throughout the study.

5.6 Duration of Follow-up

Rev. 2/17
Rev. 9/17

For this protocol, all patients will be monitored for breast cancer diagnosis for a total of 3 years following the year 1 AB-MR and DBT. Patients in follow-up are to be contacted through follow-up visits, emails, or phone calls every 6 months (+/- 1 month) for 3 years after year 1 imaging to check to see if the patient was diagnosed with cancer. If **neither** of the baseline imaging tests are completed, the patient will be excluded from the study and no further data will be collected. If a patient completes **only one** of the baseline imaging tests, baseline data and 1 year of follow-up data are still required to be collected and must be submitted through Medidata Rave according to the schedule in the EA1141 Forms Completion Guidelines. However, the year-1 DBT and AB-MR will not be performed and no further follow-up data beyond 1 year will be collected. All other patients are required to collect and submit all requested data through Medidata Rave according to the schedule in the EA1141 Forms Completion Guidelines.

The 1 year patient follow-up should be performed immediately prior to the year 1 imaging to confirm the patient has not been diagnosed with an interval breast cancer.

If a patient is diagnosed with a primary cancer during the study period, no subsequent follow up or further study imaging will be performed. Pathology reports and site standard tests are required to be submitted upon the diagnosis of a primary cancer. Data are required to be collected and submitted through Medidata Rave according to the schedule in the EA1141 Forms Completion Guidelines for that visit. If a primary cancer is detected at Year 0, the PRO/QOL assessment is expected to be completed two weeks after the protocol scheduled screening and included in the final data collection.

6. Study Parameters

Rev. 2/17
Rev. 9/17
Rev. Add4

	Pre-Study	Year 0[5,10]	6 Months	Year 1[5,10]	Year 2-4 Follow-up[5,6,10]
Blood creatinine[1]	X[1]			X[1]	
Serum or Urine Pregnancy Test[2]	X[2]	X[3]		X[3]	
DBT		X[9]		X[9, 13]	
AB-MR[8]		X[9]		X[9, 13]	
PRO/QOL Questionnaires[7]		X[7]			
Participant Genetic and Medical History Questionnaire	X[17]				
Core Needle Biopsy[11]		X		X	
Patient Follow-up Contact			X[14]	X[16]	X[15]
Tumor tissue from on study biopsies from consenting patients submitted per Section 9					
FFPE tumor tissue[4]			X		X
Blood for banking from consenting patients submitted per Section 9					
Plasma, one (1) 10mL K2EDTA purple top tube[12]			X		
Whole Blood, one (1) 10mL EDTA purple top tube[12]			X		

1. If required by local site as standard of care.
2. For women of childbearing potential suspected of being pregnant or unsure of their pregnancy status, or as per local site standard of practice in women undergoing DBT and MRI, a pre study pregnancy test must be done within 2 weeks prior to randomization.
3. A pregnancy test must only be done prior to the year 0 and year 1 imaging studies in women suspected of being pregnant or unsure of their pregnancy status as per local site standard of practice.
4. Submit from patients with newly detected cancers. All submissions must be logged and tracked within the ECOG-ACRIN Sample Tracking System (STS). See Section 9.
5. Copies of reports associated with any assessment of the tissue, including (but not limited to) pathology reports, OncotypeDx, and PAM50 are to be uploaded into Medidata RAVE.
6. Every 6 months (+/- 1 month) for years 2-4.
7. PRO/QOL Questionnaires will be timed to arrive approximately 2 weeks after the Year 0 (baseline) screening tests (AB-MR and DBT)
8. As outlined in Section 5.2.1, AB-MR is to be performed using Multihance (no substitutions allowed) gadolinium contrast agent.
9. As outlined in section 5.1.1 and 5.1.2; patients randomized to Arm A of this study will undergo DBT followed by AB-MR, patients randomized to Arm B of this study will undergo AB-MR followed by DBT.
10. For patients that are diagnosed with a primary cancer, no subsequent follow-up or further study imaging will be performed. Pathology reports and site standard tests are required to be submitted upon diagnosis of a primary cancer. Data are required to be collected and submitted through Medidata Rave according to the schedule in the EA1141 Forms Completion Guidelines for that visit. If a primary cancer is detected at Year 0, the

PRO/QOL assessment is expected to be completed two weeks after the protocol scheduled screening and included in the final data collection.

11. If a suspicious lesion is detected on one or both of the modalities at the baseline or one-year post-baseline time points, a biopsy will be performed per local standard of care practices.
12. Collect blood from consenting patients that are recommended for breast biopsy of suspicious lesions detected on the AB-MR or DBT at either year 0 or year 1.

    NOTE: Blood draw should occur prior to biopsy.
13. The year 1 follow up imaging must be completed no less than 11 months from baseline imaging and no more than 13 months from baseline imaging.
14. Patients are to be contacted via a follow-up visit, email, or phone call months (+/- 1 month) after year 0 imaging to see if the patient was diagnosed with cancer during the interval between year 0 and year 1 imaging.
15. Patients in follow-up are to be contacted through follow-up visits, emails, or phone calls every 6 months (+/- 1 month) for 3 years after year 1 imaging to see if the patient was diagnosed with cancer.
16. The 1 year patient follow-up contact should be performed immediately prior to the year 1 imaging, via a follow-up visit, email, or phone call, to confirm the patient has not been diagnosed with an interval breast cancer. Patients diagnosed with breast cancer in the interval between the year 0 and year 1 imaging studies will have no subsequent follow up and will not undergo the year 1 study imaging.
17. Participant data will be collected for the Participant Genetic and Medical History questionnaire.

7. Statistical Considerations

7.1 Overview

Rev. 2/17
Rev. 9/17

This phase II trial is conducted to compare the rates of detection of invasive cancers by AB-MR and DBT. At baseline and at Year 1 post baseline, participants will undergo both tests on the same day and in randomized order. The randomization was added as a safeguard against potential bias that may result if one test systematically precedes the other in the course of the study. Per protocol, participants will be consented in advance of imaging, and both the AB-MR and DBT will be performed on the same day (or within a 24hr period) and interpreted independently by two different radiologists blinded to the results of the other modality. Although it is very unlikely that the interpreting radiologists will inadvertently access information from the independent reading of the other modality, the randomization is an additional assurance against such an eventuality. In addition, the randomization will help ensure that participants will be consented in advance of the imaging exams thus minimizing the potential of selection on the basis of imaging results.

Participants will be followed for an additional period of 3 years. The length of three years of follow up was chosen as feasible and also based on the following heuristic. We hypothesize that AB-MR detects at least an additional 9 invasive cancers per thousand, equalling approximately 2 years of advanced detection compared to DBT. Thus the incident cancer rate of DBT should take approximately 2-3 years to return to the expected rate of 5/1000.

DBT and AB-MR will be interpreted locally at the participating sites. The two modalities will be interpreted independently, and readers will be blinded to the results of the other modality. If DBT is the first test, any additional imaging (spot compression/magnification view and or ultrasound) recommended from the screening DBT views should be completed and a final recommendation recorded on the DBT imaging data forms by the interpreting radiologist prior to the AB-MR. If AB-MR is performed first, the results should be recorded on the AB-MR imaging data forms prior to DBT. No biopsies should be performed until the results of both the DBT and AB-MR have been independently recorded on their respective imaging data forms. All suspicious findings on either the DBT or AB-MR should be biopsied regardless of the recommendation of the other modality. The recommendations and results of subsequent biopsies based on results from either modality will be recorded to determine the cancer yield, PPV, call back rate, and frequency of recommendations for short-term follow up for both DBT and AB-MR.

The primary aim of the trial is to compare rates of detection for invasive cancer. Secondary aims evaluate and compare measures of diagnostic and predictive accuracy of the two modalities, measures of patient preference, molecular characteristics of cancers found, and incident breast cancer rate during the 3-year follow up period.

7.2 Primary Endpoint

The primary aim for this study is to compare the rate of detection of invasive cancers with AB-MR and DBT

For each modality, the detection rate of invasive cancers is defined as the proportion of participants who had an invasive cancer detected by the modality and verified by pathology. Because of the paired design, the comparison of the invasive cancer detection rates will be made using McNemar's test.

Sample size considerations: We are not aware of previous studies comparing AB-MRI to DBT. Our choice of plausible values for the additional yield of AB-MRI at Year 0 was based on a recent comparative study of MRI to FFDM, which reported an additional yield of about 12/1000 *invasive* cancers in a population of women at average risk.[20,21] We conservatively assumed that the difference in yield between AB-MR and DBT will be smaller and computed the sample size required to detect a difference as low as 9/1000. The following table presents computations of the required sample size to ensure power 90% using a two-sided McNemar's test of level 0.05 and for a range of values of the difference in detection rates and total rates of discordant pairs. Based on these computations we selected a sample size of 1363 cases with complete data from both tests and pathology. This sample size is needed to ensure power 90% for a difference in the rates of invasive cancer detection of 9/1000 when the discordant pair rate is in the middle of the range. Assuming that adequate information to evaluate the primary endpoint will not be available on up to 6% of cases, a sample size of **1450** will provide power 90% to compare the diagnostic yield in invasive cancer of the two modalities. Women that complete either only the AB-MR or only the DBT and not both studies at Year 0 will not be included in the analysis.

Power	Sample size	Difference in invasive cancer rates (ABMR –DBT)	Proportion of discordant cases
0.90	1191	0.009	0.010
0.90	1363	0.009	0.011
0.90	1552	0.009	0.012
0.90	1057	0.010	0.011
0.90	1197	0.010	0.012
0.90	949	0.011	0.012

7.3 Secondary Endpoints

Rev. 9/17

a. *To compare the positive predictive value (PPV) of biopsies, call back rates, and short-term follow up rates after AB-MR and DBT on both the initial and 1 year follow up studies,*

Estimates of each quantity of interest will be derived separately for the baseline and the Year 1 screen. The year 1 screen is defined as imaging performed no less than 11 months from baseline screen and no more than 13 months from baseline screen. For each screening occasion the estimates of call-back and short-term followup rates of the two modalities will be compared using McNemar's test to account for the paired design. GEE regression modeling will be used in the comparison of PPVs.[30] In addition, the change between baseline and Year 1 screen will be estimated separately for each modality. If a woman does not complete both the AB-MR and DBT on the 1

year follow up study, they will be included for analysis of the primary endpoint but not of the secondary endpoints.

b. *To estimate and compare the sensitivity and specificity of AB-MR and DBT, using the 1 year follow up to define a reference standard.*

   The analysis for this aim will use data from the baseline screen and subsequent 1-year followup. The year 1 follow up must be completed no less than 11 months from baseline screen and no more than 13 months from baseline screen. The sensitivities and specificities of the two modalities will be estimated using a reference standard comprising the information from any subsequent workup and the information from the 1-year followup. The information from the Year 1 screens will not be included in the reference standard. Estimates will be compared using McNemar's test to account for the paired design.

c. *To compare patient-reported short-term quality of life related to diagnostic testing with of AB-MR and DBT using the Testing Morbidities Index.*

   Separate TMI scores will be computed for each modality after the baseline screen. Scores will be compared using a nonparametric test that accounts for the pairing of scores by participant.

d. *To compare willingness to return for testing with AB-MRI vs DBT within the recommended screening interval and explore factors associated with willingness to return for screening.*

   We will estimate the proportions of participants willing to return for screening with either test, AB-MRI only, DBT only, or not willing to return for either test. We will use polytomous logistic regression to examine factors associated with willingness to return, including screen result, cancer status, and demographic characteristics.

e. *To compare the tumor biologies of invasive cancers and DCIS detected on AB-MR and DBT;*

   The analysis for this aim will be descriptive. Cancers detected during the study period will have tissue banked centrally that will undergo genetic profiling. For all invasive cancers detected during the study period, the NanoString PAM50 will be performed. The frequencies of cancer types determined by the NanoString analysis will be tabulated and compared. For DCIS, if the Oncotype-DCIS score was performed, the distributions of scores will be tabulated and compared.

f. *To estimate the incident cancer rate during 3 years following the year-1 AB-MR/DBT when patients return to standard screening.*

   Breast cancer incidence will be estimated over the 3 year followup period. Person-years will be measured from the beginning of the 3-year period, which will be at Year 1 post baseline.

7.4 Gender and Ethnicity

Rev. 2/17

Using data from ACRIN 6652 (DMIST) and ACRIN 6666 we are making the following projections regarding gender and race enrollment for EA1141: Ethnic Category

	Gender		
	Females	**Males**	**Total**
Hispanic or Latino	132	0	132
Not Hispanic or Latino	1318	0	1318
Ethnic Category: Total of all subjects	**1450**	**0**	**1450**

Racial Category			
American Indian or Alaskan Native	3	0	3
Asian	58	0	58
Black or African American	143	0	143
Native Hawaiian or other Pacific Islander	3	0	3
White	1236	0	1236
More than one race	7	0	7
Racial Category: Total of all subjects	**1450**	**0**	**1450**

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

However, since the AB-MR can be performed at any community site with standard breast MRI and as the study will cover the cost of the AB-MR, the trial should be equally accessible to all populations. Accrual of minorities will be monitored quarterly. Overall and individual site minority accrual rates will be closely monitored. Sites with low minority accrual rates will be contacted to determine their specific issues and help them target minority accrual.

Domestic Planned Accrual

Racial Categories	Not Hispanic or Latino: Female	Not Hispanic or Latino: Male	Hispanic or Latino: Female	Hispanic or Latino: Male	Total
American Indian/Alaska Native	3	0	0	0	3
Asian	55	0	0	0	55
Native Hawaiian or Other Pacific Islander	3	0	0	0	3
Black or African American	119	0	17	0	136
White	990	0	112	0	1102
More Than One Race	5	0	1	0	6
Total	1175	0	130	0	1305

INTERNATIONAL (including Canadian participants) PLANNED ACCRUAL

Racial Categories	Not Hispanic or Latino: Female	Not Hispanic or Latino: Male	Hispanic or Latino: Female	Hispanic or Latino: Male	Total
American Indian/Alaska Native	0	0	0	0	0
Asian	3	0	0	0	3
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	7	0	0	0	7
White	132	0	2	0	134
More Than One Race	1	0	0	0	1
Total	143	0	2	0	145

7.5 Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Coordinating Center.

8. Patient Reported Outcomes (PRO) and Quality of Life (QOL) Administration

8.1 PRO/QOL Assessment Schedule

Patients will be asked to complete forms approximately 2 weeks after the Year 0 (baseline) screen.

Questionnaires will be timed to arrive approximately 2 weeks after the Year 0 (baseline) screening tests (AB-MR and DBT). We have chosen two weeks with the hope that it will be recent enough for participants to recall their experience, but distant enough that patients will have been notified of their results prior to completing questionnaires. This survey will ask participants about fear/anxiety, pain/discomfort, embarrassment, difficulties with daily activities experienced with each test, as well as their willingness to undergo each test again, and their preference for male or female technologists.

8.2 PRO/QOL Data Collection Process

Rev. 5/17

Patients will be recruited at the time of randomization into the patient reported outcomes portion of the study. At the time of randomization at the sites, patients will complete a **Participant Contact Information Form**. The form collects information used to maintain contact with the participant over the course of the trial, including name, address, phone number, and e-mail (if available).

This form is retained in the study participant's chart at the site and is not submitted to the ECOG-ACRIN master database. The completed form is faxed to the central ECOG-ACRIN Outcomes and Economic Assessment Unit (OEAU) located at Brown University so that the participants can be contacted for the Patient Reported Outcomes (PRO) portion of the study. The contact information is stored in a dedicated SQL database and **IS NOT** linked to the master ECOG-ACRIN database. The OEAU RA will not have access to the main ECOG-ACRIN database that contains screening results.

8.2.1 On the Participant Contact Information Form, patients will be asked to express a preference for on-line or paper administration of patient reported outcome (PRO) forms. Patients may choose to complete questionnaires using a web-based application (see Section 8.3 for a description) or by mail. Administration of questionnaires, both web-based and paper will be coordinated by the OEAU. Administration of the questionnaires will be triggered based on completion of study milestones marked by submission of forms in RAVE.

Patients will be prompted to complete web-based forms via an email prompt. These emails will include a link to the web site for questionnaire completion. Questionnaires will be completed on-line using a unique patient account. The web site will reference a study-specific toll-free phone number that patients can use to reach the OEAU staff should they have questions or need assistance. All data will be stored on a secure server. If patients do not complete the web questionnaire within 10 working days of the date of the e-mail, a second email will be sent, which will ask the patient to confirm that the

patient has been able to access the questionnaire on the web. If patients have still not responded within 20 working days of the original e-mail, the OEAU Research Associate will attempt to telephone the patient and administer the questionnaire by telephone. If questionnaires are telephone-administered, they will be marked as such in the data base.

8.2.2 Mailed questionnaire completion

Mailed questionnaire packets will include a letter introducing the study and include a study-specific toll-free phone number that patients can use to reach the OEAU staff should they have questions or need assistance, questionnaires, and pre-addressed, stamped envelopes for return mailing to the OEAU. If patients do not complete the paper questionnaire within 10 working days of the date of the mailing, the OEAU RA will attempt to telephone the patient. If the patient has not received the paper questionnaires, additional questionnaires will be sent after confirming the correct mailing address. If the questionnaire is available to the patient, the OEAU RA will urge the study patient to complete and return the questionnaire. If patients have still not responded within 20 working days of the original mailing, the OEAU will attempt to telephone the patient and telephone administer the questionnaire. If questionnaires are telephone-administered, they will be marked as such in the data base.

8.3 ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO)

8.3.1 A secure environment for control of user records, information, and transactions (SECURIT).

Provides a secure – limited access point for entering data into the restricted secure Personally Identifiable Information (PII) Database, for management of user data, creating user accounts, and reporting. The SECURIT web management interface requires the secure hypertext transfer protocol (HTTPS) to ensure encryption of transmitted data.

8.3.1.1 PII database: is a dedicated secure limited access database, used to store protected PII.

8.3.1.1.1 Secure: All communications to the PII database through SECURIT are encrypted. The database resides behind a firewall and cannot be reach from outside the OEAU.

8.3.1.1.2 Limited access: this database is restricted not only by username and password but is also restricted to specified internal OEAU computers by IP address, so that only authorized users logging in at the OEAU from pre-specified computers may access/enter PII. At no time is outside access allowed to this database.

8.3.1.1.3 Protected restricted PII (eg., SSN) are encrypted at the time of data entry and double data entered for verification. All users regardless of their security level are blinded to this protected data, and it cannot be decrypted without the encryption key, housed in a safe, in a location separate from the OEAU. This type of data is generally collected for long term follow-up where it may be needed to be decrypted for select patients in order to search registries like the national death index to determine survival status of lost participants. In these instances, with appropriate approvals, the Database Administrator will decrypt this data in accordance with the approved retrieval specification.

8.3.1.2 User records: This functionality allows OEAU personnel, using specific computers within the OEAU, to create user records, enter user information into the PII database, and establish user web accounts in the separate user database. Allows the management of users and their data, including the ability to update a participants preferred contact method, address, and participation status (eg., no longer wishes to be contacted with respect to the PRO component of the study).

8.3.1.3 Information: This functionality allows the OEAU to record all participant contact, document any changes to the participant, and make any important notes related to the participant.

8.3.1.4 Transactions: SECURIT provides a reporting and monitoring interface to the PRO database, which is used to store non-PII patient reported survey responses.

8.3.1.4.1 Allows OEAU to monitor per patient form completion status using the tracking management facility. This facility reports on what data is currently expected from participants, CRAs, and the OEAU interviewers.

8.3.1.4.2 Aggregate reporting: this series of reports allows the OEAU to monitor the distribution of patients over data completion methods and form completion methods (both overall and by site).

8.3.2 <u>Database utility and control environment (PRO-DUCE).</u>

This utility interfaces with the main clinical database containing CRF/trigger data (Medidata RAVE), monitors the clinical database for events (eg., participant registrations, scheduled procedures, and other triggers) and establishes event scheduling. The system sets up email reminders to CRAs, participants [and SMS text message reminders, when applicable to the study], and OEAU personnel to ensure timely completion of surveys.

8.3.3 Web entry systems (PROWESs).

A website where participants complete online surveys.

8.3.3.1 PROWESs provides a front facing web portal for participants to complete questionnaires and have those results stored in the PRO database.

8.3.3.2 Secure site using HTTPS and requiring a username and password login.

8.3.3.3 On login, user is presented with brief instructions; including the approximate time for completion, number of questions to be completed in this session, and any important information regarding this survey (including help and contact information)

8.3.3.4 PROWESs is a one-way interface, data cannot be returned from the PRO-database to the user.

8.3.4 Valet Interface and data entry system (PROVIDES).

8.3.4.1 The PROVIDE system is a web interface that allows site CRAs and OEAU RAs to act as a valet and enter a participants responses to a survey into the PRO database. This allows Site CRAs to enter forms completed by the patient on site and allows the OEAU staff to enter participants responses acquired via phone, mail and fax competed surveys.

8.3.4.2 Secure site using HTTPS and requiring a username and password login.

8.3.4.3 Which forms can be entered is restricted by username, site affiliation, and role; thus, Sites RAs can only enter surveys predesignated as on-site data collection surveys and only for their own patients.

8.3.4.4 On login, user is presented with brief instructions; is requested to select the protocol, case number, timepoint and verify the case ID by providing the participant birthdate.

8.3.4.5 PROVIDES is a one-way interface, data cannot be returned from the PRO database to the user.

9. Specimen Submissions

Rev. 2/17

Tumor tissue samples are requested to be submitted from study patients who have cancers (DCIS and invasive) detected and have consented to allow the submission of the tissue for research. Samples should only be submitted after clinical management of the patient has been determined from the tumor tissue. Tumor tissue samples should be submitted from all cancers unless there is inadequate material for submission.

Blood samples are requested to be submitted from study patients that are recommended for breast biopsy of suspicious lesions detected on the AB-MR or DBT at either year 0 or year 1 and have consented to allow the submission of blood for future research for discovery/validation of potential circulating biomarkers that could be used to risk stratify patients in the future.

All specimens must be labeled with the ECOG-ACRIN protocol number (EA1141), the patient's initials and ECOG-ACRIN patient sequence number, and if applicable, the GHI requisition number/barcode from the kit, the collection date, and the type of sample. For pathology materials, it is strongly recommended that full patient names be provided.

All specimens must be logged and tracked via the ECOG-ACRIN Sample Tracking System (STS) Web Application (Section 9.3) and submitted with an STS generated shipping manifest.

NOTE: If tumor tissue is submitted to Genomic Health, Inc (GHI) for Onco*type* assessments, it is requested that the patient's participation is noted on the Onco*type* Requisition Form and that the submission be logged into STS. This will assist in communications between ECOG-ACRIN and GHI regarding the proper routing and use of the residuals after completion of the assay.

If tumor tissue is not available for submission, please indicate this in STS.

NOTE: From all patients with tumors detected, copies of the pathology report and other standard of care assessments performed on the tumor tissue samples are to be submitted in RAVE. This is required and not impacted by the patient's consent for submission of the tissue for research.

Guidelines for pathologists are provided in Appendix II.

Rev. 2/17

9.1 Tumor Tissue and Blood Submissions to ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF)

Tumor tissue and blood are to be submitted from patients who answer 'Yes' to 'My samples and related information may be kept in a Biobank for use in future health research.'

Rev. 2/17

9.1.1 Tumor Tissue Submissions

For invasive cancers detected and biopsied during the study period (and all patients from whom only slides were submitted to GHI for the OncotypeDX DCIS assessment), formalin fixed paraffin-embedded tumor tissue samples are requested to be submitted for the laboratory research studies defined in Section 10 and for future research studies.

9.1.1.1 *Submission requirements:*

Forms

The relevant pathology and surgical reports must accompany all tissue submissions:

- Copy of the diagnostic or surgical Pathology Report
- Other Immunologic and cytologic reports
- STS generated shipping manifest for all submitted tissue.

Tumor tissue submissions:

Representative formalin fixed paraffin embedded (FFPE) tumor tissue blocks.

NOTE: If blocks are unavailable for submission, cores and slides are to be submitted. All cores and slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirement:

- One (1) H&E slide
- Twenty (20) 4-5 µm unstained air-dried plus slides
- Two (2) 4 mm cores

9.1.2 Blood Submissions

Rev. 2/17
Rev. Add4

Blood samples are requested to be submitted for future research studies from patients that are recommended for breast biopsy of suspicious lesions detected on the AB-MR or DBT at either year 0 or year 1.

NOTE: Blood draw should occur prior to biopsy.

Rev. 2/17

9.1.2.1 *Plasma*

- Draw 10mL of peripheral blood into one (1) plastic K2EDTA purple top tube
- Immediately invert tube 10 times
- Centrifuge within 30 minutes of draw at room temperatire at 1500g for 20 minutes in a swing bucket or fifteen (15) minutes for a fixed angle centrifuge
- Aliquot plasma into four (4) cryovials
- Replace the cap on the purple top tube
- Freeze cryovials and residual cells at –70ºC. Batch ship quarterly overnight on dry ice. If specimens cannot be stored at –70ºC, store at –20ºC and ship on dry ice within one (1) week of collection.

Rev. 2/17

9.1.2.2 *Whole Blood*

- Draw 10mL of whole blood into one (1) plastic EDTA purple top tube
- Immediately invert 10 times

- Freeze at –70ºC
- Batch ship quarterly overnight on dry ice. If specimens cannot be stored at –70ºC, store at –20ºC and ship on dry ice within one (1) week of collection.

Rev. 2/17

9.1.3 Shipping Procedures:

The pathology materials are to be submitted within one month of performance of the procedure. Tissue samples are to be shipped at ambient (use a cool pack in warm weather).

Frozen blood samples must be shipped overnight on dry ice Monday-Thursday only, do not ship the day before the weekend or holiday.

Shipping manifest form generated from the ECOG-ACRIN STS must accompany the tissue and blood samples.

Access to the shipping account for shipments to the ECOG-ACRIN CBPF at MD Anderson can only be obtained by logging into fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org

Ship to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

9.2 Tumor Tissue Submissions to Genomic Health Inc (GHI)

Rev.2/16

This section outlines the submission of tumor tissue for the Onco*type*DX DCIS Score Assay.

For DCIS cancers detected and biopsied during the study period, formalin fixed paraffin-embedded tumor tissue samples are requested to be submitted for the laboratory research studies defined in Section 10.1.

9.2.1 Ordering the Onco*typeDX* Specimen Kit

Contact Genomic Health Customer Service (866-662-6897) and request the “Onco*type* Specimen Kit”.

The kit will be shipped overnight and will contain instructions, a shipping kit (includes cryotubes and slide cassette), a mailer, and a requisition form containing barcode labels to place on the submitted materials. One Onco*type* Specimen Kit and Requisition Form should be completed per patient.

DO NOT MIX BARCODE LABELS BETWEEN PATIENTS.

Rev. 2/17

9.2.2 Tumor Tissue and Form Submissions

Tumor tissue submissions to GHI must be logged into the ECOG-ACRIN Sample Tracking System (STS). Participating sites will correspond directly with GHI, not via STS. The CBPF will log receipt of materials from GHI into the STS. Receipt logging will not occur in real time. For more information on the STS, see Section 9.4.

- Submit the following utilizing the kit and forms provided by GHI:
- Completed requisition form and STS manifest (see Appendix II for insuctions on how to complete the requisition form, please note the STUDY NAME/CODE must be filled out as: **'01-194-IIS-EA1141.'**
- DCIS Tumor Tissue Block (place barcode label on back of cassette).

  OR

- Fifteen (15) 5 µm serial unstained slides, oriented similarly and air dried. Label each slide with barcode and number in the order they were cut.

  NOTE: Proper sterile sectioning technique MUST be followed. Failure to follow sterile technique can affect testing and delay results. If sterile technique cannot be followed, submission of a tumor block is strongly recommended. If only slides are submitted, additional materials are to be submitted to the CBPF per Section 9.1.

  NOTE: Pathology reports are to be FAXed to the ECOG-ACRIN CBPF. Label with EA1141, ECOG-ACRIN patient sequence number, and the GHI requisition number.

9.2.3 Notification of Results

Genomic Health will notify the institution of the DCIS Score (DS) via the mechanism selected on the Onco*typeDX* Requisition Form within 14 days of receipt of the tissue by Genomic Health. If you do not receive a report within 14 days, contact GHI Customer Service at (866) 662-6897. Genomic Health will not distribute reports directly to the ECOG-ACRIN Operations Office – Boston.

The institution must upload a redacted copy of the first page of the "OncotypeDX Patient Report" (labeled with protocol number EA141, patient initials, and ECOG-ACRIN patient sequence number) to the 'DCIS Score' eCRF in Medidata Rave.

9.2.4 Central Laboratory: Specimen Processing and Routing

Specimens submitted will be processed to maximize their utility for current and future research projects and may include, but not limited to, extraction of plasma, serum, DNA and RNA. Invasive tumor

specimens will be routed for the research studies outlined in Section 10. If tumor tissue is submitted to Genomic Health, Inc and the patient's participation in this trial is noted on the Onco*type* requisition form, residuals will be forwarded to the CBPF to be used in future research.

Specimens from patients who consented to allow their specimens to be used for future approved research studies will be retained in an ECOG-ACRIN-designated central repository. For this trial, specimens will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility. Residual specimens from any laboratory research studies, including the DCIS Score Assay by Genomic Health, will also be returned to the ECOG-ACRIN CBPF for possible use in future approved research studies. Specimens will be de – identified prior to distribution for any approved research projects.

If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future study. Pathology materials may be retained for documentation purposes or returned to the site. All other specimens will be destroyed per guidelines of the respective repository.

9.3 ECOG-ACRIN Sample Tracking System

It is **required** (barring special circumstances) that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). As of June 2007, the software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst.

Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html. Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest must be generated and shipped with all sample submissions.

Please direct your questions or comments pertaining to the STS to ecog-acrin.tst@jimmy.harvard.edu.

If the STS is unavailable, the Generic Specimen Submission Form (#2981) is to be used as a substitute for the STS shipping manifest. The completed form is to be faxed to the receiving laboratory the day the samples are shipped. Indicate the appropriate Lab on the submission form:

- ECOG-ACRIN CBPF
- Genomic Health, Inc

Retroactively enter all sample collection and shipping information when STS is available.

Note that GHI will not indicate receipt within STS.

9.4 Sample Inventory Submission Guidelines

Inventories of all samples submitted will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of samples forwarded and utilized for approved laboratory research studies will be submitted by the laboratory to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

10. Laboratory Research Studies

For patients diagnosed with invasive cancer, tissues will be sent to the CBPF as outlined in Section 9.1, and the PAM50 assessment will be performed as a research test. PAM50 results will not be returned to the site.

If the site submits tissues for the Oncotype DX Breast Cancer Assay, performed by Genomic Health, Inc. (GHI) and the patient's participation in EA1141 is reported to GHI, GHI will distribute test results and tissue residuals to ECOG-ACRIN for use in future research. Results will be returned to sites per GHI standard procedures.

10.1 Oncotype DX for DCIS Score Assay

This assessment is performed by Genomic Health, Inc.

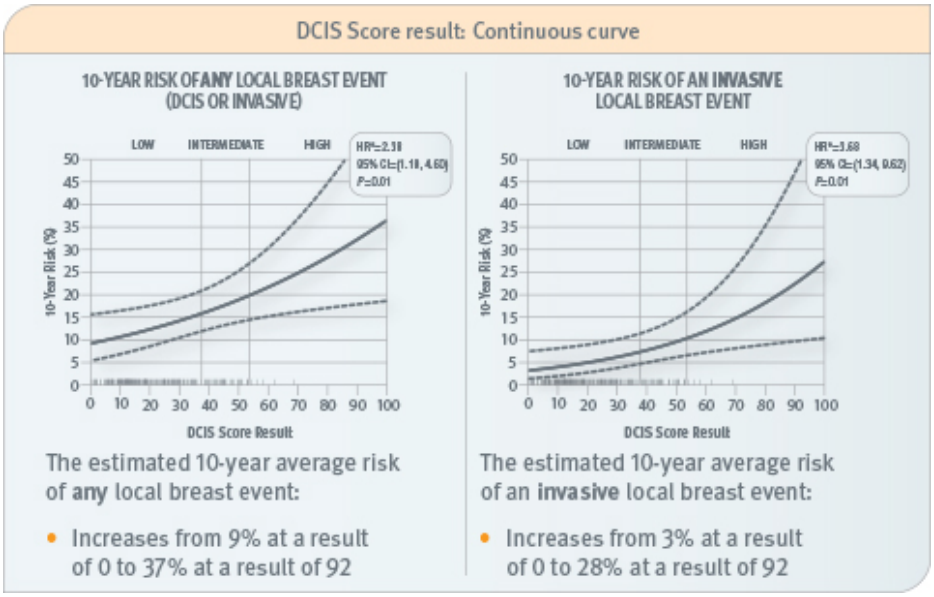
The Onco*type* DX® Breast Cancer Assay analyzes RNA derived from fixed paraffin-embedded tissue using RT-PCR. The quantitative RT-PCR assay is capable of quantifying up to 400 genes from small RNA fragments (50–250 bp) extracted from three 10-micron FPET sections. The assay machine measures mRNA abundance by recording real-time fluorescence and time to a certain amplification threshold. The assay (Onco*type* DX™ Breast Cancer Assay, Genomic Health, Redwood, CA; http://www.genomichealth.com/oncotype) is performed within 10-14 days.

Using manually microdissected DCIS tissue the Onco*type* DX® Breast Cancer Assay is run which includes all 21 genes from the Recurrence Score. The DCIS Score result is generated from 12 of the 21 Recurrence Score, these genes specific to the calculation of the DCIS Score result, and they include 7 cancer-related and 5 reference genes (Table 1). This subset of genes were selected for inclusion in the DCIS Score algorithm because they are strongly prognostic and predict local recurrence risk regardless of tamoxifen use.

Table 1: Genomic Health DCIS Score Algorithm (Onco*type* DX)

Group	Genes
Proliferation	Ki67, STK15, survivin, cyclin B1, MYB2
Hormone Receptor	PR
Reference	Beta-actin, GDPDH, RPLPO, GUS, TFRC
GSTM-1	GSTM-1

The DCIS Score result is evaluated both as a continuous variable (from 0 to 100) and as a categorical variable (based on 3 prespecified risk groups: low, intermediate and high). The DCIS Score™ result quantifies the risk of any local recurrence, as well as the risk of an invasive local recurrence.[35]



*HR=hazard ratio.

Table 2. Genomic DCIS Score, Results from Validation Study[35]

Recurrence Score (1–100)	Risk group	No. (%)	10-year risk of any local breast event (95% C.I.)	10-year risk of an invasive local breast event (95% C.I.)
< 39	Low	230 (70%)	10.6% (6.9, 16.2)	3.7% (1.8, 7.7)
39 –54	Intermediate	53 (16%)	26.7% (16.2, 41.9)	12.3% (5.1, 27.8)
> 54	High	44 (13%)	25.9% (14.8, 43.1)	19.2% (9.5, 36.4)

10.2 PAM50 Assessment

This assessment will be directed by Brian Leyland-Jones, MD.

The PAM50 assay will be performed on tumor tissue submitted from all patients diagnosed with invasive breast cancer. The assessments will be performed retrospectively at the end of the trial. Results will not be returned to the site or patient.

PAM50 Background

In 2009, a 50-gene set (PAM50) was proposed for standardizing subtype classification. The PAM50 Breast Cancer Intrinsic Classifier is the clinical manifestation of this gene set using a digital gene expression assay on the NanoString nCounter Dx Analysis System that has been validated on formalin-fixed, paraffin-embedded tissues. Multivariable analyses using the PAM50 subtypes and other clinical data (e.g., node status, grade, ER-status) show that the PAM50 is an independent predictor of survival in breast cancer. The PAM50 test provides additional information about the tumor biology and quantitative data on biomarkers already used for treatment decisions. Along with a categorical classification of breast cancer subtype, the clinical PAM50 test also determines a quantitative value for proliferation. The PAM50 gene set testing will be performed using an Investigational Use Only (IUO) PAM50 Assay on the nCounter Dx Analysis System produced by NanoString Technologies. The IUO

PAM50 assay uses the same reagents, procedures and algorithm as the Prosigna Gene Expression Assay, which have all been analytically validated and cleared for use by the FDA as a prognostic test in ER+ breast cancer patients who are treated with endocrine therapy alone. In this study, it is anticipated that only a small number of invasive cancers will be detected in premenopausal women; although the PAM50 is not FDA approved for premenopausal women, evidence suggests the PAM50 scoring is also predictive in this group of women as well.[31-33]

Assay Description

Used together, the PAM50 and nCounter Dx Analysis System are a nucleic acid hybridization, visualization and image analysis system based upon coded probes designed to detect the messenger RNA transcribed from 58 genes. The test input is purified RNA from FFPE breast tumor specimens. The PAM50 assay uses gene-specific probe-pairs that hybridize directly to the mRNA transcripts in solution. The nCounter Dx Analysis System delivers direct, multiplexed measurements of gene expression through digital readouts of the relative abundance of the mRNA transcripts.

Specifications are included to control for sample quality, RNA quality, and process quality. The PAM50 assay utilizes prototypical expression profiles (centroids) which are associated with and define each of the four intrinsic subtypes of breast cancer. Patients are categorized into one of the four subtypes based upon how close their gene expression pattern is to each of the centroids (Luminal A, Luminal B, Her2-Enriched, and Basal-Like).

Specimens and Processing:

Formalin-fixed paraffin-embedded (FFPE) tumor tissue block from the residual disease on the definitive surgical specimen will be collected and submitted to the CBPF. Tissue specimens and an H&E stain will be routed to the Leyland-Jones Laboratory. The tissue will be evaluated for tumor area and cellularity, processed, and the tumor areas will be transposed to unstained slides. Tissue will be macrodissected and RNA will be extracted with a manual kit and subjected to PAM50 analysis, as described above.

10.3 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research study will be submitted electronically using a secure data transfer to the ECOG-ACRIN Operations Office – Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the investigator.

11. Electronic Data Capture

Please refer to the EA1141 Forms Completion Guidelines for the forms submission schedule. Clinical data collection will be performed exclusively in Medidata Rave.

Imaging studies are to be submitted via TRIAD

Quality of Life study data are to be submitted via Medidata Rave

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

12. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

13. References

3. Berg WA, Blume JD, Cormack JB, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA. 2008;299(18):2151-63.
4. Fletcher SW, Elmore JG. Clinical practice. Mammographic screening for breast cancer. N Engl J Med. 2003;348(17):1672-80.
5. Humphrey LL, Helfand M, Chan BK, Woolf SH. Breast cancer screening: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2002;137(5 Part 1):347-60.
6. Medicine Io. Saving Women's lives: integration and innovation: a framework for progress in early detection and diagnosis of breast cancer. 2005.
7. Welch HG, Passow HJ. Quantifying the benefits and harms of screening mammography. JAMA internal medicine. 2014;174(3):448-54.
8. Berlin L. Point: Mammography, breast cancer, and overdiagnosis: the truth versus the whole truth versus nothing but the truth. J Am Coll Radiol. 2014;11(7):642-7.
9. Carney PA, Miglioretti DL, Yankaskas BC, et al. Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography. Ann Intern Med. 2003;138(3):168-75.
10. Kerlikowske K, Grady D, Barclay J, Sickles EA, Ernster V. Effect of age, breast density, and family history on the sensitivity of first screening mammography. JAMA. 1996;276(1):33-8.
11. Pisano ED, Gatsonis C, Hendrick E, et al. Diagnostic performance of digital versus film mammography for breast-cancer screening. N Engl J Med. 2005;353(17):1773-83.
12. Ciatto S, Houssami N, Bernardi D, et al. Integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study. Lancet Oncol. 2013;14(7):583-9.

13. Skaane P, Bandos AI, Gullien R, et al. Prospective trial comparing full-field digital mammography (FFDM) versus combined FFDM and tomosynthesis in a population-based screening programme using independent double reading with arbitration. Eur Radiol. 2013;23(8):2061-71.
14. Skaane P, Bandos AI, Gullien R, et al. Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program. Radiology. 2013;267(1):47-56.
15. Friedewald SM, Rafferty EA, Rose SL, et al. Breast cancer screening using tomosynthesis in combination with digital mammography. JAMA. 2014;311(24):2499-507.
16. Price ER, Hargreaves J, Lipson JA, et al. The California breast density information group: a collaborative response to the issues of breast density, breast cancer risk, and breast density notification legislation. Radiology. 2013;269(3):887-92.
17. Hooley RJ, Greenberg KL, Stackhouse RM, Geisel JL, Butler RS, Philpotts LE. Screening US in patients with mammographically dense breasts: initial experience with Connecticut Public Act 09-41. Radiology. 2012;265(1):59-69.
18. Sprague BL, Stout NK, Schechter C, et al. Benefits, harms, and cost-effectiveness of supplemental ultrasonography screening for women with dense breasts. Ann Intern Med. 2015;162(3):157-66.
19. New Choice Health Care Market Place. http://www.newchoicehealth.com/Directory.
20. Berg WA, Zhang Z, Lehrer D, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA. 2012;307(13):1394-404.
21. Kuhl C, Weigel S, Schrading S, et al. Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. J Clin Oncol. 2010;28(9):1450-7.
22. Kuhl CK, Schrading S, Strobel K, Schild HH, Hilgers RD, Bieling HB. Abbreviated breast magnetic resonance imaging (MRI): first postcontrast subtracted images and maximum-intensity projection-a novel approach to breast cancer screening with MRI. J Clin Oncol. 2014;32(22):2304-10.
23. Schrading S KC. MRI screening of women at average risk of breast cancer. J Clin Oncol. 2013;31:(suppl 26; abstr 1).
24. Mango VL, Morris EA, David Dershaw D, et al. Abbreviated protocol for breast MRI: are multiple sequences needed for cancer detection? European journal of radiology. 2015;84(1):65-70.
25. Melsaether A GY, Seuss S, Heacock L, Moy L. Abbreviated MRI (AB-MR) of the Breast – Do We Need a Second Post-Contrast Scan? Oral presentation, RSNA, Chicago 2015. Abbreviated MRI (AB-MR) of the Breast – Do We Need a Second Post-Contrast Scan? Oral presentation, RSNA, Chicago 2015.
26. Heacock L MA, Pysarenko KM, Toth H, Moy L. Sensitivity of an Abridged Breast MRI Protocol to Detect Biologically Significant Breast Cancers. Oral presentation, RSNA, Chicago, 2014.

27. Sung JS, Stamler S, Brooks J et al. Breast Cancers Detected on High Risk Screening MRI and Mammography: Method of Detection Reflects Tumor Histopathology. Radiology. 2016 Sep;280(3):716-22. doi: 10.1148/radiol.2016151419. PMID: 27097237

28. Swan JS, Kong CY, Hur C, Halpern EF, Itauma O, Williams O, Motazedi T, Lee JM. Comparing morbidities of testing with a new index: screening colonoscopy versus core-needle breast biopsy. J Am Coll Radiol. 2015 Mar;12(3):295-301. doi: 10.1016/j.jacr.2014.08.014. Epub 2014 Oct 13. PubMed PMID: 25441485.

29. Humphrey KL, Lee JM, Donelan K, Kong CY, Williams O, Itauma O, Halpern EF, Gerade BJ, Rafferty EA, Swan JS. Percutaneous breast biopsy: effect on short-term quality of life. Radiology. 2014 Feb;270(2):362-8. doi: 10.1148/radiol.13130865. Epub 2013 Nov 11. PubMed PMID: 24471385; PubMed Central PMCID: PMC4228748.

30. Swan JS, Hur C, Lee P, Motazedi T, Donelan K. Responsiveness of the testing morbidities index in colonoscopy. Value Health. 2013 Sep-Oct;16(6):1046-53. doi: 10.1016/j.jval.2013.07.008. PubMed PMID: 24041354.

31. Swan JS, Kong CY, Lee JM, Itauma O, Halpern EF, Lee PA, Vavinskiy S, Williams O, Zoltick ES, Donelan K. Patient and societal value functions for the testing morbidities index. Med Decis Making. 2013 Aug;33(6):819-38. doi: 10.1177/0272989X13487605. Epub 2013 May 20. PubMed PMID: 23689044; PubMed Central PMCID: PMC3817009.

32. Leisenring W, Alonzo T, Pepe MS. Comparisons of predictive values of binary medical diagnostic tests for paired designs. Biometrics. 2000;56(2):345–351.

33. Chia SK, Bramwell VH, Tu D, et al. A 50-gene intrinsic subtype classifier for prognosis and prediction of benefit from adjuvant tamoxifen. Clin Cancer Res. 2012;18(16):4465-72.

34. Fan C, Oh DS, Wessels L, et al. Concordance among gene-expression-based predictors for breast cancer. N Engl J Med. 2006;355(6):560-9.

35. Liu S, Chapman JA, Burnell MJ, et al. Prognostic and predictive investigation of PAM50 intrinsic subtypes in the NCIC CTG MA.21 phase III chemotherapy trial. Breast Cancer Res Treat. 2015;149(2):439-48.

Appendix I

Rev. Add4

American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to mammography

1. BRCA mutation
2. First-degree relative of BRCA carrier, but untested
3. Lifetime risk ~20–25% or greater, as defined by BRCAPRO or other models that are largely dependent on family history
4. Recommend Annual MRI Screening (Based on Expert Consensus Opinion)
5. Radiation to chest between age 10 and 30 years
6. Li-Fraumeni syndrome and first-degree relatives
7. Cowden and Bannayan-Riley-Ruvalcaba syndromes and first-degree relatives
8. Insufficient Evidence to Recommend for or Against MRI Screening
    - Lifetime risk 15–20%, as defined by BRCAPRO or other models that are largely dependent on family history
    - Lobular carcinoma in situ (LCIS) or atypical lobular hyperplasia (ALH)
    - Atypical ductal hyperplasia (ADH)
    - Heterogeneously or extremely dense breast on mammography
    - Women with a personal history of breast cancer, including ductal carcinoma in situ (DCIS)

Rev. 2/17

Appendix II

Pathology Submission Guidelines

The following items are included in Appendix II:

1. Guidelines for Submission of Pathology Materials
   (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. ECOG-ACRIN Generic Specimen Submission Form (#2981)

Guidelines for Submission of Pathology Materials

1. Tumor Tissue Submissions to Genomic Health from Patients with DCIS

Contact Genomic Health Customer Service (866-662-6897) and request the "Onco*type* Specimen Kit."

One Onco*type* Specimen Kit and Requisition Form should be completed per patient.

DO NOT MIX BARCODE LABELS BETWEEN PATIENTS.

- Tumor Tissue Block (place barcode label on back of cassette)

OR

Fifteen (15) 5 µm serial unstained slides, oriented similarly and air dried. Label each slide with barcode and number in the order they were cut.

NOTE: Proper sterile sectioning technique MUST be followed. Failure to follow sterile technique can affect testing and delay results. If sterile technique cannot be followed, submission of a tumor tissue block is strongly recommended.

- Shipping Manifest Form from Sample Tracking System (STS)
- Completed Onco*type* DX Requisition Form

This form is to be completed on-line or written as instructed in the kit except for the following fields:

- "STUDY NAME/CODE" enter the protocol number 01-194-IIS-EA1141 and the ECOG-ACRIN EA1141 patient sequence number assigned at randomization.
- BILLING INFORMATION (section V): Please leave blank.
- ADDITIONAL PHYSICIAN (section III): Enter the contact information of the institutional CRA coordinating the EA1141 study.
- BLOCK RETURN" information (section VI). After testing, all residual block material will be forwarded by Genomic Health to the ECOG-ACRIN CBPF.
  - BLOCK RETURN CONTACT = ECOG-ACRIN Central Biorepository and Pathology Facility
  - BLOCK RETURN PHONE NUMBER = (844) 744-2420

2. Tumor Tissue Submissions to CBPF from Patients with Invasive Cancer (and all patients from whom only slides were submitted to GHI for the OncotypeDX DCIS assessment)

1. Adequate patient identifying information must be included with every submission. It is strongly recommended that full patient names be provided. The information will be used only to identify patient materials, and will expedite any required communications with the institution (including site pathologists).
2. Pathology materials:

Representative tumor tissue (DCIS or invasive) is submitted after all local assessments required for patient care are complete and are requested to be submitted within 30 days of the procedure.

Forms

The relevant pathology and surgical reports must accompany all tissue submissions:

- Copy of the diagnostic or surgical Pathology Report
- Other Immunologic and cytologic reports
- STS generated shipping manifest for all submitted tissue.

Tumor tissue submissions:

Representative formalin fixed paraffin embedded (FFPE) tumor tissue blocks.

NOTE: If blocks are unavailable for submission, cores and slides are to be submitted. All cores and slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirement:

- One (1) H&E slide
- Twenty (20) 4-5 µm unstained air-dried plus slides
- Two (2) 4 mm cores

NOTE: Since blocks are being used for laboratory studies, in some cases the blocks may be depleted and therefore may not be available for return.

Keep a copy of the STS- Shipping Manifest or Submission Form for your records.

Double-check that ALL required forms, reports and pathology samples are included in the package to the CRA.

The CRA will Mail pathology materials to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility.

ECOG-ACRIN
cancer research group
Reshaping the future of patient care

Robert L. Comis, MD, and Mitchell D. Schnall, MD, PhD
Group Co-Chairs

MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____

SUBJECT: Submission of Pathology Materials for EA1141: Comparison of Abbreviated Breast MRI and Digital Breast Tomosynthesis in Breast Cancer Screening in Women with Dense Breasts

The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of, as appropriate, tumor tissue specimens (DCIS or invasive) for laboratory research studies.

Keep a copy of the submission for your records and return any relevant completed forms, the surgical pathology report(s), the slides and/or blocks and any other required material (see List of Required Material) to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF) and Genomic Health as appropriate.

Pathology materials submitted for this study will be retained at the ECOG-ACRIN Central Repository for future studies per patient consent. Paraffin blocks will be returned upon request for purposes of patient management.

Please note: Since blocks are being used for laboratory studies, in some cases the material may be depleted, and, therefore, the block may not be returned.

If you have any questions regarding this request, please contact Genomic Health Customer Service (650-556-9300) or the Central Biorepository and Pathology Facility at (1-844-744-2420 (713-745-4440 Local or International Sites) or email: eacbpf@mdanderson.org

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address:_____

Phone: _____

Thank you.

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time-point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

Appendix III

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we hope to improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

Appendix IV

Rev. Add4

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.