Update #08

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A011104

EFFECT OF PREOPERATIVE BREAST MRI ON SURGICAL OUTCOMES, COSTS AND QUALITY OF LIFE OF WOMEN WITH BREAST CANCER

ClinicalTrials.gov Identifier: NCT01805076

[X]	**Update:**	[ ]	**Status Change:**
[ ]	Eligibility changes	[ ]	Activation
[ ]	Therapy / Dose Modifications / Study Calendar changes	[ ]	Closure
[ ]	Informed Consent changes	[ ]	Suspension / temporary closure
[ ]	Scientific / Statistical Considerations changes	[ ]	Reactivation
[X]	Data Submission / Forms changes		
[X]	Editorial / Administrative changes		
[ ]	Other :		

Expedited IRB approval is allowed. The proposed changes in this amendment are minor and do not affect the overall risk/benefit ratio.
IRB approval (or disapproval) is required within 90 days. Please follow your local IRB guidelines.

UPDATES TO THE PROTOCOL:

Contact Information (page 2):
-The note above the table with instructions to direct all questions to the QA Specialist identified below has been removed, as the QA Specialist title is no longer applicable.
-The Disease Site Committee Chairs have been changed to [redacted] All contact information has been updated.
-The Basic Sciences Committee Chair has been removed, as this is an outdated ACOSOG role.
-[redacted] as Alliance Data Manager. All contact information has been updated.
-The Regulatory Affairs Manager title has been updated to Alliance Regulatory Group.

CTSU Contact Information (page 3):
The CTSU Contact Information Table has been revised in its entirety to align with the current CTSU template.

Section 3 Study Calendar (page 12):
In footnote A, the follow-up QOL questionnaire timepoints have been updated to 8 and 12 months after registration instead of following diagnosis, for consistency. A window of +/- 30 days has been added for these timepoints to account for scheduling variances in aligning the questionnaires with the clinic visits.

Section 4 Registration (page 13):
This section has been revised in its entirety to align with the current CTSU boilerplate language.

Section 5.2.3 Image Submission (page 20):
Eight new paragraphs regarding TRIAD access and instructions have been added per the current CTSU boilerplate language.

Section 9.1 Case Report Form Completion and Submission (page 26):
This section has been revised in its entirety to align with the current CTSU boilerplate language.

Section 9.3 Data Quality Portal (page 27):
This new section has been added to align with the current CTSU boilerplate language.

Section 13.1.1 Study Design (page 37):
-The 8- and 12-month QOL questionnaire timepoints for both arms have been updated to 8 and 12 months post-registration instead of post-op, for consistency. A window of +/- 30 days has been added for these timepoints to account for scheduling variances in aligning the questionnaires with the clinic visits.
-In the second paragraph under the "Subset of the FACT-G" heading, the phrase "or online" has been removed from the second sentence as there is no online mechanism for completion of these questionnaires.

UPDATES TO THE MODEL CONSENT FORM:

Title page (page 50):
-A new second sentence regarding public funding has been added to the first paragraph per the current NCI Model Informed Consent template.
-All notes to local investigators have been removed from the consent form per the current NCI Model Informed Consent template.

What will happen if I take part in this research study? (page 51)
Under the "After surgery…" heading under "8 and 12 months after surgery," a parenthetical note has been added next to the questionnaires about quality of life, to clarify that these are to be done 8 and 12 months after registration.

Will My Medical Information Be Kept Private? (page 55):
This section has been updated in its entirety to align with the current NCI Model Informed Consent Form template.

A replacement protocol document and model consent form have been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

Alliance for Clinical Trials in Oncology
ECOG-ACRIN

Alliance A011104 / ACRIN 6694

Effect of Preoperative Breast MRI on Surgical Outcomes, Costs and Quality of Life of Women with Breast Cancer

Version Update #8

Participating Organizations: Alliance/Alliances for Clinical Trial in Oncology (lead)
ECOG-ACRIN/ECOG-ACRIN Medical Research Foundation, INC.
SWOG/SWOG
NRG/NRG Oncology

Contact Information

	Name & Location	Telephone	e-mail
Study Chair	[redacted]	[redacted]	[redacted]
Disease Site Committee Chairs	[redacted]	[redacted]	[redacted]
Community Oncology Co-chair	[redacted]	[redacted]	[redacted]
Alliance Statisticians ACRIN Statistician	[redacted]	[redacted]	[redacted]
ACRIN Radiologist	[redacted]	[redacted]	[redacted]
Radiation Oncology	[redacted]	[redacted]	[redacted]
Quality of Life	[redacted]	[redacted]	[redacted]
Comparative Effectiveness	[redacted]	[redacted]	[redacted]
Correlative Science	[redacted]	[redacted]	[redacted]
Alliance Biorepository at Washington University (WUSTL)	[redacted]	[redacted]	[redacted]
Alliance Pt Advocate ACRIN Pt Advocate	[redacted]	[redacted]	[redacted]
Alliance Data Manager	[redacted]	[redacted]	[redacted]
ACRIN Data Managers	[redacted]	[redacted]	[redacted]
Protocol Coordinator	[redacted]	[redacted]	[redacted]
For questions related to IRB review	Alliance Regulatory Group		[redacted]

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

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. (Sign in at [redacted] and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk [redacted] regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN can be accessed at [redacted] Contact the CTSU Help Desk with any OPEN-related questions at [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Refer to 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 page located on the CTSU members' website [redacted] 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 log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (i.e. patient eligibility or treatment-related questions) All questions should be directed to the Alliance Study Chair, Nursing Contact, Protocol Coordinator, or Data Manager		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – [redacted] All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at: [redacted]		

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1 Introduction

1.1 Background

Surgical planning and local-regional treatment of breast cancer relies on adequate assessment of the extent of disease in the breast including the size of the primary tumor and the presence or absence of multiple tumor foci, either within the same quadrant (multifocality) or in different quadrants of the breast (multicentricity). Macroscopic multifocal or multicentric disease is considered to result in higher rates of local recurrence and therefore is generally a contraindication to breast conservation[1,2]. Estimates of the frequency of multifocality and multicentricity in breast cancer vary widely, and depending on the specific criteria used can range from 7% to 63%[3,4 5,6]. With the concern for high local failure rates, women with multifocal or multicentric disease at presentation may not be ideal candidates for breast conservation. Preoperative identification of these patients is important for appropriate surgical planning and treatment.

As a diagnostic modality in breast cancer patients, MRI of the breast has been shown to have high sensitivity (94-100%)[7-9]. MRI has proven to be important in facilitating breast conservation in patients with unusual presentations such as nipple discharge and axillary node metastases [10 11]. MRI has also shown efficacy over conventional surveillance methods for patients at high risk of developing breast cancer [12 13]. However, for the majority of patients with breast cancer, the role of MRI remains controversial. Several small studies have described changes in the treatment of their patient cohorts based on MRI findings [9,14-17]. Recently, data from a large multicenter trial of MRI in patients with breast cancer demonstrated a nearly 10% increase in detection of multicentric/multifocal disease in the index breast [18]. Furthermore, MRI also detected clinically and mammographically occult cancer in the contralateral breast in 3.1% of patients [19]. Such findings have led to changes in surgical management of breast cancer patients in nearly 20% of women who undergo preoperative MRI with most cases converting from breast conserving therapy to mastectomy[17].

Despite the enhanced sensitivity of breast MRI, its clinical application for preoperative surgical staging of breast cancer patients has remained controversial. In part, this is due to high false positive rates which lead to additional biopsy procedures.[20 16 21] However, the primary reason for the continued debate regarding the utility of preoperative breast MRI stems from the lack of data demonstrating an oncologic benefit. Specifically, the biologic and thus clinical significance of additional foci of carcinoma detected only by MR imaging is unknown. Strikingly, the frequency of occult disease detected by MRI is 2-3 fold higher than the rates of local recurrence (LR) among women who undergo BCT without the benefit of preoperative breast MRI. Data from many clinical trials suggest that local recurrence following breast conserving surgery and adjuvant systemic therapy is low, less than 10% at 10 years. In contrast, the results of MRI based studies demonstrate 15-20% conversion rate from BCT to mastectomy on the basis of greater extent of disease or additional foci detected by MRI. Although some of this increase in mastectomy rates may be due to more accurate assessment of the size of the index carcinoma, a substantial portion is due to identification of additional foci of disease at a distance from the primary tumor. These rates of conversion from BCT to mastectomy are higher than most 10 year reports of LR rates in BCT patients. This therefore suggests that not all of the additional multifocal/multicentric disease that is detected by MRI is biologically relevant, or alternatively that it may be adequately treated with adjuvant radiation or adjuvant systemic therapy. Therefore, it is possible that too many women are undergoing mastectomy based on MR imaging. In order to assess the biologic relevance of these additional areas of carcinoma detected by MRI, long term studies that assess the impact of MRI staging on local recurrence need to be undertaken.

Two retrospective studies have attempted to address this issue but have reached opposing conclusions. Fisher and colleagues reported that among 346 breast cancer patients undergoing BCT, there was a statistically significant difference in LR rates between cohorts imaged with MRI preoperatively and those who did not undergo preoperative MRI (1.2% vs. 6.5% respectively). Unfortunately, the two groups in this retrospective series were not balanced. Specifically, patients in the no MRI arm had more advanced disease and importantly, less use of adjuvant therapies which are known to impact local control. In addition, more recent data from a larger retrospective cohort from the University of Pennsylvania suggested no improvement in LR among women undergoing preoperative MRI for staging [22].

Although breast MRI is clearly the most sensitive imaging modality for determining the extent of the primary carcinoma, for identifying additional occult foci of multicentric and/or multifocal disease, its impact on the most relevant clinical endpoint, local control, has not been studied. Furthermore, recent data in the literature

has raised concerns that routine use of preoperative breast MRI is associated with increased rates of mastectomy and delays to surgery. In a series of over 5000 patients from the Mayo Clinic, Katipamula and colleagues reported that use of MRI was significantly associated with choice of mastectomy [23] . Similarly, data from Fox Chase Cancer Center demonstrate that mastectomy as first procedure increased from 19.5% amongst women who did not undergo breast MRI to 27.7% in the cohort of women who had preoperative breast MRI [24]. In addition, in this latter group, time from diagnosis to surgery increased from 38.1 days to 56.9 days. Conversely, there are no studies that demonstrate that non-utilization of MRI in the staging of breast cancer patients adversely impacts clinically important outcomes such as local control and rates of re-operation. In fact, data recently made public from the COMICE trial, a multicenter, randomized clinical trial conducted in the UK, reported that women undergoing breast MRI did not have lower rates of re-excision [25] and as already discussed there is minimal and conflicting retrospective data regarding MRI and local control. This lack of demonstrated benefit and increased awareness of potential harms has led to concerns that use of MRI is leading to an over-diagnosis of occult breast cancer and subsequently to more aggressive surgical interventions than would be otherwise warranted. In light of these recent publications, it has become even more imperative to determine whether preoperative MRI improves clinical outcomes.

A key component of this trial is the collaboration between ACRIN and the Alliance. This collaboration was undertaken for two main reasons. First, to help ensure quality control of the MRI study. Second, there are currently no standards for how MRI findings should be clinically interpreted and implemented. Thus, a major emphasis of this collaborative effort is to establish standards for structuring the image report data and creating guidelines for subsequent patient intervention.

1.2 Rationale for Trial Design

To distinguish whether preoperative breast MRI improves local staging and ultimately improves local regional control, we propose that women deemed eligible for BCT by standard criteria be randomized between current standard of care, clinical examination and mammography (+/- ultrasound) and current standard of care plus preoperative breast MRI. In order to maximize the probability of deriving benefit from preoperative MRI, the study will focus on women with ER/PR/HER-2 negative (triple negative) and HER-2 amplified breast cancers. Recent data has demonstrated that amongst breast cancer subtypes, these 2 groups of patients have the highest risk of local regional recurrence at 5 years following BCT with rates as high as 17-20% at 5-10 years of follow-up (see table below). In contrast, women with ER/PR positive breast cancer had 5-year local recurrence rates following BCT of 0.8-1.5%. Given such low rates of in breast recurrence in the ER positive population, it would be challenging to achieve further significant lowering of local recurrence rates. Furthermore, if patients with ER/PR positive tumors are included in the trial, this will lower the risk of local recurrence in the control arm and thus require at least a doubling of the sample size to detect a meaningful reduction in local recurrence in the experimental (MRI) arm. **Therefore, this multicenter trial will target women at the highest risk of local recurrence and test the hypothesis that increased rates of multifocality and multicentricity in this population accounts for the higher reported rates of local recurrence.**

	Nguyen [26]	**Millar [27]**	**Haffty [28]**	**Voduc [29]**	**Abdulkarim [30]**
Endpoint	Local recurrence	Local regional recurrence	Local regional recurrence	Local regional recurrence	Local regional recurrence
Follow-up	5 yr	5 yr	5 yr	10 yr	5 yr
HER-2+	8.4%	15%	n/a	21% in breast 16% nodal	n/a
Basal/TN	7.1%	6-7%	17% in breast 6% nodal	8-14% in breast 7-14% nodal	6%

1.3 Rationale for the Inclusion of Neoadjuvant Chemotherapy Patients

Although response to chemotherapy is known to be prognostic, sequencing of chemotherapy and surgery has not been shown to impact outcomes. However, with increasing adoption of neoadjuvant chemotherapy in recent years, inclusion of this population of breast cancer patients has become important in order for study findings to be generalizable to current standard of care. In particular, lack of inclusion of this population risks biasing enrollment to only low risk subsets (T1 N0) and may result in under powering the trial for its primary endpoint.

Since neoadjuvant chemotherapy has not been shown to impact outcomes compared to a comparable cohort of patients who receive adjuvant therapy, we do not expect neoadjuvant chemotherapy vs adjuvant chemotherapy patients in our study to impact the study design and assumptions. However, neoadjuvant chemotherapy may change MRI characteristics of the tumor and thus potential MR interpretation. There is currently no clear data on this consideration. Therefore, in order to minimize potential biases that may arise because of effect of chemotherapy on the MRI interpretation, will now stratify patients enrolled for receipt of neoadjuvant chemotherapy. Although there is practice specific variability in the proportion of newly diagnosed breast cancer patients who undergo neoadjuvant chemotherapy vs adjuvant chemotherapy, given the generally widespread use of this sequencing strategy, we expect at least half of those enrolled after the activation of Update #06 will have undergone neoadjuvant chemotherapy.

1.4 Significance

This proposed randomized trial of preoperative breast MRI in patients deemed eligible for breast conserving surgery by conventional clinical criteria will provide important information about the clinical and biologic relevance of occult disease identified by MRI alone. Currently, the importance of these additional MRI detected foci remains controversial and there is concern that the enhanced sensitivity of breast MRI may result in unnecessary mastectomy. The results of this trial evaluating local recurrence rates in women who do and those who do not undergo preoperative MRI will therefore provide critical information about the significance of these additional MRI detected foci. If the trial results demonstrate that women who undergo BCT without the benefit of preoperative MRI have higher local recurrence rates compared to women staged preoperatively with breast MRI, then this would suggest that the occult areas of carcinoma, detected by MRI alone, are clinically relevant and if not surgically addressed, result in inferior local control. This finding would thus justify the routine use of preoperative MRI for staging of patients and selection for BCT. However, if the use of preoperative breast MRI does not improve on long term local control rates, this would suggest that the increased sensitivity of breast MRI in detecting otherwise occult disease is not clinically significant and/or these additional areas are well controlled through the use of adjuvant radiation and systemic therapies. Therefore, the use of preoperative MRI for routine staging of women prior to breast surgery would not be warranted and the increased rates of mastectomy seen with utilization of breast MRI would not be justified.

In addition, we have included a cost effectiveness component to this study. This will allow us to capture significant in depth data regarding the costs associated with the two treatment strategies and test the hypothesis that although preoperative breast MRI is expensive, these costs will be offset, in the short term, by reducing the number of operative interventions required to achieve margin negative BCT and, in the long term, by reduction in local recurrence events. We believe that the information obtained from this CER study will be as important as the primary and secondary endpoints. The CER study has the potential to alter clinical management even if we are unable to demonstrate oncologic benefit of routine preoperative breast MRI. It is possible that even though the rates local recurrence or re-operation between the two arms do not appear to differ (i.e. the p-value is not significant), a decrease in either parameter in the MRI arm may still be sufficient to make preoperative MRI a cost effective strategy and thus warranted for routine use in the clinic.

Registration fatigue/uniscale assessment: QOL measurements of fatigue and overall perception of QOL are routinely included in Alliance studies and will be assessed upon registration in this study. Evidence has arisen indicating that baseline single-item assessments of fatigue and overall QOL are strong prognostic indicators for survival in cancer patients, independent of performance status. This evidence was derived from two separate meta-analyses recently presented at ASCO, the first involving 23 NCCTG and Mayo Clinic Cancer Center oncology clinical trials, the second involving 43 clinical trials. Routine inclusion of these measures should be considered similar to that of including performance status, either as stratification or prognostic covariates.[79]

1.5 Objectives

1.5.1 Primary Objective

To compare the rates of local-regional recurrence (LRR) following attempted breast conserving therapy in a cohort of women with triple negative or HER-2 amplified breast cancer randomized to preoperative staging with mammography (control arm) or mammography plus breast MRI (MRI arm).

1.5.2 Secondary Objectives

1. To compare the re-operation rates following attempted breast conserving therapy between women assessed preoperatively with breast MRI to those assessed without the use of breast MRI.
2. To compare local recurrence rates between women who undergo BCT on the control arm to women who undergo BCT on the MRI arm.
3. To compare the conversion rate to mastectomy secondary to persistent positive margins or poor cosmesis within the first 6 months of attempting BCT (prior to the administration of RT) between women assessed preoperatively with breast MRI to those assessed without the use of breast MRI.
4. To compare the contralateral breast cancer rates in women randomized to preoperative breast MRI to those not receiving pre-operative breast MRI.
5. To compare the disease-free survival rates between women assessed preoperatively with breast MRI to those assessed without the use of breast MRI.
6. To compare breast cancer specific and overall survival outcomes of women assessed preoperatively with breast MRI to those assessed without the use of breast MRI.
7. To estimate the rate of MRI-guided localization assisted surgery.
8. To estimate the rate of multi-centric disease in the index breast for women in the MRI arm.
9. To evaluate the accuracy of index lesion characteristics and other factors in predicting multi-centricity in the cohort randomized to breast MRI.
10. To assess the positive predictive values (PPV) of MRI in detecting ipsilateral multi-centric disease and contralateral disease in women with breast cancer undergoing preoperative breast MRI.
11. To estimate the false positive rate for detection of multiple foci of breast cancer by MRI.

Correlative Science Objectives

1.5.3. Quality of Life

1. To compare patient reported QOL parameters between women randomized to the preoperative breast MRI arm and women randomized to the no pre-operative breast MRI arm.
2. To explore the impact that preoperative MRI has on patient QOL.
3. To compare the QALY in patients randomized to the preoperative breast MRI arm versus those randomized to the no preoperative breast MRI arm.
4. To contribute to a bank of normative data of QOL outcomes in cancer patients.

1.5.4 Cost Effectiveness

1. To compare the estimated mean costs of breast cancer treatment between women randomized to the pre-operative breast MRI arm and women randomized to the no pre-operative breast MRI arm.
2. To determine the incremental cost-effectiveness ratio of pre-operative breast MRI.
3. To determine the impact of preoperative breast MRI using a net-benefit regression framework.

1.5.5 Translational Studies

1. To determine molecular profile of chemonaive and chemoresistant breast cancer
2. To determine whether clinical-pathologic variables predict LRR.
3. To determine molecular characteristics that correlate with LRR and disease-free survival.

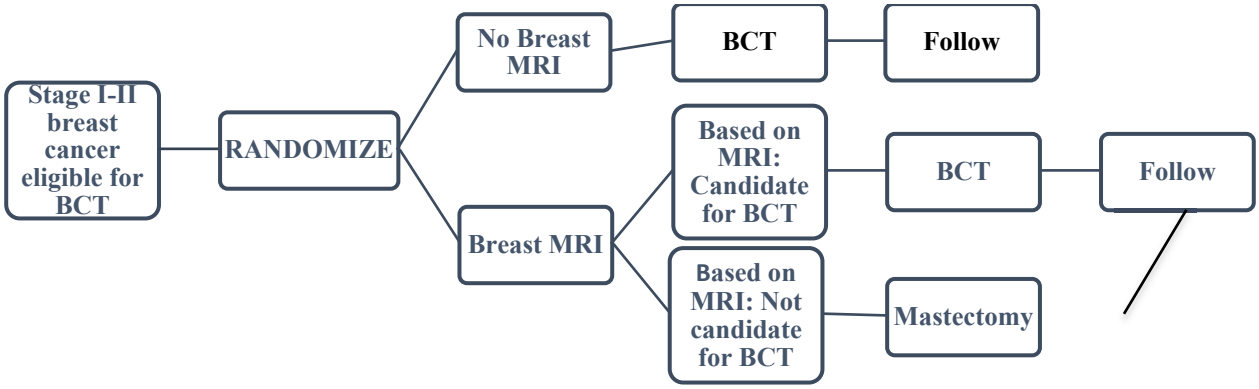
4. To determine molecular alterations that develops between primary tumors and recurrent tumors

1.6 Accrual Goal

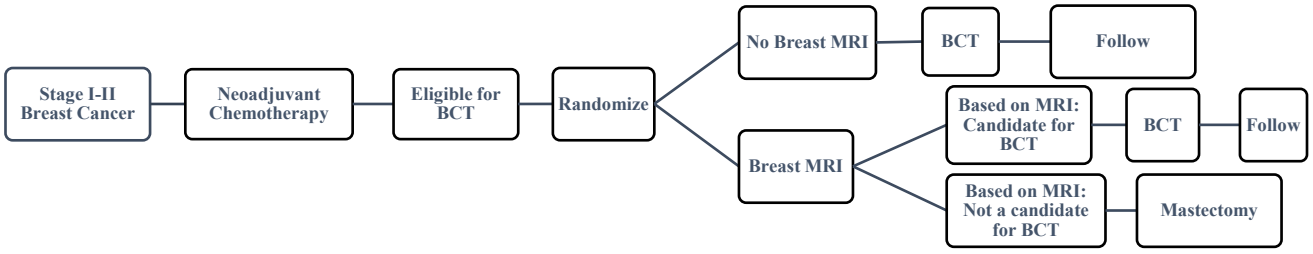
The target accrual for this trial is 288 eligible patients. An over-accrual of at most 29 women will be allowed to account for patient withdrawals after randomization and for women deemed to be ineligible. Hence, the maximum accrual for this trial is 317 women.

1.7 Schema

For patients undergoing up front surgery:



For patients undergoing neoadjuvant chemotherapy:



Stratification factors: clinical T stage (T1-2 vs T3), enrolling institution, triple negative vs HER2 positive, receipt of neoadjuvant chemotherapy.

2 Patient Selection

Each eligibility criterion must be evaluated and documented in the patient's medical record. No eligibility exceptions are permitted. NOTE: All staging examinations must be done at time of diagnosis.

2.1 Eligibility Criteria

A patient will be eligible for inclusion in this study only if **ALL** of the following criteria apply:

1. Female. Men are excluded from this study because the number of men with breast cancer is insufficient to provide a statistical basis for assessment of effects in this subpopulation of people with breast cancer.
2. Pathologically confirmed diagnosis of breast cancer, clinical stage I-II (T1-3 N0 M0, T0-2 N1 M0). Diagnosis must be by needle biopsy; patients diagnosed by surgical excision are excluded. For patients enrolled after receipt and completion of neoadjuvant chemotherapy, the clinical stage must be determined based on pre-chemotherapy assessment.
3. Patients must have either:
    a. ER negative/PR negative (<10% by IHC staining) and HER-2 negative breast cancer.

    OR

    b. ER negative/PR negative (< 10% by IHC staining) and HER-2 positive tumors.
    c. HER2 status will be determined as per the 2013 ASCO CAP guidelines[31]:
        i. HER2 is considered positive if a) there is IHC 3+ staining or b) ISH positive using either single probe ISH or dual probe ISH
        ii. HER2 is considered negative if a) there is IHC 0 or 1+ staining or b) ISH negative using either single probe ISH or dual probe ISH
    d. For patients enrolling after neoadjuvant therapy, the ER, PR, and HER2 markers are based on assessment prior to initiating neoadjuvant treatment.
4. No patients with previous ipsilateral or contralateral invasive breast cancer or DCIS.
5. No patients with bilateral breast cancer.
6. No patients with known deleterious mutations in BRCA genes.
7. No history of receiving endocrine therapy, tamoxifen, and or aromatase inhibitors for therapeutic measures. These agents used previously as chemoprevention are allowed.
8. Patients receiving neoadjuvant chemotherapy or recently completed neoadjuvant chemotherapy and will undergo surgery within 6 weeks are eligible.
9. No patients scheduled to receive partial breast irradiation following breast conserving surgery.
10. Eligible for BCT based on clinical examination, mammography and, if standard practice at a given institution, ultrasound and/or tomogram. Women who cannot be appropriately selected for BCT based on these standard imaging studies, and for whom additional imaging is recommended to clarify local disease extent, will not be eligible for this trial. For patients who have neoadjuvant therapy, eligibility for BCT is determined at completion of therapy. Repeat mammogram +/- US of the affected side only will be required at completion of neoadjuvant chemotherapy to determine eligibility for BCT.
11. No patients with multicentric or multifocal disease scheduled to undergo multiple lumpectomies. Multifocal disease that can be encompassed in a single operative bed can be enrolled. For patients with multifocal or multicentric disease enrolled after completion of neoadjuvant chemotherapy, histologic confirmation of multifocality/multicentricity must have been completed before initiation of chemotherapy.
12. Suitable to undergo MRI and receive the contrast agent gadolinium (exclusions follow):
    a. No history of untreatable claustrophobia;
    b. No presence of metallic objects or implanted medical devices in body (i.e., cardiac pacemaker, aneurysm clips, surgical clips, prostheses, artificial hearts, valves with steel parts, metal fragments, shrapnel, tattoos near the eye, or steel implants);

c. No history of sickle cell disease;

d. No contraindication to intravenous contrast administration;

e. 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 [redacted] for reaction definition and premedication guidance);

f. No findings consistent with renal failure, as determined by glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2 based on a creatinine level obtained within 28 days prior to registration;

g. Weight lower than that allowable by the MRI table;

13. No prior MRI of the study breast within the 12 months prior to registration.
14. Non-pregnant and non-lactating. Patients of child-bearing potential must have a negative pregnancy test within 7 days prior to registration. Perimenopausal patients must be amenorrheic > 12 months to be considered not of child-bearing potential.
15. ≥ 18 years of age.
16. Signed study-specific informed consent prior to registration.

2.2 Staging Criteria

Patients will be staged prior to registration according to the clinical staging criteria adapted from the American Joint Committee on Cancer (AJCC) Cancer Staging Data Forms of the AJCC Cancer Staging Manual, 7th Edition, 2009 (See Appendices). Note: For consistency purposes, AJCC 7th Edition will continue to be used throughout the entire study enrollment period.

3 Study Calendar

TESTS & EVALUATIONS	Prior to Registration	After Registration	At Surgery	Post-Op Visit(s)*	Follow-up**
History and Physical (including weight), Performance Status	X(1)			X	X
Blood creatinine	X(2)				
Pregnancy test (for women of childbearing potential)	X(4)				
Bilateral Mammogram	X				
Breast biopsy	X				
Adverse event assessment				X	
Fatigue/Uniscale assessment	X(3)				
QOL questionnaires	A			A	A
Medical care costs data		X		B	X
MRI		C			
Image submission to ACRIN		X			
Whole blood***		X			
Tissue submission***		X	X		D

* As clinically indicated; all data should be submitted for all post-operative visits.

** Every 4 months after final oncologic surgery until 2 years following registration, then every 6 months for 3 years.

*** For patients who consent to these additional studies. Patients undergoing surgery first will have surgical sample collection. Patients who undergo chemotherapy first will have collection of their diagnostic core biopsy as well as residual tumor at surgery.

A QOL questionnaires for patients on Arm 1 are to be completed at enrollment/prior to randomization, at first and last postop visit (if undergoing re-operation), and at 8 and 12 months (+/- 30 days) following registration. QOL questionnaires for patients on Arm 2 are to be completed at enrollment/prior to randomization, after MRI but prior to surgery, at first and last postop visit (if undergoing re-operation), and at 8 and 12 months (+/- 30 days) after registration.

B If more than one surgery is performed, medical care costs data is to be collected at every post-op visit.

C For patients randomized to Arm 2. MRI must be performed within 30 days following last mammographic study. For neoadjuvant chemotherapy patients, repeat mammogram (+/- US) of the affected side only will be required prior to enrollment in order to meet this 30-day window.

D Tissue collected at the time of cancer recurrence only.

1. Within 16 days prior to registration.
2. Within 28 days prior to registration.
3. Within 21 days prior to registration (see Appendix V)
4. Within 7 days prior to registration.

4 Registration

4.1 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 at [redacted] 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 acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at [redacted]

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
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 Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

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

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance).

Additional information is located on the CTEP website at [redacted] For questions, please contact the RCR Help Desk by email at [redacted]

4.2 CTSU Site Registration Procedures

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

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at [redacted] to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling [redacted]

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to the CTSU members' website [redacted] using your CTEP-IAM username and password;
- Click on Protocols in the upper left of your screen

O Enter the protocol number in the search field at the top of the protocol tree, or

O Click on the By Lead Organization folder to expand, then select Alliance, and protocol number A011104

• Click on Documents, select Site Registration, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

4.2.2 Requirements for A011104 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)

4.2.3 Submitting Regulatory Requirements

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website → Regulatory → Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at [redacted] in order to receive further instruction and support.

4.2.4 Checking Your Site's Registration Status

You can verify your site's registration status on the members' side of the CTSU website.

- Log on to the CTSU members' website;
- Click on Regulatory at the top of your screen;
- Click on Site Registration;
- Enter your 5-character CTEP Institution Code and click on Go.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. 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.

4.3 OPEN Registration System Requirements

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR

or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

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

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- 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.

Access OPEN at [redacted] or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at [redacted] or [redacted] For any additional questions, contact the CTSU Help Desk at [redacted]

4.4 Patient Registration Requirements

- Informed consent: the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.
- Patient completed booklets: Patient questionnaire booklets are to be ordered prior to the registration of any patients. Patient completed booklets can be ordered by downloading and completing the CTSU Supply Request Form (located under the site registration documents section of the A011104 website) and submitting the form through the regulatory portal. Samples of the booklets are found in Appendices VI, which are to be used for reference and IRB submission only. They are not to be used for patient completion.

4.5 Stratification Factors

- Clinical tumor stage: T1-2 vs. T3
- Breast cancer type: ER-/PR-/HER2+ vs. ER-/PR-/HER2-
- Enrolling Institution
- Neoadjuvant chemotherapy Yes vs. No

4.6 Treatment Arms

Arm 1 (standard): Clinical breast examination and mammography (+/- tomogram if tomography is standard practice at the enrolling institution) with ultrasound (US) of breast and regional nodes (if US is a standard component of institutional preoperative assessments); followed by breast conserving surgery (BCS).

Arm 2 (experimental): Clinical breast examination, mammography (+/- tomogram if tomography is standard practice at the enrolling institution) with ultrasound (US) of breast and regional nodes (if US is a standard component of institutional preoperative assessments) and breast MRI; followed by breast conserving surgery (BCS) or mastectomy.

5 Interventions

5.1 Breast Conserving Therapy

Patients randomized to Arm 1 will proceed to breast conserving surgery (BCS).

Patients randomized to Arm 2 who remain eligible for breast conserving surgery after MRI (see Section 5.2), will similarly proceed to BCS.

Surgery must be scheduled within 6 weeks of registration for patients on Arms 1 and 2.

For quality control purposes, surgery must be performed at the registering institution or at an affiliated site with IRB approval for the study.

5.1.1 Oncoplastic techniques can be utilized at the surgeon's discretion.

5.1.2 A margin negative excision, defined as no tumor identified at the inked surgical margin, is required. For patients with positive margins after initial attempt at BCS, decision regarding re-excision vs. completion mastectomy will be made at surgeon's discretion.

5.1.3 Management of the axilla

5.1.3.1 Patients with clinically negative nodes (by physical exam +/- ultrasound) should undergo staging using standard sentinel node techniques.

5.1.3.2 In patients with clinically negative nodes (by physical exam +/- ultrasound), but positive sentinel node, and who otherwise conform to ACOSOG Z0011 entry criteria, axillary nodal dissection may be omitted in favor of axillary radiation or observation at the discretion of their treating physician. For patients who do not conform to ACOSOG Z0011 entry criteria, axillary dissection is recommended in the setting of a positive sentinel node.

5.1.3.3 Patients with clinically positive nodes at presentation, as determined by clinical exam +/- ultrasound and confirmed by FNA biopsy, management is dependent on receipt of neoadjuvant chemotherapy:

1) for patients who have NOT received neoadjuvant chemotherapy, axillary nodal dissection remains standard practice.

2) for patients that have received neoadjuvant chemotherapy, management as follows:

a. After completion of neoadjuvant chemotherapy, any patient with persistent, clinically, positive axilla should undergo axillary node dissection.

b. After completion of neoadjuvant chemotherapy, any patient whose axilla has converted to being clinically negative, may undergo sentinel lymph node biopsy or axillary node dissection at the discretion of the treating surgeon.

c. For patients undergoing SLN after neoadjuvant chemotherapy, the following criteria should be fulfilled:

    a. SLN should be performed using both blue dye and radioactive tracer.

    b. If the node which was proven to have been positive prior to neoadjuvant chemotherapy did not have a clip placed and fewer than three SLN's are identified, then ALND is recommended.

    c. If the node that was positive prior to neoadjuvant chemotherapy had a clip placed, it must be confirmed to be among nodes removed at time of SLN, i.e. clip must be present in specimen radiograph of nodes.

        i. For sites not able to directly localize and remove the clipped node, if the node which was proven to have been positive prior to neoadjuvant chemotherapy is confirmed to be among the SLN's removed, and a minimum of 2 SLN's are identified, then ALND is not required (as long as all SLN's are negative).

        ii. For sites that are able to localize and remove the clipped node independent of SLN biopsy, then retrieval of the clipped node and additional SLN biopsy (for a total of at least 2 nodes) will be sufficient and ALND is not required (as long as the clipped node and the SLN are negative).

    d. If a clip was placed, but the node which was proven to have been positive prior to neoadjuvant chemotherapy cannot be confirmed to be removed after neoadjuvant chemotherapy, then ALND is mandated.

    e. ALND should be performed if even one SLN (or clipped node if removed separate from SLN) is positive, regardless of the size of the metastasis and the method of detection.

5.2 Magnetic Resonance Imaging (MRI)

For patients randomized to Arm 2, MRI will be performed within 30 days of the last mammographic study.

The MRI examination to be performed in this study is considered standard of care, and should be billed to third party payers per each institution's standard procedures. ECOG-ACRIN will provide reimbursement for costs related to the ARM 2 MRI, including, but not limited to the transfer of MR images to ECOG-ACRIN as well as their corresponding data forms; this reimbursement will be paid by ECOG-ACRIN to sites upon receipt of the imaging data.

5.2.1 MRI Scanner Qualification

ACRIN requires pre-qualification of magnetic resonance imaging scanners prior to participant enrollment to the trial and must meet ACR requirements for image quality under the ACR accreditation program (see Appendix III).

5.2.2 MRI Guidelines for eligibility

Contraindications to MRI are listed in Section 2.1 under eligibility criteria.

5.2.2.1 Required Imaging Sequences

Bilateral breast MRI should contain at a minimum the following sequences:

- T2 images with fat saturation (4-5 mm slice thickness),
- 1.5T or 3.0T whole body MRI scanner
- Dedicated breast radiofrequency coil
- Patient scanned in prone position with in-dwelling IV catheter
- Single dose contrast agent injection (FDA-approved gadolinium-based contrast agent);
- The MRI exam will include a localization scan and a T2-weighted sequence followed by a contrast-enhanced T1-weighted series:
  - T2-weighted sequence performed before contrast
  - T1-weighted sequence performed once pre-contrast and multiple times post-injection using identical sequence parameters (see below); transmit and receive gain settings should remain constant for pre-contrast and post-contrast T1-weighted imaging
  - Pre-contrast T1 images should be checked prior to contrast injection to confirm acceptable fat-suppression
  - Post-contrast imaging should continue for at least 8 minutes following contrast agent injection
- Care should be taken to select the smallest FOV and slice coverage that completely encompasses both breasts and axilla

5.2.2.2 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, gadolinium contrast agent will be administered intravenously at a dose of 0.1 mmol/kg body weight and rate of 2 ml/second, followed by a 20 ml saline flush. Contrast injection will begin simultaneously with the start of data acquisition.

5.2.2.3 MRI Findings

The following algorithms will be utilized for reporting MRI findings and determining subsequent management. Site radiologist will use the study specific forms to document MRI results. These MRI results will be communicated to surgical team and documented. All breast MRIs will be reported using the following standard BIRADS guidelines.

BI-RADS® Category	Breast MRI 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

5.2.2.4 Disease Management

The size estimation of the primary cancer on MRI should include all suspicious enhancement in the location of the known carcinoma that is similar in morphology, kinetics and in a continuing distribution. MRI findings should be managed as below (summarized in Appendix IV):

1. If MRI findings match mammographic or US findings: Localization for surgical excision may be guided by either mammography or ultrasound.
2. If MRI shows cancer extent larger than on mammography or US but would not convert patient to mastectomy:
    a. If primary tumor size on MRI is larger than expected, proceed with standard localization (see Section 5.2.2.6 below for Localization Guidelines).
    b. If additional foci of suspicious enhancement seen and;
        i. Furthest extent ≤ 2 cm from primary tumor: May proceed with localization based on mammography or US but should try to incorporate MRI findings during surgery
        ii. Furthest extent > 2 cm from primary tumor: Second-look US or MR-guided core biopsy prior to surgery or MR-guided needle localization at the time of surgery. If second look ultrasound is negative, an MRI-guided core biopsy is required.
3. MRI shows cancer extent that would convert patient to mastectomy:
    a. MRI shows primary tumor size too large for BCS—further biopsy optional before proceeding with mastectomy.
    b. MRI shows additional foci of disease: Second-look US or MR-guided core biopsy prior to surgery of the most suspicious lesion that would confirm the need for mastectomy. If second look ultrasound is negative, an MRI-guided core biopsy is required.
4. BI-RADS 3 lesion management should be based on the institution's standard management.
5. Contralateral BI-RADS 4 and 5 lesions require biopsy.
    a. If the lesion cannot be biopsied under stereotactic or ultrasound guidance, an MR-guided biopsy will be required.
    b. If no enhancement is seen on the day of MRI guided biopsy, then no further attempt at biopsy is required.
6. Management of pathologic findings from biopsy of BIRADS 4 and 5 lesions:

a. If the results of biopsy are consistent with benign findings (adenosis, hyperplasia without atypia, etc) and:
   i. the findings are concordant with imaging- no further intervention required
   ii. the findings are discordant with imaging- further sampling required, to include as appropriate surgical excision

b. If the results of biopsy demonstrate increased risk lesions (ADH, ALH, LCIS), patients should be managed according to the standard practice at the institution with excision as appropriate

5.2.2.5 If MRI work-up and biopsy demonstrates contralateral breast cancer, and patient remains interested in BCT, then management should be based on same algorithms as for the index breast (see Section 5.2.2.4).

5.2.2.6 Localization Guidelines (any modality)

Localization can be performed with wire or seed placement.

Single localization: Total involvement $\leq$ 2 cm or solitary round lesions of any size.

Bracketed localization: Non spherical tumor involvement > 2cm in total size.

For all localizations: Mammogram and/or US localization images should be sent with the patient to the OR. For all MRI patients, MR maximum intensity projection (MIP) images should be provided in the axial and sagittal projections.

5.2.3 Image Submission

All breast imaging (including mammography, ultrasound, and MRI) will be transferred and stored at the ACR Imaging Core Laboratory.

For this protocol, the following images will be collected and submitted to ACRIN.

- All clinical imaging exams performed as part of standard of care for patients on Arms 1 and 2;
- MRIs performed as part of disease assessment and surgery evaluation for patients on Arm 2 only;
- Any other imaging scans performed as part of the study for patients on Arms 1 and 2.

These protocol required images must be in DICOM format on CD/DVD-ROM or submitted via the internet using secure File Transfer Protocol (FTP), and transmitted along with an Imaging Transmittal Worksheet (ITW) which can be found on the ACRIN 6694 web site [redacted]

The required images must be submitted to ACR Imaging Core Lab. ACRIN can provide electronic image submission and anonymity utilities for participating institutions via TRIAD software. For support in sending the images via the internet using TRIAD, contact the representatives of the Image Management Center (IMC) via email at [redacted]

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

Site staff that will be submitting images via TRIAD will need to register with CTEP and have a valid and active CTEP-IAM account.

• Must be registered as an Associate, Associate Plus, Non-Physician Investigator, or Investigator registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in Registration and Credential Repository (RCR).

To submit images, site staff must hold the TRIAD Site User role on an NCTN or ETCTN roster. Individuals requiring a TRIAD Site User role should contact the person holding a primary role at the site for their affiliated NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD, and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at [redacted]

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

For questions, contact TRIAD Technical Support staff via email [redacted]

5.2.3.1 If required and part of the protocol, images maintained at ACRIN Headquarters Image Archive may be distributed to other participating sites, using FTP, or CD-ROM where appropriate, for purposes of secondary review.

5.2.3.2 **Removal of Confidential Participant Information:** The header record on DICOM formatted image data, which often contains information identifying the participant by name, MUST be scrubbed before the image are transferred.

This involves replacing the following:

- Participant Name tag with the ACRIN Institution ID or number
- Participant ID tag with the ACRIN case number, and
- Other Participant ID tag with ACRIN Study Number.

5.2.3.3 **FTP Transfer:** Digitally generated image files in DICOM v3.0 format can be transmitted to the ACRIN IMC via FTP directly to the image archive. This can be performed using a customized software program or by using TRIAD software available from ACRIN. An Imaging Transmittal Worksheet (ITW) must be faxed at the time images are transmitted. Contact the ACRIN IMC for additional details at [redacted]

5.2.3.4 **Please fax the ITW to:**

[redacted]

5.2.3.5 In the event that the transfer of scrubbed image headers is not available, images may also be sent on a CD/DVD-ROM to the ACRIN IMC for transfer to the image archive. Please contact ACRIN prior to sending the media to confirm compatibility.

5.2.3.6 Images and the ITW may be mailed to:

[redacted]

5.3 Postoperative Therapy

5.3.1 Postoperative Radiation Guidelines

Radiation treatment decisions will be determined by the treating multidisciplinary team. The following guidelines may be used to aid in radiation treatment decisions for patients treated on this protocol.

All patients treated with radiation may be simulated on a conventional simulator or CT-simulator, but CT-simulation and dose planning is encouraged.

Breast Conserving Surgery

All patients undergoing breast conserving surgery should receive whole breast radiation therapy using tangential fields with appropriate dose compensation techniques to optimize dose homogeneity, at a dose of 180-200 cGy daily to a total median dose of 4500-5040 cGy. Patients should routinely receive a dose to the tumor bed of 1000-1600 cGy to a total dose of between 6000 and 6600 cGy.

Given recent results demonstrating equivalent local control, survival and cosmetic outcomes with hypofractionated whole breast radiation, patients may at the discretion of the radiation oncologist, be treated using the Canadian Hypofractionation scheme of 4250 cY in 16 fractions to the whole breast. A boost to the tumor bed of 1000 cGy in 5 fractions of 200 cGy or 1000 cGy in 4 fractions of 250 cGy may be employed at the discretion of the treating radiation oncologist. If regional nodal irradiation is planned, patients should receive conventional radiation of 180 -200 cGy per fraction as above.

For patients treated with either conventional whole breast or hypofractionated whole breast dose homogeneity should be kept at +/- 7% at the central breast axis.

Mastectomy

For those patients who undergo mastectomy, the decision for postmastectomy radiation should be made by the radiation oncologist in collaboration with the other treating physicians. All patients with 4 or more nodes should be treated with postmastectomy radiation and selected high risk patients with node negative disease and patients with 1-3 positive nodes may receive postmastectomy radiation. Patients treated with postmastectomy radiation should receive treatment to the chest wall using tangential fields or en-face electron fields at a dose of 180-200 cGy daily to a total dose of 4500-5040 cGy. Dose compensation techniques should be used to optimize dose homogeneity and bolus should be used at the discretion of the treating physician to assure adequate skin dose. A chest wall/scar boost may be administered at the discretion of the treating physicians, to a total dose not to exceed 6600 cGy.

Regional Nodal Irradiation

Patients undergoing radiation for node negative disease following BCS will not undergo RNI.

Patients undergoing radiation post mastectomy or post lumpectomy with more than 3 positive nodes or selected patients with 1-3 nodes involved nodes may undergo regional nodal irradiation as follows:

Supraclavicular Radiation

Patients should receive radiation to the supraclavicular fossa (without axillary radiation except as described below), using standard AP or APPA fields, with a daily dose of 180-200 cGy daily, to a total dose not to exceed 4500-5040 cGy. Standard matching techniques to minimize overlap with the breast/chest wall fields, and standard blocking techniques should be employed. Except when intentionally treating the full axilla as described below, the lateral border of the supraclavicular field is recommended to be placed at the coracoid process or no further lateral than the medial border of the humeral head.

Axillary Radiation

If the treating physicians feel axillary radiation is warranted, the lateral border of the supraclavicular field may be extended laterally to cover the full axilla and a posterior axillary field may be employed as clinically indicated to assure full dosimetric coverage of the axilla. Dose to the axilla should follow the guidelines for supraclavicular radiation as above.

Internal Mammary Radiation

Radiation of the internal mammary field is left at the discretion of the treating physicians. If treated, CT Simulation and planning is required to assure minimum dose to underlying cardiac and pulmonary structures and adequate coverage of the internal mammary chain. Dose to the internal mammary chain should follow the guidelines for supraclavicular radiation noted above.

6 Follow-up

All registered patients will be monitored for relapse and survival for 5 years from the date of surgery, as required by the Study Calendar. Patients will be followed a minimum of every 4 months for the first 2 years from

diagnosis and a minimum of every 6 months during years 3-5. Patients will be monitored for local, regional and distant relapse, and vital status.

6.1 Follow-up of Patients Who Do Not Have Surgery or Whose Surgical Plan Deviates from Study Schema

Patients who are randomized but do undergo surgery or who do not follow protocol specified surgical management as per the study schema will be followed for all study endpoints according to study calendar. Patients may be treated at the physician's discretion.

6.2 Follow-up of Patients with Disease Relapse after Surgery

Patients who develop local, regional, or distant relapse after surgery will be followed for survival and cost effectiveness endpoints. Patients may be treated at the physician's discretion.

Patients who develop a second primary cancer (including cancer in the contralateral breast) after surgery will be followed for all study endpoints. Patients may be treated at the physician's discretion.

7 Evaluation of Disease Outcomes

The diagnosis of a first breast cancer recurrence or second primary can be made only when both the clinical and laboratory findings confirm the presence of disease. Suspicious findings do not constitute criteria for breast cancer recurrence. PET scans may be performed at the discretion of the investigator. However PET scans, in the absence of objective findings on CT, MRI, or other imaging studies do not meet the criteria of an acceptable method of determining breast cancer recurrence for this study. Any recurrence of malignant disease should be proven by biopsy whenever possible. Treatment of a breast cancer recurrence or second primary cancer will be at the discretion of the enrolling physician.

7.1 Local Recurrence

Local recurrence is defined as evidence of invasive or in situ breast cancer (except LCIS) in the ipsilateral breast or chest wall. Patients who develop clinical evidence of tumor recurrence in the remainder of the ipsilateral breast or chest wall must have a biopsy of the suspicious lesion to confirm the diagnosis.

Given the challenges of defining a reliable definition of local recurrence vs. new primary, all recurrences in the ipsilateral breast will be considered in the analysis of the primary endpoint. This definition of local recurrence is also in keeping with the hypothesis of this trial, namely that MRI will reduce local recurrence events by detecting clinically relevant occult disease in other quadrants of the breast.

7.2 Regional Recurrence

Regional recurrence is defined as the development of tumor in the ipsilateral internal mammary, ipsilateral supraclavicular, ipsilateral infraclavicular, and/or ipsilateral axillary nodes, as well as the soft tissue of the ipsilateral axilla, after surgery. This can be confirmed with positive cytology or histologic biopsy.

7.3 Distant Recurrence

Distant recurrence is evidence of tumor in any areas of the body, with the exception of those defined as local or regional recurrence above.

7.4 Second Primary Breast Cancer

A second primary breast cancer is evidence of invasive or in situ breast cancer (except LCIS) in the contralateral breast or chest wall. The diagnosis of a second primary breast cancer must be confirmed histologically.

7.5 Second Primary Cancer (non-breast)

Any non-breast second primary cancer other than squamous or basal cell carcinoma of the skin, melanoma in situ, carcinoma of the cervix, or colon carcinoma in situ will be considered an event in the analysis of disease-free survival. The diagnosis of a second primary cancer must be confirmed histologically whenever possible.

7.6 Disease-free Survival

Disease-free survival (DFS) will be measured from date of randomization until the first disease event where the disease event is defined as local (DCIS or invasive), regional, or distant breast cancer recurrence, second primary cancer, DCIS or invasive contralateral breast cancer, and death due to any cause.

7.7 Overall and Breast Cancer Specific Survival

Overall survival will be measured from the date of randomization until the date of death from any cause. Women not known to be dead at the time of analysis will be censored at the date of last follow-up.

Breast cancer specific survival will be measured from the date of randomization until the date of death from breast cancer. Women who die from other documented causes (i.e. cause is not breast cancer) will be censored at the time of death. Women who died without a specified cause will be considered to have died of breast cancer. All women not known to be dead at the time of analysis will be censored at date of last follow-up.

8 Adverse Event Reporting

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Toxicities/adverse events must be described and graded using the terminology and grading categories defined in the most current version of the NCI's Common Toxicity Criteria (CTCAE) version 4.0. The CTCAE is available at [redacted]Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

8.1 Routine Adverse Event Reporting

All expected or unexpected adverse events, regardless of grade or treatment attribution, must be recorded on AE case report forms (CRFs) at the first postoperative visit.

8.2 Expedited Adverse Event Reporting

This is not a drug/biologics study. No expedited reporting of adverse events is required.

8.3 Expected Adverse Events

8.3.1 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 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).

8.3.2 IV Needle Placement

- Hemorrhage (hematoma at the injection site);
- Phlebitis;
- Bleeding;
- Infection;
- Bruising;
- Minor discomfort.

8.3.3 Gadolinium

- Headache;
- Nausea;
- Vomiting;
- Hives;
- Temporary low blood pressure;
- Allergic-type reaction;
- *Rare, but Serious:* Kidney impairment, details follow.

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/1.73m2) 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: [redacted]

8.3.4 Surgery

Pain, edema in breast or arm, numbness at incision site and in arm, scarring and/or indentation in the area of the incision, bleeding/hematoma/seroma, wound infection, symptoms from injury to the brachial plexus, increased susceptibility to infection.

9 Data Considerations

All CRFs are available on the study-specific page of the CTSU web site at [redacted]

Quality of Life questionnaire booklets will need to be ordered prior to enrollment of patients. Patient completed questionnaires and booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the CTSU A021202 Web Page) and faxing to the CTSU Data Operation Center. Samples of questionnaires found in Appendix VI of the protocol document are for re for reference and IRB submission only. They are not to be used for patient completion.

9.1 Case Report Form Completion and Submission

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account; and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to [redacted] for registration types and documentation required.

  O To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type;

  O To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR; and

  O To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

If the study has a Delegation of Tasks Log (DTL), individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (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 staff must log in to the Select Login [redacted] using their CTEP-IAM username and password, and click on the accept link in the upper right-corner of the iMedidata page. Site staff 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. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

Site staff 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 in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at

[redacted] or by contacting the CTSU Help Desk at [redacted]

Common Terminology Criteria for Adverse Events: This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for toxicity and adverse event reporting.

On-Study Initial Surgical Operative and Pathology Reports and Final Surgical Operative and Pathology Reports (if re-operable), and Radiation Therapy Summary Reports are to be submitted by uploading into RAVE, per the Schedule of Forms.

9.2 Patient Data Quality Control

All data received will be subjected to validation and quality-control measures. Issues arising from inaccurate, discrepant or incomplete data will be communicated to participating sites on a regular basis. Any data submitted on case report forms is subject to audit against the patient's source documents. Consistent failure to complete and submit data in a timely fashion may subject a participating site to sanction up to and including the suspension of participation in the study.

9.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

10 Statistical Considerations

10.1 Endpoints

The primary endpoint is local-regional recurrence in the ipsilateral breast following breast conserving surgery. Local-regional recurrence (LRR) is defined as ipsilateral DCIS or invasive breast tumor recurrence in the preserved breast or invasive cancer in the chest wall and skin recurrence following mastectomy, and/or invasive breast cancer in the axilla or regional lymph nodes.

Secondary endpoints include

- Re-operation rate following attempted breast conserving therapy will be computed for each arm. For women randomized to the no pre-operative breast MRI arm, this rate will be computed as the number of women who had a re-operation (including mastectomy) divided by the total number of women randomized to this arm. For women randomized to the pre-operative breast MRI arm, this rate will be computed as the number of women for whom BCT was indicated by MRI who had a re-operation (including mastectomy) divided by the number of women for whom BCT was indicated by MRI. Note that for the MRI arm, women who underwent mastectomy as the result of MRI findings will not be included in the denominator (or numerator).

- The conversion rate to mastectomy secondary to persistent positive margins or poor cosmesis within the first 6 months of attempting BCS (prior to administration of RT). The denominator will be all women for which BCT was attempted and the numerator is the number of women who underwent a subsequent mastectomy within six months of the initial surgery for whatever reason (e.g. persistent positive margins, poor cosmesis result). Note that for the MRI arm, women who underwent mastectomy as the result of MRI findings will not be included in the denominator (or numerator).
- Time to contralateral breast cancer will be measured from date of randomization until documentation of contralateral breast cancer. Women who undergo prophylactic contralateral breast mastectomy will not be included in this endpoint.
- Disease-free survival (DFS) will be measured from date of randomization until the first disease event where the disease event is defined as local, regional, or distant breast cancer recurrence, second primary cancer, DCIS or invasive contralateral breast cancer, and death due to any cause. Definitions of events are found in Section 7.
- Overall survival will be measured from the date of randomization until the date of death from any cause. Women not known to be dead at the time of analysis will be censored at the date of last follow-up.
- Breast cancer specific survival will be measured from the date of randomization until the date of death from breast cancer. Women who die from other documented causes (i.e. cause is not breast cancer) will be censored at the time of death. Women who died without a specified cause will be considered to have died of breast cancer. All women not known to be dead at the time of analysis will be censored at date of last follow-up.
- False positive rate for MRI detection of multiple disease foci: For the women randomized to a diagnostic workup including pre-operative breast MRI, the proportion of women with MRI detected multiple foci disease that was not confirmed will be estimated as the number of who underwent MRI and were indicated to have multiple foci of disease that was not histologically confirmed divided by the number of women indicated to have multiple foci of disease by MRI.
- Rate of MRI-guided localization assisted surgery. This will be computed as the number of women who underwent pre-operative MRI assessment and had MRI-guided localization assisted surgery divided by the number of women who were pre-operatively assessed with MRI.

10.2 Study Design

This is a randomized phase III superiority trial. The trial hypotheses are as follows:

Null hypothesis: The 5 year local-regional recurrence rate for women who undergo pre-operative breast MRI will be the same as the local-regional recurrence rate for women who do not undergo pre-operative breast MRI.

Alternative hypothesis: The 5 year local-regional recurrence rate for women who undergo pre-operative breast MRI will be at least 8 percentage points less than the local-regional recurrence rate for women who do not undergo pre-operative breast MRI; this is equivalent to a HR of 0.19.

Given the relatively low rate of 5-year LRR in this patient population, it is felt that in order to justify the additional cost and risk (e.g. additional biopsies, unnecessary mastectomy) associated with pre-operative breast MRI there has to be a substantial reduction in the 5-year LRR rate; this is the rationale for such a large minimum detectable difference.

A 1:1 randomization scheme will be used to assign women to standard pre-operative breast cancer disease assessment without the addition of MRI (control arm/Arm 1) or standard pre-operative breast cancer disease assessment with the use of MRI (MRI arm/Arm 2). All randomized women will be BCT candidates. This study will use a dynamic allocation procedure to allocate the proportionate number of patients to each of the diagnostic work-up approaches. This procedure will balance the marginal distributions of the clinical tumor stage, type of breast cancer (triple negative or HER2+), enrolling institution between the two arms, and neoadjuvant chemotherapy.

The primary endpoint analysis will compare local-regional recurrence (LRR) rates between women randomized to the control arm and women randomized to the MRI arm. All randomized women will be included in the primary endpoint analysis according to the arm to which they were randomized, regardless of what treatment they ultimately received. There are two planned interim analyses that will occur when 50% and 75% of the expected number of events have occurred. Study accrual will not be suspended for the interim analyses.

We will deem that the use of pre-operative breast MRI is superior to the current diagnostic procedures for breast cancer that do not include pre-operative breast MRI if the 5-year LRR associated with using pre-operative breast MRI is found to be at least 0.08 less than the 5 year LRR rate without the use of pre-operative breast MRI.

10.3 Sample Size and Monitoring Plan

10.3.1 Sample Size

Note: The statistical design changed with Update #06. Please see the revised statistical design below.

Original Statistical Design (Prior to Update #06)

The primary aim is to assess whether the use of pre-operative breast MRI as part of breast cancer diagnosis procedures confers lower LRR rates compared to conventional diagnostic procedures (that do not include pre-operative breast MRI). Specifically, this is a superiority trial designed to determine whether the LRR rate for women randomized to Arm 2 (use of pre-operative breast MRI) is lower than the LRR rate for women randomized to Arm 1 (control arm with no pre-operative breast MRI).. The sample size was determined under the following assumptions:

- The 5 year LRR among the women randomized to the diagnostic work-up regimen without MRI is 0.10
- Accrual rate of 20 patients per month for 2.1 years
- A 3 year follow-up period after the close of enrollment
- The distribution of local recurrence times follows an exponential distribution
- Minimum detectable difference of a 0.08 decrease in the 5 year LRR rate in Arm 2 compared to Arm 1 or an HR (comparing MRI arm to no MRI arm) for LRR of 0.19
- Power = 80%
- Level of significance (one-sided) = 0.05

The sample size and interim analyses boundaries are based on a two-sample "survival" (i.e. time-to-event) superiority calculation performed using EAST version 4.0, with a 5-year LRR rate of 0.10 for the control arm and a 0.08 minimum detectable difference (i.e. the 5-year LRR rate for Arm 2 is 0.02 or less under the alternative hypothesis).

A sample size of 244 eligible patients in the control arm (Arm 1) and 244 patients in the MRI arm (Arm 2) who are deemed to be BCT candidates prior to randomization is required given the null and alternative hypotheses and using the parameter values and assumptions listed above. The necessary number of LRR events is 23. Assuming that approximately 10% of patients are ineligible or lost to follow-up, the (maximum) **target accrual for the study is 536 women** (= 488 × 1.1).

The primary reasons for this statistical design amendment are: (1) to correct an error in the stated statistical power in the original design, (2) to amend the statistical design to reflect the more realistic accrual rate we have observed to date, and (3) to revise the futility monitoring rules in the original statistical design which are thought to be too conservative.

Based on the design parameters specified in the original protocol, the study would have had roughly 92% power instead of 80% to detect the targeted hazard ratio (not accounting for futility interim looks). If the assumed accrual rate is 13 patients per month, the trial will need only 335 eligible patients (instead of 488 eligible patients) to achieve the 80% stated power, assuming 2.1 years or accrual, 3 years of additional follow-up and the same targeted hazard ratio. This amendment acknowledges this inconsistency.

In the original study design, the expected accrual rate was 20 patients per month. This study was opened on 02/21/2014. As of March 18, 2016, the study has accrued 96 patients (Arm 1: 48, Arm 2: 48). Accrual to this study has been substantially slower than expected. Based on the accrual history to date, we have observed an average accrual rate (since activation) of 3.65 patients per month. A number of actions have been undertaken by the study team to improve the accrual rate. We have been a gradual uptick in average monthly accrual recently; the average monthly accrual for the first 3 months of 2016 is higher than monthly average for all of 2015 (6 patients vs 4.7 patients per month). Although the accrual rate is slowly trending up, the study team feels that the study is unlikely to attain the original accrual rate of 20 patients per month and that a major study design modification is warranted to more realistically incorporate into the design the empirical accrual rate we have observed to date

Revised Statistical Design (Effective with Update #06)

The primary aim is to assess whether the use of pre-operative breast MRI as part of breast cancer diagnosis procedures confers lower local-regional (LRR) rates compared to conventional diagnostic procedures (that do not include preoperative breast MRI). Specifically, this is a superiority trial designed to determine whether the LRR rate for women randomized to Arm 2 (use of pre-operative breast MRI) is lower than the LRR rate for women randomized to Arm 1 (control arm with no pre-operative breast MRI). The sample size was determined under the following assumptions:

- The distribution of local-regional recurrence times follows an exponential distribution
- The 5 year LRR among the women randomized to the diagnostic work-up regimen without MRI (Arm 1) is 10%
- Minimum detectable difference of a 8% decrease in the 5 year LRR rate in Arm 2 compared to Arm 1; or equivalently, an Hazard Ratio (comparing Arm 2 to Arm 1) for LRR of 0.19
- Accrual rate of 6 patients per month for 4 years
- A 3 year follow-up period after the close of enrollment
- Power = 80%
- Level of significance (one-sided) = 0.05

The sample size justification is based on a two-arm "survival" (i.e. time-to-event) superiority calculation performed using the SWOG Statistical Tools [redacted] with a 5-year LRR rate of 10% for the control arm and a 8% minimum detectable difference (i.e. the 5-year LRR rate for Arm 2 is 2% or lower under the alternative hypothesis).

A sample size of 144 eligible patients in the non-MRI arm (Arm 1) and 144 patients in the MRI arm (Arm 2) who are deemed to be BCT candidates prior to randomization is required given the null and alternative hypotheses and using the parameter values and assumptions listed above. The necessary number of LRR events is 18. Assuming that approximately 10% of patients are ineligible or lost to follow-up, the (maximum) target accrual for the study is 317 women (= 288 × 1.1).

10.3.2 Study Monitoring

Careful monitoring of this trial will occur every 6 months to coincide with the Alliance meetings. Special attention will be given to adverse events, the proportion of women whose MRI indicates they are not candidates for BCT, patient survival, and the pooled LRR rate.

Formal comparisons of LRR will be made when approximately 50% and 75% of the expected number of events have occurred (11 and 17 local recurrences, respectively). These interim analyses will be for futility and will be based on the primary endpoint of LRR. The rationale for performing futility analyses only is that this is a relatively low-risk population and the primary endpoint is LRR rather than survival and effective treatment strategies exist for locally recurrent disease. Interim analyses for futility for the primary endpoint will be conducted after 11 and 17 LRR events have been observed, using an O'Brien-Fleming type stopping boundaries. The Z-scale boundaries are −0.91, 0.70, and 0.41 for the interim analyses after 11 and 17 LRR events and for the final analysis after 23 LRR events, respectively; these correspond to p-values of 0.82, 0.24, and 0.054 and HR values of 2.40, 0.62, and 0.41 to reject superiority (the alternative hypothesis).

10.3.3 Revised Interim Monitoring Rule

Careful monitoring of this trial will occur every 6 months to coincide with the Alliance meetings. Special attention will be given to adverse events, the proportion of women whose MRI indicates they are not candidates for BCT, patient survival, and the pooled LRR rate.

Formal comparisons of LRR will be made when approximately 30% and 60% of the expected number of events have occurred. These interim analyses will be for futility and will be based on the primary endpoint of LRR. The rationale for performing futility analyses only is that this is a relatively low-risk population and the primary endpoint is LRR rather than survival and effective treatment strategies exist for locally recurrent disease. Interim analyses for futility for the primary endpoint will be conducted after 6 (30% information horizon) and 11 (60% information horizon) LRR events have been observed. The futility monitoring will be based on repeated testing of the alternative using the rule proposed by Anderson and High [80]. The Anderson and High monitoring rule is a modified procedure of the standard Fleming, Harrington, and O'Brien (FHOB) test [81] and guarantees that the futility bound for the normalized Z-test crosses zero at 50% of the expected total information (i.e. insisting that the outcome favors the alternative hypothesis when 50% of the expected information was available). This monitoring rule, as compared with the FHOB test which is considered unnecessarily conservative in some settings, is more likely to lead to a recommendation of futility when the null hypothesis is true. Based on the specified design parameters in this trial, the Anderson and High rule calls for repeated testing of the alternative hypothesis against the null at (1-sided) 0.04 significance level. This significance level corresponds to futility bounds (for the Wald test on the regression coefficient; no MRI vs. MRI) of -0.3887 and 0.1753 at 30% and 60% information fractions, respectively.

To evaluate the operating characteristics of the new futility monitoring rule in the context of this trial, we conducted 1,000 Monte-Carlo simulations. Under the null hypothesis (when the use of pre-operative breast MRI does not improve LRR rate compared to no-MRI), the probability of stopping early for futility is 57.5% (36% of the simulated trials stop at the first interim look and 21.5% of the simulated trials stop at the second interim look). Among the trials that stop at the first interim, the median time of trial termination (since study activation) is 2.73 years (range: 1.41-4.57) and the median number of patients enrolled by that time is 196 (range: 99-288). Among the trials that stop at the second interim, the median time of trial termination (since study activation) is 3.8 years (range: 2.38-5.46) and the median number of patients enrolled by that time is 274 (range: 168-288). Under the alternative hypothesis (when the use of pre-operative breast MRI improves LRR rate compared to no-MRI), the probability of stopping early for futility is 1.4%. Based on our simulations, there is only a very negligible power loss as a result of futility monitoring (power loss = 0.4%).

10.4 Study Duration

It is anticipated that 6 patients will be accrued per month. Hence, accrual will be completed in about 4 years from study activation. Final analysis will occur when the total information (i.e. 18 LRR events) has been observed or after all enrolled patients have been followed for at least 4 years, whichever occurs first.

10.5 Analysis Plans

10.5.1 Primary analysis: LRR

The comparison for the primary analysis of LRR is an intent-to-treat analysis. The primary analysis will exclude patients who cancel (withdraw consent) prior to surgery we will tabulate the number (percent) of patients who withdraw prior to surgery and take actions if this percent appears to be greater than 5%. Patients who are randomized but received the opposite pre-operative diagnostic evaluation to which they were randomized will be included in the analysis according to the arm to which they were randomized; it is expected that the rate of patient crossover will be low. A sensitivity analysis using the diagnostic work-up received approach will also be performed. The primary endpoint will be analyzed using a one-sided stratified, log-rank test comparing the LRR events of the two arms. If the p-value of the final analysis is less than 0.05 using pre-operative breast MRI (Arm 2) will be declared superior to not using pre-operative breast MRI (Arm 1).

Time-to-event Approach

The primary endpoint is local-regional recurrence; LRR time will not be censored at the documentation of regional/distant recurrence.

A logrank test and stratified Cox model will be used to compare the distribution of LRR times with respect to diagnostic work-up approach. The Cox model stratification will account for the trial stratification factors (tumor stage, enrolling institution, neoadjuvant vs. adjuvant chemotherapy, menopausal status).

Cox modeling with will be used to examine the strength of association between LRR and such additional potential prognostic factors as age, chemotherapy, radiation therapy, number of positive lymph nodes, Nottingham grade, post-menopausal status, and Ki-67 expression.

Competing Risks Approach

As recurrence at other locations or death without a local-regional recurrence may be competing risks, the cumulative incidence for local-regional recurrence will be estimated in the competing risk framework as described by Marubini and Valsecchi (Analysing Survival Data from Clinical Trials and Observation Studies, John Wiley & Soons, 1995).

Gray's test will be used to explore whether the cumulative incidence of local-regional recurrence differs with respect to such factors as type of work-up, age, tumor stage, menopausal status, chemotherapy, radiation therapy, ER, PR, number of positive lymph nodes, HER-2/neu expression, Nottingham grade, and Ki-67 expression.

10.5.2 Re-operation rate

Women included in this analysis are all women randomized to the control arm and women randomized to the MRI arm for which MRI indicated they were a candidate for BCT. The re-operation rates will be compared between the two groups using a chi-square test if appropriate. If the expected cell sizes are too small, the rates will be compared with a Fisher's exact test.

10.5.3 Local recurrence rates

The comparison of local recurrence (LR) rates will be between women randomized to the control arm and women randomized to the MRI arm for which MRI indicated they were candidates for BCT. Women who were randomized to the MRI arm for which MRI indicated that they are not a candidate for BCT are not included in the LR analysis. This analysis will be done using a stratified logrank test and a stratified Cox regression comparing the time-to-event (LR) between arms.

10.5.4 Mastectomy conversion rate

Women included in this analysis are all women randomized to the control arm and women randomized to the MRI arm for which MRI indicated they were a candidate for BCT. The conversion rates from BCT to mastectomy will be compared between the two arms using a chi-square test if appropriate. If the expected cell sizes are two small, the rates will be compared with a Fisher's exact test.

10.5.5 Contralateral breast cancer rate

Women included in this analysis are all randomized women who did not undergo a prophylactic contralateral breast mastectomy. Two different rates will be compared. The first will be the rate of (confirmed) contralateral breast cancers detected at the time of the ipsilateral breast cancer. For each arm this will be computed as the number of women with a histologically confirmed contralateral breast cancer at the time of diagnosis of the ipsilateral breast cancer (i.e. within 4 weeks) divided by the number of women randomized to the arm. The two rates will be compared between arms using a chi-square test if appropriate. If the expected cell sizes are too small, the rates will be compared with a Fisher's exact test. The second analysis will be a time-to-event analysis. This analysis will include all women who did not have a contralateral breast cancer diagnosed within 4 weeks of entry into the trial. The contralateral breast cancer rates will be compared between the two groups using a log-rank test and stratified Cox regression model.

10.5.6 Disease-free survival

The disease-free analysis will be based on the first occurrence of a disease-event: local recurrence, regional recurrence, distant recurrence, second primary cancer (including contralateral breast cancer), and death. The analysis will be done on an intent-to-treat basis and will include all patients that were randomized. Disease-free survival experiences between the arms will be compared with using a log-rank test and stratified Cox regression model.

10.5.7 Survival analyses

The overall survival and breast cancer specific survival analyses will be done on an intent-to-treat basis and will include all patients that were randomized. Overall survival and breast cancer specific survival experiences between the arms will be compared with using a log-rank test and stratified Cox regression model.

10.5.8 False-positive multiple foci of disease detection rate

Women included in this analysis are all women randomized to the MRI arm who underwent a pre-operative MRI assessment, which indicated they had multiple foci of disease. A binomial point estimate and exact binomial 95% confidence interval will be used to estimate the false-positive rate for the detection of multiple foci of breast cancer disease by MRI.

10.5.9 MRI-guided localization assisted surgery rate

Women included in this analysis are all women randomized to the MRI arm who underwent a pre-operative MRI assessment. A binomial point estimate and exact binomial 95% confidence interval will be used to estimate the proportion of women in this group who had MRI-guided localization assisted surgery.

10.5.10 Rate of multi-centric disease

We will calculate the rate of occurrence of multi-centric disease in the MRI arm. Additionally, a bionomial point estimate and exact bionomial 95% confidence interval will be used to estimate the proportion of multi-centric disease in the MRI arm.

10.5.11 Accuracy of index lesion characteristics and other factors

We will evaluate the accuracy of each index lesion characteristic and other factors in predicting multi-centricity in the cohort randomized to breast MRI. Index lesion characteristics include lesion size, tumor type, and shape. Other factors include chest wall involvement and skin involvement. The relationship between each characteristic and multi-centricity (Yes or No) will be examined by conducting chi-square tests. The ROC curves and their area under the ROC curve (AUC) will be calculated for continuous and ordinal measures, and sensitivities and specificities will be estimated for binary measures.

10.5.12 Positive predictive values (PPV) of MRI in detecting ipsilateral multi-centric and contralateral diseases

MRI results are based on BI-RADS scores. We will estimate the probability of having multi-centric and contralateral disease in women with breast cancer undergoing preoperative breast MRI, given that the patients were assigned to BI-RADS categories 4 or 5.

11 Regulatory Considerations

11.1 Registering Physician

The registering physician must be a member in good standing of a cooperative group.

All enrolling investigators must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to the Pharmaceutical Management Branch.

11.2 Registering Institution

Patients must be enrolled at clinical sites that have a valid assurance number from the United States Office for Human Research Protections (OHRP). Most institutions have a Multiple Project Assurance (MPA), Cooperative Project Assurance (CPA) number or Federalwide Assurance (FWA). If the clinical site does not have such an assurance, the clinical site must apply and obtain an assurance before patients can be enrolled to this study.

Unaffiliated Investigator Agreements (UIAs) are needed from investigators who independently accrue patients on ambulatory protocols outside an institution (e.g., in private practice) but who rely on an institution's IRB for review of protocols.

11.3 Submission of IRB Approval

Documentation of IRB approval must be submitted to CTSU for entry into the Regulatory Support System (RSS) before patient registration will be allowed. Submission instructions and coversheets are available at [redacted]

11.4 Inclusion of Women and Minorities

This study will be available to all eligible female patients, regardless of race or ethnic origin. There is no information currently available regarding differential effects of this protocol in subsets defined by race or ethnicity; and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in accuracy based on racial groupings, the sample size is not increased in order to provide additional power for such subset analyses.

Men are excluded from this study because the number of men with breast cancer is insufficient to provide a statistical basis for assessment of effects in this subpopulation of people with breast cancer.

Race and Ethnicity Table

Racial Categories	**Ethnic Categories**				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	2	0	0	0	2
Asian	7	0	0	0	7
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	34	0	6	0	40
White	223	0	41	0	264
More Than One Race	3	0	0	0	3
Total	270	0	47	0	317

11.5 Clinical Site Audits

All clinical sites at which patients are enrolled are subject to an audit in accordance with guidelines provided by and available from the Clinical Trials Monitoring Branch (CTMB) of the NCI. Information on these regulations may be obtained from the CTMB web site at [redacted]

11.6 Clinical Monitoring

This study will be monitored by the current version of the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

11.7 Data Safety and Monitoring

The Alliance Data and Safety Monitoring Board will review the data available from the trial at each of its biannual meetings. This will include accrual data, adverse events, and results of interim analyses when available. In determining whether the trial should be continued, the DSMB will consider the results of each interim analysis, as described above. The DSMB will also consider the evidence regarding safety, i.e. adverse events and the feasibility of completing the trial, i.e. the accrual rate. Weighing the adverse events and the feasibility of study completion is complex and therefore no particular cut-offs of these measurements are provided in advance. The DSMB will use its discretion in weighing these measurements.

12 Biospecimen Collection

All participating institutions must ask patients for their consent to provide specimens for correlative studies, although patient participation is optional.
All specimens will be stored and governed by the Alliance Biorepository at Washington University (WUSTL).

12.1 Specimen Collection and Processing

Specimen registration and tracking

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: [redacted] using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted] For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted]

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

12.2 Required Specimens

12.2.1 Summary of Biospecimen Types

Time Point	Material	Quantity	Shipping
Prior to surgery	Whole blood	1, 10 ml K-EDTA tube	Invert thoroughly to prevent coagulation. Ship immediately to ALLIANCE WUSTL
Post-surgery	Paraffin Block / Slides	Representative malignant	Ship to ALLIANCE WUSTL
Pre-chemotherapy Core Biopsy (For patient undergoing preoperative chemotherapy)	Paraffin Block/Slides	Representative malignant	Ship to ALLIANCE WUSTL
Recurrence	Paraffin Block/Slides	Representative locoreginal recurrent or distant recurrence	Ship to ALLIANCE WUSTL

12.2.2 Whole Blood

One 10 mL KEDTA (lavender top) tube of whole blood should be collected by standard venipuncture. The tube should be inverted thoroughly for 30 sec. to prevent coagulation. The tube should be labeled with that patient's Alliance ID number and the date and time of collection. Whole blood should be maintained at room temperature and shipped to the ALLIANCE WUSTL within 24 hours of the time of collection. Once received by the Alliance WUSTL, whole blood will be spun and the peripheral blood nucleated cell layer (buffy coat) isolated, aliquoted, and snap frozen. Frozen peripheral blood nucleated cells will be used for subsequent genomic DNA isolation.

Blood Specimens for Correlative Science Studies

Patients will have peripheral whole blood specimens collected by routine venipuncture at the following time points:

- **Baseline (After randomization and prior surgery)**
  One, 10 mL lavender top (K-EDTA) tube. This tube of whole blood will be sent to the Alliance WUSTL for genomic DNA isolation.

12.2.3 Formalin Fixed Paraffin Embedded Tissue

FFPE tissue should be sent to the Alliance Biorepository at Washington University. If blocks cannot be released **fifteen** (15) unstained sections of a representative primary tumor block from the surgical specimen. **One** H/E stained slide of a representative section should be also sent. For patients who have a locoregional recurrence or distant metastasis, block or sections of the recurrence will also be collected.

Fixed Tissue Specimens for Correlative Science Studies

The following materials, derived from formalin fixed, paraffin embedded diagnostic pathology tissue blocks, are required for correlative studies:

1. One block or fifteen (15) unstained sections, cut at 5-6 micron thickness, of a representative primary tumor block from the surgical specimen
2. One H/E stained slide of a representative tumor section
3. One block or fifteen (15) unstained sections, cut at 5-6 micron thickness, of a block from locoregional recurrence or distant recurrence
4. One H/E stained slide of a representative section from locoregional recurrence or distant metastasis

The de-identified surgical pathology report, coded with the Alliance patient ID number, and BioMS shipping manifest must accompany all tissue sample submissions.

12.3 Specimen Shipping

All samples should be labeled with institutional surgical pathology number (tumor samples), study number, patient ID number patient initials, sample collection date and time and be accompanied by the completed specimen submission forms which is generated by BioMS.

Note for CRA – The following PHI must be removed or blacked out for all specimens or reports: signature, name, date of birth, other identifying information, except initials and study identification number.

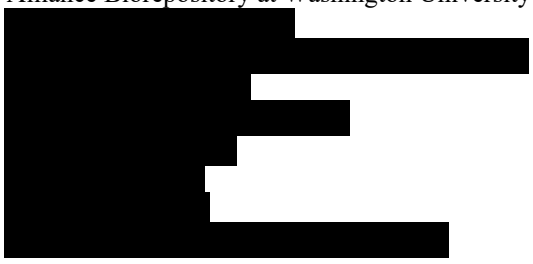
All samples should be shipped to the Alliance-WUSTL.

Specimens may be sent to the Alliance Biorepository at Washington University on Monday through Thursday for next day delivery. **The Bank cannot receive specimens on Saturdays, Sundays or holidays. Do not send specimens on Friday or the day before a holiday.**

The institution is expected to pay the cost of mailing specimens and will be reimbursed through capitation fees set for each individual study.

Arrange for Federal Express pick-up through your usual institutional procedure. Ship specimens to the address below:

Alliance Biorepository at Washington University (WUSTL)



On the day that specimens are sent to the biorepository, please contact the bank by phone, fax, or e-mail to notify what is being sent and when the shipment is expected to arrive.

13 Correlative Science Studies

13.1 Impact of Pre-operative MRI on Patient-Reported Quality of Life Parameters

13.1.1 Study Design

Quality of life (QOL) instruments will be administered to patients on both arms of the study. Research staff will be required to request that patients answer all questions at the appointed time. Completed questionnaires will be collected by research staff and entered into the Alliance database.

Consenting patients will complete questionnaires at the following time points:

Arm 1:

- At enrollment, prior to randomization
- At first post op visit
- At last post op visit (for women undergoing re-operation)
- At 8 months (+/- 30 days) post-registration
- At 12 months (+/- 30 days) post-registration

Arm 2:

- At enrollment, prior to randomization
- After the MRI exam
- At first post-op visit
- At last post-op visit (for women undergoing re-operation)
- At 8 months (+/- 30 days) post-registration
- At 12 months (+/- 30 days) post-registration

The following QOL instruments will be administered:

PROMIS 10: The Patient Reported Outcomes Measurement Information System (PROMIS 10) is a 10 item questionnaire that addresses physical and mental health. It is a relatively new QOL measure developed by the National Institutes of Health PROMIS Network. In addition, the PROMIS 10 has been shown to predict EQ-5D preference scores and thus can estimate quality adjusted life years (QALY). [31-33]

Assessment of Survivor Concerns (ASC): The ASC is a six item instrument specific to fear of cancer recurrence and fear of health issues in general. It is designed to serve as an adjunct to other QOL instruments. This instrument is valid in both short term and long term survivor populations.[34]

Subset of the FACT-G: The Functional Assessment of Cancer Therapy-General (FACT-G) is a 27-item measure of health-related quality of life originally developed for cancer patients and comprises four subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being. An algorithm has been developed to convert FACT-G responses to time trade-off based health utilities that uses 4 items from the FACT-G.[35] These 4 items (I have a lack of energy, I feel sick, I am able to work, I am able to enjoy life) will be administered in this study.

Patients will complete the 19 item questionnaire at the time points described above. The questionnaires can be completed on paper. The PROMIS 10 will measure overall general physical and mental health and will capture data that can be mapped to QALY. It is a short questionnaire that addresses many of the concerns that newly diagnosed breast cancer patients face early in their treatment which will fit our patient population in this study. The subset of 4 FACT-G questions will allow for calculation of time trade-off based utilities. The ASC will measure fears and anxiety in cancer specific population and is designed to serve as an adjunct to other QOL instruments. The ASC will capture elements of a patient's QOL that apply to newly diagnosed cancer patients like those in this study unlike other QOL instruments which are targeted more at patients undergoing certain chemotherapy or hormonal treatments and focus on treatment effects. Although the majority of these patients will undergo adjuvant chemotherapy, the primary aim of this corollary study is to determine the impact of MRI on patient's anxiety and stress prior to receiving any adjuvant treatment.

13.1.2 Hypotheses

Data on MRI's effect on newly diagnosed breast cancer patient's QOL is limited. There has been one randomized study of preoperative breast MRI in newly diagnosed breast cancer patients that was conducted in the United Kingdom, the COMICE trial.[36] In this trial 1623 women with biopsy proven breast cancer were randomized to receive either MRI or no further imaging and the primary endpoint was the proportion of patients undergoing repeat operation or avoidable mastectomy. The trial used the FACT-B QOL instrument and overall found no difference between the two arms of the study. Additionally, they used the EQ-5D to evaluate health related QOL and found that the MRI group incurred more costs then the no MRI group but this finding was not statistically significant. There was a study published in the New England Journal of Medicine in 2007[37] looking at contralateral breast cancers in women with newly diagnosed breast cancer who were undergoing preoperative MRI. MRI detected 3.1% additional contralateral cancers but there was no QOL assessment in this study. Previous studies have looked at the cost effectiveness of MRI for the high risk population, but [38]. To determine the comparative effectiveness of preoperative MRI, QOL assessment is necessary, preferably utilizing a QOL instrument that will map to quality adjusted life years (QALY) to determine cost effectiveness as well. We hypothesize that patients undergoing preoperative MRI will experience more anxiety and decreased quality of life initially after the MRI but that these effects will dissipate at one year after surgery.

The specific aims of this correlative study are:

1. To compare the impact of preoperative breast MRI on patient reported QOL parameters.
2. To explore the impact that preoperative MRI has on patient QOL.
3. To compare the QALY in patients who have undergoing preoperative breast MRI versus those not undergoing preoperative breast MRI.
4. To contribute to a bank of normative data of QOL outcomes in cancer patients.

The QOL team is well positioned to conduct these studies as they have pioneered the use of responder-type investigation and have experience in QOL studies in other surgical randomized trials.

13.1.3 Statistical Design

The primary endpoint for this correlative study will be the impact of preoperative MRI on patient's quality of life. The comparative effectiveness of preoperative MRI will likely be a function of the impact of MRI on the patient's physical and emotional health.

The trial expects to enroll approximately 20 patients per month with a total expected accrual of 488 eligible patients (maximum accrual of 536 patients including planned over-accrual) over a 2.1-year period. We expect approximately 80% compliance with the QOL questionnaires which will put us at approximately 16 patients per month completing the QOL questionnaires with a total of 390 eligible patients.

Prior to conducting any analyses, questionnaire compliance will be evaluated. Patterns of missing data across the time points will be summarized. Questionnaires will be scored according to developers' instructions. The completeness of the questionnaire data will be described by calculating the number of forms actually completed. A questionnaire will be considered completed if enough questions were answered to obtain a valid total score. If at least one question was answered, a questionnaire will be considered "attempted." The baseline characteristics of patients with and without complete QOL data will be compared using chi-square statistics, t-tests, and analysis of variance.

Mean scores and standard deviations for the PROMIS 10 and ASC scores will be calculated for each assessment. As the primary analysis, two-sample t-tests will be used to evaluate differences between arms at each assessment. We will also implement mixed effects models for repeated measures to evaluate the PROMIS 10 and ASC scores longitudinally.[39] Mixed effects models describe the rate of change in scores over time for each treatment arm (fixed effect), taking into account the between-patient variability by incorporating each patient's individual starting point and individual rate of change (random effect) into the model. The PROMIS 10 and ASC scores will be the dependent variables in these models. Independent variables will include time, study arm, baseline stratification factors, and the interaction between time and study arm. An unstructured correlation matrix will be used to model the correlation between repeated observations. If indicated by the evaluation of the missing data, we will also fit pattern-mixture models for analysis of longitudinal data in the presence nonignorable missing data.[41]

Change from baseline will be calculated at each assessment for the PROMIS 10 and ASC scores. Patients will be classified as improved, worsened or unchanged based on these scores. T-test analysis will be used to compare these response classifications between study arms at each assessment.

For calculation of quality-adjusted life years (QALY), EQ-5D health utility scores will be calculated from the PROMIS 10 as described in Revicki et al. We will then use these utility scores in a quality-adjusted survival analysis to estimate the QALY in each arm.[42]

Assuming a total of 390 eligible patients (approximately 195 patients on each arm) with follow-up data and a two-sided alpha of 0.05, this study will have 80% power to detect effect sizes (mean difference between arms / standard deviation) of 0.30 or greater. Studies suggest that effect sizes 0.30 indicate a small effect.[43] Others have found that effect sizes in the range of 0.30 to 0.50 generally correspond to the minimally important difference for questionnaire scores.[44,45] This study has over 99% power to detect an effect size of 0.50.

13.2 Medical care costs and cost-effectiveness associated with preoperative breast MRI prior to surgical therapy

13.2.1 Correlative study design and data collection:

All women in both arms of the study will have information collected at initial enrollment, post op visits, and at all follow-up visits regarding: 1) whether an initial breast MRI was performed; 2) whether subsequent ipsilateral and/or contralateral breast imaging and biopsies (percutaneous or surgical) and additional second-opinion consultations were performed as a result of the MRI findings; 3) what breast and axillary surgery/surgeries (including breast reconstructive surgeries) and adjuvant therapies (radiation, chemotherapy, targeted therapy) were performed/administered; 4) what follow-up clinic visits with breast cancer providers (surgeon, medical oncologist, radiation oncologist, plastic surgeon) were performed since last assessment; 5) what ipsilateral and contralateral breast imaging studies (mammogram, ultrasound, MRI) and biopsies were performed since last assessment; 6) if there were any subsequent associated diagnoses (LR, new ipsilateral or contralateral cancer) and treatments that were performed since last assessment. This information will be collected on the data forms and will serve as the basis to estimate medical costs for each arm.

The effectiveness measures for the cost-effectiveness analysis will include life year (LY) and quality-adjusted life year (QALY). Information on life year will be obtained directly from the survival information collected in the trial. Information on quality-adjusted life year (QALY) for each study participant will be obtained from the quality-of-life (QoL) correlative study. Investigators in the QoL correlative will derive EQ-5D scores from PROMIS 10 using an established algorithm to map to a QoL instrument to health utilities. We will calculate QALY for each patient by combining health utilities associated with various health states and survival.

13.2.2 Hypotheses

The literature to date on the cost-effectiveness of breast MRI has focused on screening high-risk women for breast cancer using breast MRI alone, mammogram alone, or the combination of both imaging modalities.[36, 46-49] Four of these studies were performed using decision modeling and show that, when compared to mammogram alone, breast MRI alone or in combination with mammogram studies are not always cost-effective but are more likely to be cost-effective among a subset of high-risk women, especially in the younger BRCA mutation carriers.[38,46-48]

No cost or cost-effectiveness studies have been performed addressing the use of preoperative breast MRI for women undergoing BCT for breast cancer with respect to LRR rates, number of additional surgeries performed to achieve negative margins, and QALYs. This will be the first study of its kind. This study will test the hypothesis that although preoperative breast MRI is expensive, these costs will be offset, in the short term, by reducing the number of operative interventions required to achieve margin negative BCT and, in the long term, by reduction in LR events. Even if cost-savings is not achieved, we hypothesize that preoperative breast MRI may still be cost-effective as a result of higher QALYs associated with better clinical benefit or quality-of-life. If breast MRI proves to be cost-effective in this particular population -- women with the highest risk of LRR after BCT, our study will pave the way for future analyses exploring the cost-effectiveness of preoperative breast MRI among the more general population of women with breast cancer.

13.2.3 Statistical Design

Cost Analysis

Clinical events gathered from the data collection form provide information on resource utilization over time. Denote Q_i is the count of resource *i* (e.g., MRI, office visits) and P_i is the unit cost for the health care resource, costs will be calculated as: $P_1 \times Q_1 + P_2 \times Q_2 + \ldots + P_N \times Q_N$. Each item of resource utilization will be identified from DRG, ICD-9 diagnosis/procedure code or CPT codes. The "unit cost" or price associated with each type of clinic visits, imaging studies, surgeries and other procedures will be obtained using information from published sources. The unit cost information obtained from published sources will provide information on the ranges of unit cost for a specific item of resource. For example, inpatient costs for a specific admission diagnosis or ICD-9 procedure will be retrieved from the HCUPnet [redacted] an on-line query system based on data from the AHRQ's Healthcare Cost and Utilization Project. Outpatient costs will be based on Medicare's resource-based relative value scales (RBRVS) fee schedule. Using DRG 582 (mastectomy for malignancy) from the HCUPnet, we can obtain the ranges of hospital costs for mastectomy across various regions of the country, ranging from $8813 in the South to $11564 in the West. These values will reflect costs, not charges, because the HCUP data have applied the cost-to-charge ratios to convert charges to costs. Thus, researchers can retrieve both costs and charges information from the HCUP.net. Similar range for a CPT code can be found in Medicare fee schedule [redacted] from adjustments across geographic regions. These form the range of unit cost values for each item of resource. For each patient, we will match patients' geographic region with unit costs reported for that region from the published sources to obtain unit costs most relevant to the patient. Once we obtain information on the "counts" of each resource item from the trial, we will combine the unit cost value with counts to calculate the cost associated with a specific resource item. We then aggregate all resource items to obtain the cost for that patient. That is, all costs of breast cancer care will be tallied for each participant. For indirect costs, we will identify clinical events that are likely to be associated with work loss (e.g., hospitalization, office visits) and multiply the days of these events with the average wage rate for women who share similar sociodemographic characteristics (in terms of age, race, and geographic region) with the patient.

Differential mean costs will be compared between the two groups (without preoperative MRI vs. with preoperative MRI). To examine whether patients randomized to the two groups (with vs. without preoperative MRI) have different costs after controlling for confounding factors, we will rely on multivariate statistical models. In addition to the main impact variable —the binary indicators for the "treatment group" (i.e., with preoperative MRI) — all analyses will control for patient and hospital characteristics that might differ by chance among patients in the two randomization groups. Because cost estimations are generally highly skewed, we will model all of our cost equations using the method of extended estimation equation (EEE).[50] Contrary to the traditional approach of applying least squares to log-transformed data, the EEE method is a recently developed econometric method that specifies a highly flexible mean model to accommodate data of various functional forms, including highly skewed cost data.

Cost-Effectiveness Analysis

We will then conduct cost-effectiveness analysis using cost information obtained above and QALY provided by the QoL correlative team. Other effectiveness measures will include the additional number of surgeries to achieve margin control and the number of LRR events avoided.

Using individual-level costs and effectiveness data, we will estimate the overall mean costs and effectiveness for each group. We can then compute the incremental cost-effectiveness ratio, calculated as the differential mean costs of one treatment approach versus the other divided by the differential mean effectiveness [mean(Cost_MRI) – mean(Cost_NoMRI)] / [mean(QALY_MRI) – mean(QALY_NoMRI)]. We will employ nonparametric bootstrapping method to address statistical uncertainty for cost-effectiveness analyses that include data on both costs and quality-adjusted life year. This approach is commonly used in cost-effectiveness analysis using patient-level data.[51] We will use the percentile method to report the 95% confidence interval of the ICER based on results from the bootstrap analysis. In addition, we will also conduct Bayesian cost-effectiveness analysis to obtain the cost-effectiveness acceptability curve,[52] which will inform decision makers of the probability that the MRI strategy is more cost-effective than the non-MRI strategy corresponding to a certain level of willingness to pay.

To account for covariate effects in cost-effectiveness analysis, we will then expand the above structure to the net-benefit regression framework.[53] Net benefit for each person will be calculated as $NB(\lambda) = \lambda \bullet \Delta E - \Delta C$, where λ represents a societal willingness-to-pay, ΔC represents the incremental costs; and ΔE represents the

incremental effectiveness. Then individual-level net benefit will be regressed on covariates, plus the binary variable indicating treatment. Using the "no preoperative" arm as the reference group, the regression coefficients associated with the treatment binary variable will provide information on the cost-effectiveness of preoperative MRI compared to no MRI. A Bayesian version of net-benefit regression model will also be applied to better address uncertainties and allow periodic update of information.[54] In addition to the main analysis, where sample size permits, separate analyses will also be conducted for the subgroup of triple-negative and HER-2/neu-positive participants. The rationale for this approach is that it may reveal differing patterns of results across cancer characteristics that would be masked in an analysis that combined data on all patients.

Sample Size

Gardiner et al. (2000) demonstrated that for a clinical trial to be sufficiently powered for cost-effectiveness analyses, the sample size would need to be many times greater than that based on effectiveness alone.[55] Because cost-effectiveness analysis is often not the primary endpoint of clinical trials, the sample size very rarely is powered for cost-effectiveness analyses both due to budgetary and human subject protection concerns. The design of our trial followed the conventional approach and determined the sample size based on rate of local-regional recurrence at 5 years, the primary endpoint of our study. The sample size was determined to be 256 for each arm (MRI vs. non-MRI pre-operatively).

We assessed whether the above sample size provided sufficient power for cost-effectiveness analysis. Our power calculation for cost-effectiveness analyses was based on information from a number of sources, including the hypothesized rate of local-regional recurrence used in the original sample size calculation (i.e., 10% for the non-MRI group and 2% for the MRI group), the cost of breast cancer at various treatment stages obtained from the literature,[56] and the 58% 5-year survival among breast cancer patients after treatment for a local –regional recurrence.[57]

We first converted the incremental cost-effectiveness ratio to net health benefit, calculated as $NHB(\lambda) = \Delta E - \Delta C/\lambda$, where λ is the societal willingness to pay for one additional life year gained, ΔE is the incremental effectiveness (i.e., difference in mean effectiveness between the MRI and non-MRI group), and ΔC is the incremental costs. Following Willan (2001),[58] the power calculation for cost-effectiveness analysis would test the null hypothesis of $NHB(\lambda) \leq 0$ against the alternative hypothesis of $NHB(\lambda) > 0$. The calculation would require information on ΔE, ΔC, the standard deviation for E and C for each arm, as well as the correlation between ΔE and ΔC. Using the above information, the estimated difference in 5-year life expectancy between the MRI and non-MRI arm was 4.70 and 4.63, respectively. We then performed simulations to obtain estimates of standard deviation for the effectiveness of each arm (SD_MRI=0.007 and SD_NoMRI=0.016). Using cost of breast cancer reported in the literature, the estimated 5-year cost for women with triple negative breast cancer was around $40,000. For patients who have HER-2 amplified breast cancers, costs will be higher during the first year of treatment due to receipt of trastuzumab; however, these costs would be incurred in both the MRI and no-MRI arms of the study and would be cancelled out in the calculation of incremental cost, ΔC.

The literature does not provide information on the standard deviation of costs; therefore, we based our power calculation on two scenarios of cost distribution: (a) SD = mean = $40,000, and (b) SD = 1.5 x mean = $60,000. The standard deviations used in these scenarios were because medical costs tend to be highly skewed. The table below summarizes the power associated with 10%, 15% and 20% reduction in costs for each of the above scenarios at different values of societal willingness to pay (WTP):

	10% reduction in costs		15% reduction in costs		20% reduction in costs	
Societal WTP (λ)	SD=M	SD=1.5M	SD=M	SD=1.5M	SD=M	SD=1.5M
λ=50,000	0.564	0.2926	0.7663	0.433	0.9019	0.5825
λ=75,000	0.744	0.4145	0.889	0.564	0.963	0.7048
λ=100,000	0.8749	0.5453	0.9568	0.6882	0.9887	0.8073
λ=125,000	0.9439	0.6713	0.9864	0.794	0.9972	0.8844
λ=150,000	0.9837	0.7802	0.9966	0.8749	0.9995	0.9366

As shown, whether the planned sample size (N=256 for each arm) was adequately powered (> 0.8) for cost-effectiveness would depend on the magnitude of cost reduction, the distribution of costs, as well as the societal WTP.

13.3 Prospective assessment of clinical-pathologic and molecular predictors of ipsilateral breast cancer recurrence-free survival, recurrence-free survival and distant recurrence-free survival

13.3.1 Rationale and Significance:

Breast-conserving surgery is now the preferred surgical approach to breast cancer. However, 4-15% of patients who undergo breast conservation have local recurrence (LR). More recently it has become clear that local control matters; 1 of 4 local recurrences translate into a breast-cancer specific death.[59] Although several clinical-pathologic factors have been linked to a higher risk of local recurrence, most of these factors are not considered a contraindication to breast-conserving surgery. Although recently a predictive tool based on clinical-pathologic variables has been reported,[60] it has not been prospectively validated.

With the evolution of molecular oncology many novel tools have been developed to assist systemic therapy planning. To date little work has been done to identify markers of risk for local relapse and to incorporate these into clinical practice.

Although previous work has been done to evaluate molecular predictors of local recurrence in breast cancer, none have led to a marker or marker set hat has been incorporated into practice. It is now, commonly accepted that tumor subtype predicts local recurrence risk and that patients with hormone receptor positive disease have a lower risk of recurrence compared to patients TNBC and HER2+ cancer.[27] Our trial is focused on TNBC and HER2+ subtypes, thus we have an opportunity for prospective biomarker analysis in this higher risk cohort.

The NSABP analyzed the Oncotype-DX recurrence score assay and its ability to quantify the risk of LR in patients with node negative, HR positive breast cancer from two NSABP trials, B14 and B20.[61] Eight-hundred and ninety-five patients were treated with tamoxifen, 355 treated with placebo only and, 424 were treated with chemotherapy and tamoxifen. Patients were treated with mastectomy alone or breast conservation therapy with radiation therapy. The Oncotype-DX recurrence score was significantly associated with local recurrence for all subsets of patients. Tumor size and grade did not have a statistically significant interaction. The association between recurrence score and LR rates was independent of age in mastectomy treated patients but in patients treated with breast conservation the relationship was not straight forward. This assay has only been researched in the estrogen positive patient population which limits the clinical utility for patients in the Z1101 trial.

A few previous studies have focused on identifying molecular predictors of LR rates in tumors unselected by subtype. Cheng et al. analyzed 94 patients treated with mastectomy without post-mastectomy radiation therapy and found two sets of gene profiles (one with 258 genes and the other with 34 genes) to be predictive of LR rate.[62] The Netherlands group explored three gene profiles (wound response profile, 70 gene prognosis profile and hypoxia induced profile) in 161 patients treated with breast conservation therapy including radiation treatment. All patients were under the age of 53 at the time of diagnosis and an additional radiation boost was employed. Thirty seven patients did not have negative margins. Seventeen patients had a LRR and of the three signatures only the wound response profile showed evidence of predicting an LR rate (10 year local control with low versus high scores were 95 and 71 percent, respectively p=0.0008).[18] An expansion of this cohort to 165 patients, 56 of whom developed an LR found that genes associated with cell proliferation were expressed

at higher levels in tumors from patients with an LR. The group was unbalanced for tumor grade, with those in the no LR group having a significantly larger proportion of low grade tumors. The association of tumor molecular subtype had a significant impact on LR rate. A 70 gene analysis and the chromosomal instability signature were also found to be significant predictors of LR rates, respectively. However, the wound response signature's ability to predict LR rate was not confirmed in this larger cohort. Nimeus-Malmstrom et al. found an 81 gene profile that could significantly distinguish those at high risk for LR rate after breast conservation therapy but their results were not confirmed by the re-analysis performed by Kreike et al. on the Netherlands cohort.[13,63] Finally, some recent studies have reported that DEAD Box1 (DDX1) and Ductal epithelium-associated RING Chromosome 1) DEAR1expression is associated with local control after breast conservation,[64,65] however the prognostic value of these markers have not been validated.

There has been a lot more effort put into identifying markers predictive of distant-disease free survival. The 70-gene recurrence score has been shown to be predictive of short interval to distant metastases,[66] however this marker set is being testing prospectively in the ongoing MINDACT trial and is not commonly used in the United States for decision-making. Thus there are not routinely used molecular predictors that can determine which patients are at high risk of relapse and need treatment, or alternately are at low risk, and thus systemic treatment can be spared. Recent retrospective studies have suggested that even small HER2 positive tumors confer at a high risk of recurrence[67] and should be considered for HER2-targeted therapy. However the molecular profile of the tumor such as PTEN status and PIK3CA mutation status may affect the biology of these tumors as well as therapy responsiveness.

There is a growing appreciation that tumors evolve at a molecular level. Indeed with treatment some HER2+ tumors have been shown to lose Her2 amplification, and molecular markers such as PIK3CA mutation status and PTEN status have been shown to be discordant between primary and metastatic tumors.[68,69] There has been a great interest in understanding whether this evolution occurs due to genomic instability and acquired mutations, or due to selection of rare clones, a question that can be answered with prospective collection of primary tumors and recurrences.

In summary, previous studies have shown that tumor subtype is predictor of LR rate and that patients with HR+ tumors are at lower risk recurrence and among HR+ tumors, Oncotype DX recurrence score may have predictive value. There remain no clinically adapted predictors of IBTR, recurrence-free survival (RFS) and distant recurrence-free survival (DRFS) in TNBC and HER2+ disease. Identification of patients at risk for local relapse and distant recurrence can help us further personalize breast cancer therapy by offering patients at higher risk other surgical options (mastectomy or larger excisions with oncoplastic remodeling), or therapies targeting the pathways driving local and systemic recurrence. Comparing primary tumors and recurrences will give us critical insights into molecular evolution.

13.3.2 Hypothesis:

Our hypothesis is that the molecular profile of breast tumors predicts LRR and DFS after breast-conserving therapy. We also hypothesize that recurrent tumors will demonstrate additional oncogenic aberrations compared to the original primary tumor.

Objectives:

1. To determine molecular profile of chemonaive and chemoresistant breast cancer
2. To determine whether clinical-pathologic variables predict LRR
3. To determine molecular characteristics that correlate with LRR and disease free survival.
4. To determine molecular alterations that develop between primary tumors and recurrent tumors

Our long-term goal is to determine oncogenic drivers that dictate breast cancer behavior and to use this information to design individualized surgical and systemic therapies. The purpose of our study is to determine the molecular features that correlate with risk of LR and DFS. We will do this with a comprehensive approach evaluating RNA and DNA and selected protein markers. Prospective collection of tumor samples will allow us to also compare primary and recurrent tumors in order to assess molecular evolution.

With this study we will test an existing clinical-pathologic predictor and determine whether molecular profiling can improve on predictive ability of clinical-pathologic variables. With our study we expect to identify molecular aberrations that predict local recurrence and recurrence-free survival which will be further pursued

by 1) validating predictive profiles in a independent cohort, 2) determine whether these aberrations confer risk of local relapse with mastectomy as well, 3) develop a molecular/clinicopathologic predictor of local relapse that can be used for patient counseling 4) validation of abnormalities at an individual gene level, and 5) develop targeted therapies that can modify local and systemic recurrence risk.

13.3.3 Methods:

We will collect clinical-pathologic variables associated with ipsilateral breast cancer recurrence (LR), as well as determining each tumor's molecular phenotype at the protein, RNA, and DNA level. All patients with a local recurrence (LR), regardless of whether they have distant metastasis, will be considered to have local failure.

Clinical-pathologic variables: We will collect the following clinical-pathologic variables that have been associated with LR: Tumor size, margin width, presence of ductal carcinoma in situ, ER status, HER-2 status, grade, multifocality, lymphovascular invasion, nodal status, patient age, family history, XRT (administration of boost) type, and systemic therapy. For patients with an LR, we will determine the distance between primary tumor and the LR, and histologic and biologic subtype of the recurrence to stratify patients into possible true recurrences (TR) versus new primaries (NP). We will obtain samples of recurrent tumors for molecular characterization.

Molecular Phenotype: We will collect formalin-fixed, paraffin-embedded tissue for validation studies. We will obtain samples of recurrent tumors for molecular characterization; we will try to obtain local as well as distant recurrences when possible.

RNA Analysis: RNA analysis will be performed with transcriptional profiling of primary tumors. RNA will be extracted. The amount and quality of RNA will be considered adequate for further analysis if the optical density 260/280 ratio is ≥1.8 and the total RNA yield is ≥1μg. Adequate RNA for microarray profiling, without amplification, from a single FNA pass can be obtained in 90% of cases. Currently microarray based profiling is available at M.D. Anderson in a CLIA-approved lab. RNA generation and second-strand cDNA synthesis will be performed as described previously.[71] The RNA is currently profiled on Affymetrix U133A chips (Santa Clara, CA). However, the technology for transcriptional profiling is rapidly evolving. The state of the art transcriptional profiling approach available at the completion of the study will be used for RNA profiling. As technology evolves, sequencing may be performed in lieu of transcriptional profiling.

DNA Analysis: Tumor DNA (primary tumor and recurrence if available) and normal DNA (from blood) will be extracted for targeted exome sequencing or whole genomic/exomic sequencing. DNA analysis may be performed at MD Anderson Cancer Center or may be performed at an outside institution (including industry partners Illumina, Myriad, Foundation Medicine, or academic partners Broad Institute). Any sample sent out to industry partners will be de-identified.

We will use a reference (GRCh37/hg19) sequence-guided alignment and assembly tool, MOSAIK, to process the short read data sets. MOSAIK works with paired-end reads from Illumina GAII/HiSeq 2000, and uses both a hashing scheme and the Smith-Waterman algorithm to produce gapped alignments. MOSAIK is also multithreaded and able to fully take advantage of MD Anderson's 8000 cores Super-Linux Cluster. The resulting pair-wise alignments will then be consolidated into a multiple sequence alignment (assembly) and saved as an ACE assembly file. These assemblies can be visualized and viewed by programs such as consed. Starting with the multiple read alignments produced by the MOSAIK aligner and assembler, we will analyze the resulting alignments using the Bayesian model-based software GigaBayes that enables efficient analysis of billions of aligned short-read sequences. The program evaluates each aligned base and its base quality value at each position to indicate putative single-nucleotide variations (SNVs) and short insertion-deletions (INDELs), and their corresponding SNV probability value (PSNV). We will filter out all known SNVs and INDELs in UCSC dbSNP 132 and 1000 human genome project SNP database, and recovered any mutations, which are in Catalogue of Somatic Mutations in Cancer (COSMIC) database curated by Wellcome Trust Sanger Institute. We will also determine the somatic status of each SNVs (or INDELS) by comparing the genotypes between matched normal and tumor samples. Finally, each somatic mutation or INDELs will be annotated with functional effect by SIFT or alternate algorithms to determine if a mutation candidate is synonymous or non-synonymous.

We will use molecular inversion probe (MIP v3) technology (Affymetrix) or state of the art technology at completion of the study to assess DNA level alterations. MIP technology requires as little as 40 ng; we will obtain normal tissue and tumor tissue from primary tumors and recurrences in FFPE. MIP technology has been used is several studies at M. D. Anderson with of FFPE-archived samples. More than 330,000 markers can be examined for good coverage across the genome. In additional to absolute copy number data, this approach

provides individual allele copy number information, which can be used to detect copy-neutral loss of heterozygosity (LOH), infer contamination of tumor sample with normal tissue, and examine preferential allele amplification. Copy number assessment technologies are evolving. The most robust technology with the least tissue requirement available at the completion of this trial will be used for DNA copy number analysis. Additional technologies for DNA rearrangements may also be utilized.

13.3.4 Statistical Analysis:

Molecular Profile of Chemonaive and Chemoresistant Breast Cancer
We will use descriptive statistics to determine the molecular characteristics of chemotherapy naïve and post-chemotherapy residual tumors. When available we will compare the pre-chemotherapy molecular characteristics to post-chemotherapy molecular profile.

Clinical Pathologic Predictors
Univariable and multivariable Cox regression analyses will be used to determine associations between clinical and pathologic characteristics and LR, and again for disease-free survival. The Kaplan-Meier method will be used to generate survival curves and these will be compared with a two-sample log rank test. .
Next we will evaluate the predictive value of a web-based tool (IBTR!), to determine relative LR risk based on 7 clinical-pathologic factors.60 The predicted risk of LR will be calculated for each patient by using this tool. The discrimination of IBTR! will be assessed by calculating the value of a modified c-statistic obtained by performing a Cox regression with the IBRT! value as a variable.72 It is generally accepted that c-values of 0.7 to 0.8 represent reasonable discrimination, whereas c-values values exceeding 0.8 represent good discrimination. Time-dependent ROC curves will be constructed and analyzed. Cox regression will be used to estimate the increased hazard ratio of an LR per 10-unit increase in the prediction by IBTR! model. It is expected that there will be samples available for approximately 45% of the women. With 240 women with samples and primary clinical end point of local recurrence- in 5 yrs, 20 local recurrences are expected. Thus we will have at least 80% power to estimate the ROC curve (conjectured at 0.8) within a half-width of 0.08.73,74

Molecular Predictors
RNA and DNA mutation and copy number data will be analyzed separately, determining associations of molecular characteristics a) with LR, and b) with putative TR, and c) with any DFS. We will analyze the data for the presence of clusters based on differential protein or RNA expression or mutations by using available methods with the R statistical software package [redacted] A predictive signature of outcome will be developed using a LASSO analysis. We will also use a variety of unsupervised clustering methods (including hierarchical clustering, K-means, and gene shaving) to classify the samples into statistically similar groups. We will evaluate the robustness and statistical significance of these groups by using bootstrap resampling of the data. To detect the genes/mutations that are differentially expressed between the primary tumors and recurrent tumors, we will perform repeated Measures/Mixed-Model ANOVA. A Beta-uniform (BUM) model for P-values of sensitivity in the samples will be used to refine p-value cut-offs, however, tentatively we will use a False Discovery Rate (FDR) of 0.05 to select markers of interest. In addition, we will build an integrative model that incorporates RNA and DNA predictors. In addition to the primary clustering analysis based on all measured proteins, we will perform secondary bootstrap-resampled cluster analyses looking putative markers of LR such as loss of PTEN or intrinsic subtype, 75 expression of a proposed local recurrence signature,8 wound-response signature;[76,77] as well as estimated 21-gene recurrence score. We will also look at putative markers of RFS including 70-gene profile, and genomic grade.78 We will retain clusters that a) are robust to bootstrap resampling; b) are found by multiple clustering algorithms; and c) contain > 10% of the samples. An integrated analysis will be performed with significant variables. Each molecular predictor will be tested in a multivariate analysis that includes all significant clinical-pathologic factors. Molecular profile or primary tumor and recurrence will be compared as an exploratory analysis

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15 Model Informed Consent Document

A011104 / 6694: Effect of Preoperative Breast MRI on Surgical Outcomes, Costs and Quality of Life of Women with Breast Cancer

This is a clinical trial, a type of research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have either breast cancer that is HER-2 positive, or breast cancer that is negative for estrogen, progesterone and HER-2 (triple-negative disease), and your tumor can be removed by breast-conserving surgery.

Why is this study being done?

The purpose of this study is to test whether patients undergoing a breast MRI (magnetic resonance imaging) before breast surgery will have better results after the surgery.

MRI is a medical imaging method that uses magnets to make images of the body. MRI helps doctors to tell the difference between cancer and normal tissue in the body. MRI uses dyes ("contrast agents") that are injected into the veins to help create the images of the body's tissues.

Breast tumors are routinely evaluated using mammograms and ultrasound before surgery. This study would like to find out if using MRI in addition to mammography before surgery improves our ability to evaluate tumors and decide what kind of surgery is best for the patient.

The goals of this study are:

- To see if using MRI improves decision-making when choosing what type of surgery is best for the patient (mastectomy or lumpectomy).
- To see if using MRI affects how well patients do after surgery.
- To examine the effect of using MRI on patients' quality of life.
- To examine the effect of MRI on overall medical costs.

How many people will take part in the study?

About 317 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study…

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Physical exam and medical history
- Mammogram (with ultrasound if recommended by your doctor)
- Breast biopsy to confirm your diagnosis
- Pregnancy test if you are of childbearing potential

During the study…

You will be randomly assigned (like flipping a coin) or "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either group.

Group 1

If you are in Group 1 (often called "Arm 1"), you will have breast conserving surgery (also called “lumpectomy”).

Group 2

If you are in Group 2 (often called "Arm 2"), you will have a breast MRI before your surgery. Based on the results of the MRI, you and your doctor will decide which type of surgery – lumpectomy or mastectomy – is best for you, and then you will have surgery.

Images and reports from the MRI exam will be sent to the ECOG-ACRIN (formerly the Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network) for review by the study radiologist. This is for quality assurance purposes. The images and reports will not contain any of your identifying information (e.g., your initials, birth date or medical record number). The accompanying paperwork will contain your initials and a study identification number.

Patients in both groups will be asked to complete questionnaires about their general health and quality of life. These surveys are being done to compare the quality of life of the patients randomized to have MRI to the patients who do not have MRI. These questionnaires should take about 20 to 40 minutes to complete. The first time that you will be asked to complete these questionnaires will be at the time you enroll to the study. If you are randomized to Group 2, you will also be asked to complete these questionnaires after the MRI (but before surgery).

Some medical cost information will be collected to help researchers better understand the costs of adding MRI to patients’ pre-operative evaluation.

After surgery...

You will see your doctor at post-operative visits, and then every 4 months for 2 years and then every 6 months for 3 years. At those visits, you will have the following tests and procedures:

Post-surgery visits:

- Physical exam
- Questionnaires about your quality of life

4 months after surgery:

- Physical exam

8 and 12 months after surgery:

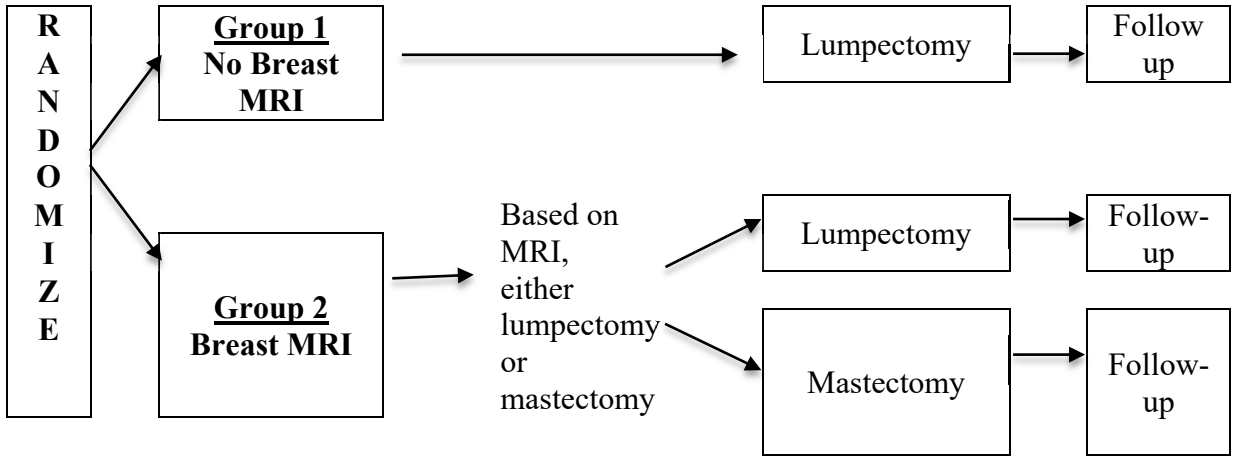
- Physical exam
- Questionnaires about your quality of life (8 and 12 months after enrolling on the study)

16, 20 and 24 months after surgery, then, every 6 months until 5 years after you started the study:

- Physical exam

Study Plan

Another way to find out what will happen to you during the study is to read the study plan below. Start reading at the left and follow the arrows.



How long will I be in the study?

You will be in the study for a little over five years.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study procedures can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the MRI exam (Group 2)

LIKELY:

- Anxiety/stress
- Claustrophobia
- Discomfort

RARE, BUT SERIOUS:

- Injury related to the presence of metallic or surgical implants or metal pieces in the body and the MR magnet; it is important that you let the MRI team know about whether you have these before the MRI procedure.

Risks and side effects related to the IV Needle Placement (Group 2)

LIKELY:
- Minor discomfort

LESS LIKELY
- Swelling
- Bleeding
- Infection
- Bruising

Risks and side effects related to the drug used for MRI (called Gadolinium) (Group 2)

LESS LIKELY:
- Headache
- Nausea
- Vomiting
- Hives
- Temporary low blood pressure
- Allergic-like reaction

RARE BUT SERIOUS:
- Kidney impairment

Risks and side effects related to surgery (Groups 1 and 2):

There are no additional risks from surgery beyond the risks related to standard breast cancer surgery. Your doctor will provide more information about these risks.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

There may or may not be direct medical benefits to you from your taking part in this study. We hope that information learned from this study will help patients with breast cancer in the future.

What other choices do I have if I do not take part in this study?

Your other choices may include:
- Having surgery for your cancer without being in a study
- Taking part in another study
- Having no surgery

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The Alliance for Clinical Trials in Oncology (Alliance);
- The Alliance Data and Safety Monitoring Board, a group of experts who regularly review the progress of the study;
- The local IRB (a group of people who review the research to protect your rights) of this institution;
- ECOG-ACRIN. ECOG-ACRIN is an organization funded by the National Cancer Institute (NCI) to provide expert review of imaging data;
- The National Cancer Institute (NCI);
- The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials;
- Other government agencies, like the Food and Drug Administration (FDA) and the Office for Human Research Protection (OHRP), involved in keeping research safe for people;
- Other oncology research groups who have endorsed this study.

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

There are laws that protect your genetic information. However, there is a risk that someone could get access to your genetic information and identify you by name. In some cases, employers could use your genetic information to decide whether to hire or fire you. The study doctors believe the risk of this happening is very small. However, the risk may increase in the future as people find new ways of tracing information. For more information about the laws that protect you, ask your study doctor.

A description of this clinical trial will be available on [redacted] as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

What are the costs of taking part in this study?

You and/or your health plan / insurance company will need to pay for some or all of the costs of treating your cancer in this study. Taking part in this study may or may not lead to added cost to you or your insurance company for more than the cost of getting regular cancer treatment. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out more information.

If you are randomized to "Arm 2", you will have a breast MRI before surgery. Your health care plan may not pay for some or all of the costs of the breast MRI. You are encouraged to speak with the research team about potential out-of-pocket expenses.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's web site at [redacted]

You can print a copy of the "Clinical Trials and Insurance Coverage" information from this web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

You will not be paid for taking part in this study.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*

You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at [redacted] (from the continental US only). *[*Only applies to sites using the CIRB.]*

RELATED STUDIES

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

Optional Study: Research on tissue and blood

With your permission, researchers would like to study samples of your tumor tissue collected at the time of your surgery, and during follow-up if your cancer returns. In addition, about 1 tube of blood would be collected at the time of surgery for this additional study. If you have had chemotherapy before surgery, in addition researchers would like samples of your initial tumor biopsy. You may still take part in the main treatment study even if you say 'no' to taking part in the additional study on tissue and blood.

In this additional study, researchers will use a test called "immunohistochemical staining" to study the molecular characteristics of your tumor. These characteristics are called tumor markers. The purpose of these studies is to identify tumor markers that may mean that cancer is more likely to come back. Some of the studies will involve your DNA (also called genetic testing). Results of these tests will not be given to you or your doctor nor will they be used to make any decisions about your treatment.

The tissue samples and blood will be stored at a central laboratory called the Alliance Biorepository at Washington University. The samples will not contain any of your identifying information (for example, your initials, birth date or medical record number). The accompanying paperwork will contain your initials and a study identification number.

Your tissue samples are called "specimens". You can learn more about how biological specimens are used for research at [redacted]

The research that may be done with your specimens is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the specimens for research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your specimens can be used for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then any specimens that remain will no longer be used for research and will be discarded.

In the future, people who do research may need to know more about your health. While the Alliance may give those people reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new products in the future, but you will not be able to benefit financially from the new products.

Genetic Research

Sometimes specimens are used for genetic (DNA) research.

The purpose of doing genetic research is to discover changes in genes (or DNA) related to the development or outcome of cancer. This could lead to better ways to prevent, detect, and treat cancer and, perhaps, other diseases as well. Due to advances in the techniques and tests used to analyze genetic material in specimens (DNA), it is likely that your specimens could be used for this type of research, if you allow it.

Body tissues are made up of cells. Cells contain DNA, which is part of your unique genetic material that carries the instructions for your body's development and function. DNA can be analyzed so that your unique, exact genetic code or the altered genetic code of your tumor cells can be identified and compared to other patients. Cancer can result from changes in a person's genetic material (DNA) that causes cells to divide in an uncontrolled way and, sometimes, to travel to other organs. Currently, researchers and doctors know some of the genetic changes that can cause cancer, but they do not know all of the genetic changes that can cause cancer.

By studying the genetic code of cancer cells and the people who have cancer, scientists expect to identify most of the genetic changes associated with different kinds of cancer. The Alliance and scientists who work with Alliance members, such as your doctor, would also like to compare genetic information obtained from your biological specimens with information available from your progress on the Alliance study. With this knowledge, future treatments for cancer could become customized to a patient's unique genetic make-up (this is known as personalized medicine).

Your specimens and medical information collected as part of the Alliance study will be labeled with a code.

Only the Alliance will have the information that matches the code to traditionally-used identifying information, such as your initials, birth date or medical record number. The Alliance will keep the information that matches the code to this traditionally-used identifying information in a safeguarded database. Only very few, authorized people, who have specifically agreed to protect your identity, will have access to this database. All other researchers and personnel, including those who will be working with your samples and medical information, will not have access to any of the traditionally-used identifying information about you.

Information from analyses of your coded specimens and your coded medical information will be put into databases along with information from other research participants. These databases will be accessible by the internet. The purpose of making sequence and medical information available is so that they can be used by scientific researchers throughout the world to study cancer and other diseases.

Please note that traditionally-used identifying information about you, such as your initials, birth date or medical record number would NOT be put into the databases.

Even if your specimens are used for this kind of research, the results will not be put in your health records and although you can learn more about this type of research, individual information about your genetic code or your tumor will not be available to you.

Benefits

The benefits of research using specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

- Your privacy is very important to us and we will use many safety measures to protect your privacy. However, in spite of all of the safety measures that we use, it is impossible to guarantee that links between you and the genetic information we would obtain will never become known. Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other relatives. Consequently, it may be possible that genetic information from them could be used to try and identify your sample from the publicly available information. Similarly, it may be possible that genetic information from you could be used to help identify them.
- While the databases used to store your genetic information would not contain information that is traditionally used to identify you, such as your initials, birth date or medical record number, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you.

  We would like to emphasize that we will do everything we can to protect your private information. However, because of the nature of the issues, we feel that we should explain these issues to you carefully.

- An additional risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.
- A federal law (Genetic Information Non-Discrimination Act, GINA) will help lower the risk from health insurance or employment discrimination on the basis of genetic information. The federal law does not include other types of misuse by life insurance, long-term care or disability insurance. If you want to learn more about the GINA Law, which went into effect in 2009, you can find information about it on the internet or ask the study staff. In addition to the federal law, some states have laws that also help protect against genetic discrimination.

Making Your Choice

Please read the sentence below and think about your choice. After reading the sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at _____ [IRB's phone number].

No matter what you decide to do, it will not affect your care. Even if you agree to have these tests done now, you may change your mind at any time. Just contact us and let us know that you do not want to continue with these tests.

1. My tissue and blood collected at surgery, and during follow-up if my cancer returns, may be used for the related research studies described above. If I have had chemotherapy before surgery, an additional tissue sample will also be collected before I have surgery and start chemotherapy.

Yes____ No____

Optional Storage of Specimens for Future Research

The researchers would also like to store any portion of the tissue and blood that is not used up by the related studies described above. These samples may be stored indefinitely. You can still take part in the treatment study, and the additional research study described above without giving your consent for your specimens to be stored.

It is not possible for you or the Alliance to know what studies of cancer may be appropriate in the future. We ask that you give permission in advance for other studies to be performed using the tissue and blood without being re-contacted to give permission for each test.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at _____ *[IRB's phone number]*.

No matter what you decide to do, it will not affect your care. Even if you agree to have these tests done now, you may change your mind at any time. Just contact us and let us know that you do not want to continue with these tests.

2. My coded tissue and blood samples and related coded information **may be kept for use** in future research to learn about, prevent, find or treat **cancer**. This may also include research on inherited traits (genes passed on in families).

   Yes____ No____

3. My coded tissue and blood samples and related coded information **may be kept for use** in future research to learn about, prevent, find or treat **other health problems** (for example: diabetes, Alzheimer's disease, or heart disease). This may also include research on inherited traits (genes passed on in families).

   Yes____ No____

4. Someone from my hospital or the Alliance may contact me in the future to ask me to take part in more research.

   Yes____ No____

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

[redacted]

You may also visit the NCI Web site at [redacted]

- For NCI's clinical trials information, go to: [redacted]
- For NCI's general information about cancer, go to [redacted]

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant Signature _____ Date _____

Appendix I: Staging Reference

(Selected elements from the AJCC Cancer Staging Manual, 7th edition, 2009)

Primary Tumor (T)	
T0	No evidence of primary tumor
Tis	Carcinoma in situ, ductal carcinoma in situ, lobular carcinoma in situ, or Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted.
T1	Tumor 2 cm or less in greatest dimension
T1mi	Microinvasion 0.1 cm or less in greatest dimension
T1a	Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
T1b	Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
T1c	Tumor more than 1 cm but not more than 2 cm in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules). Note: Invasion of the dermis alone does not qualify as T4.
T4a	Extension to chest wall, not including pectoralis muscle adherenc/invasion
T4b	Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
T4c	Both T4a and T4b
Regional Lymph Nodes (N)	
N0	No regional lymph node metastases.
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted, or in clinically detected* ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastases
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected* ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement, or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)

** Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, for example, cN1. Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment..*	
Distant Metastasis (M)	
MO	No clinical or radiographic evidence of distant metastasis
M1	Distant detectable metastases as determined by classic clinical radiographic means and/or histologically proven larger than 0.2mm

Appendix II: ECOG/Zubrod Performance Status Scale

0 - Asymptomatic and fully active.

1 - Symptomatic; fully ambulatory; restricted in physical strenuous activity.

2 - Symptomatic; ambulatory; capable of self-care; more than 50% of waking hours are spent out of bed.

3 - Symptomatic; limited self-care; spends more than 50% of time in bed, but not bedridden.

4 - Completely disabled; no self-care; 100% bedridden.

Appendix III: ACR Breast MRI Accreditation

Prior to patient enrollment, all participating sites must be accredited for breast MRI.

Sites not previously ACR Breast MRI accredited will have to submit a quality assurance form during the site qualification process. Each site will submit test images to ACRIN and will receive training examples for MRI findings management. In addition, each interpreting radiologist must meet the ACR Breast MRI Accreditation standards for breast MRI training and each breast MRI study must meet the ACR Breast MRI Accreditation technical parameter requirements. Details of these standards are provided below:

ACR Breast MRI Radiologist Training Requirements

Board Certified

- ***Certification*** in Radiology or Diagnostic Radiology by the
  - American Board of Radiology, ***or***
  - American Osteopathic Board of Radiology, ***or***
  - Royal College of Physicians and Surgeons of Canada, ***or***
  - Le College des Medecins du Quebec

AND

- Supervision, interpretation and reporting of ***150 breast MRI examinations*** in the last 36 months, ***or***
- Interpretation and reporting of ***100 breast MRI examinations*** in the last 36 months ***in a supervised situation****

OR

Not Board Certified

- Completion of an Accreditation Council for Graduate Medical Education (ACGME) or American Osteopathic Association (AOA) approved diagnostic radiology residency program, ***and***
- Interpretation and reporting of ***100 breast MRI examinations*** in the last 36 months ***in a supervised situation****

AND

15 hours of Category 1 Continuing Medical Education (CME) in MRI (including clinical applications of MRI in breast imaging, MRI artifacts, safety, and instrumentation)

Continuing Experience: Upon renewal, **75** breast MRI examinations in the prior **24 months**†

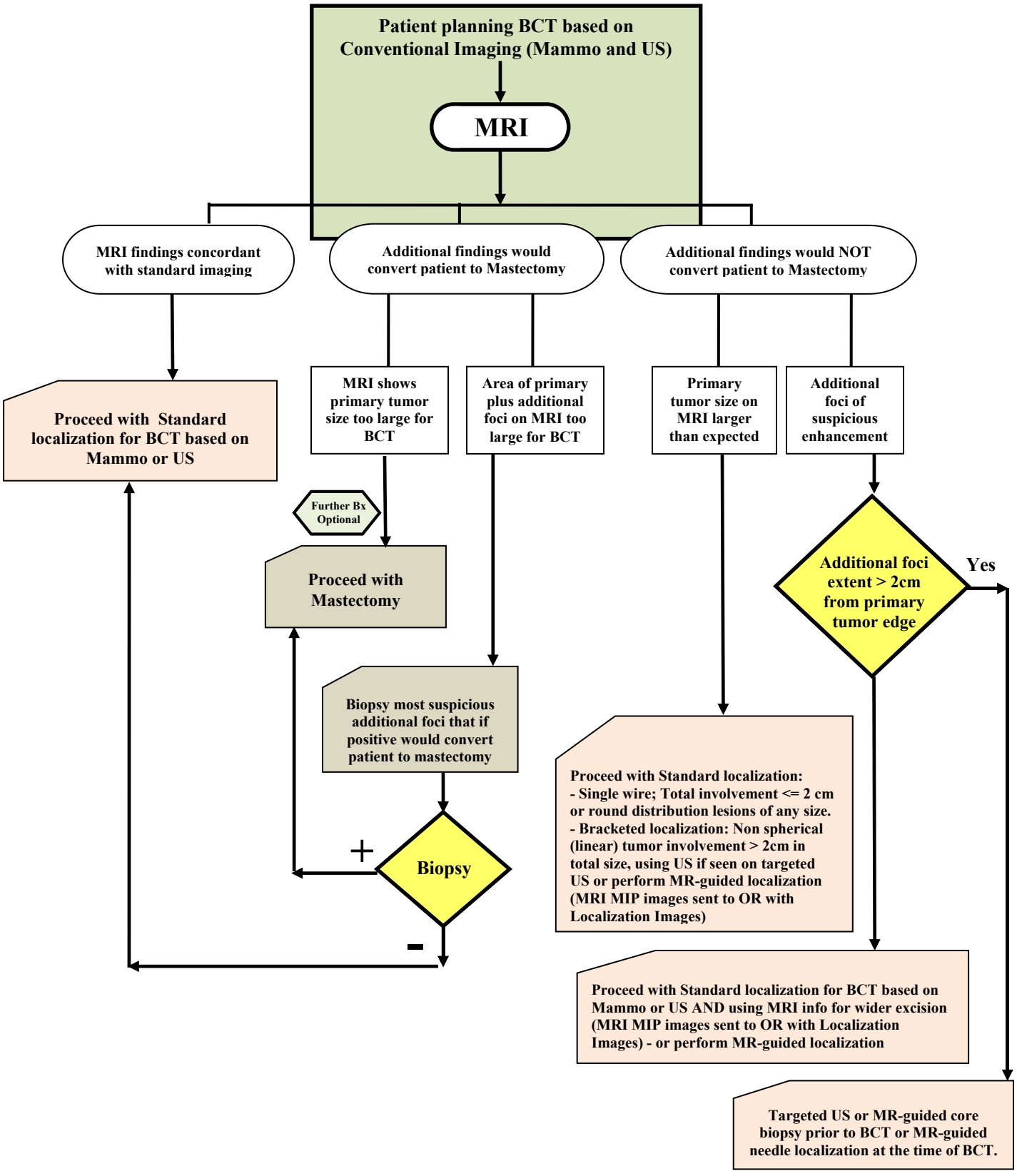
Continuing Education: Upon renewal, **5** hours Category 1 CME in breast MRI in the prior **36 months**

*The supervising interpreting physician reviews, discusses, and confirms the diagnosis of the physician being supervised. The supervising interpreting physician does not have to be present at the time of initial interpretation. However, the supervising physician must review and, if necessary, correct the final interpretation. Supervision may also be accomplished through a formal course that includes a lecture format in addition to all of the following: 1) a database of previously performed and interpreted cases, 2) an assessment system traceable to the individual participant, and 3) direct feedback regarding the responses. Examples of suitable assessment systems are an audience response system, a view box or monitor based program or an individual CD-ROM or web-based instruction system.

ACR Breast MRI technical parameter requirements: For the pre-contrast and post-contrast T1-weighted series, the following parameters must be met:

Sequence	Slice Thickness	Gap	Maximum In Plane Pixel Dimension for Phase and Frequency
Sagittal, Axial and/or Coronal	< 3 mm	0 mm	<1 mm

Appendix IV: MRI Findings Management Flow Chart



Appendix V: Registration Fatigue/Uniscale Assessment

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and recorded on the Registration Fatigue/Uniscale Assessment Form (see Forms Packet).

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										Fatigue as bad as it can be

your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

Appendix VI: Quality of Life Measures

FACT-G (version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>**

	Not at all	A little bit	Some-what	Quite a bit	Very much
1. I have a lack of energy	0	1	2	3	4
2. I feel ill	0	1	2	3	4
3. I am able to work (include work at home)	0	1	2	3	4
4. I am able to enjoy life	0	1	2	3	4

Assessment of Survivor Concerns

Please respond to each item by marking one box per row.

	Not at all	A little bit	Some-what	Very much
5. I worry about future diagnostic tests	1	2	3	4
6. I worry about another type of cancer	1	2	3	4
7. I worry about my cancer coming back	1	2	3	4
8. I worry about dying	1	2	3	4
9. I worry about my health	1	2	3	4
10. I worry about my children's health	1	2	3	4

PROMIS

Please respond to each item by marking one box per row.

	Excellent	Very good	Good	Fair	Poor
11. In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
12. In general, would you say your quality of life is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
13. In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
14. In general, how would you rate your mental health, including your mood and your ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
15. In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
16. In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

	Completely	Mostly	Moderately	A little	Not at all
17. To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

In the past 7 days	Never	Rarely	Sometimes	Often	Always
18. How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	None	Mild	Moderate	Severe	Very Severe
19. How would you rate your fatigue on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

20. How would you rate your pain on average?	☐ 0 No pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 Worst imaginable pain