AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6667

MRI Evaluation of the Contralateral Breast in Women with a Recent Diagnosis of Breast Cancer

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

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- Participants will be women with a recent (within 60 days) diagnosis of breast cancer. Date of diagnosis of breast cancer is defined in the study as the date of the first tissue diagnosis of breast cancer (by fine needle aspiration, core needle biopsy, or excisional biopsy). Cancer is defined as ductal carcinoma in situ (DCIS) and/or any invasive cancer in the breast. Participants will receive an MRI of the breast contralateral to the breast with known cancer. A negative or benign mammogram and CBE of the study breast are required within 90 days prior to the MRI to be eligible for the study. Suspicious lesions identified on the MRI will receive additional work-up, which may include repeat MRI, US, diagnostic mammography and/or biopsy.

Eligibility (see section 5 for details)

- Women ≥ 18 years in age.
- All women in this study will have a recent history of unilateral breast cancer in the non-study breast. Recent history is defined as initial biopsy proven (including FNA) cancer diagnosis (DCIS and/or any invasive cancer in the breast), within 60 days prior to the MRI.
- A negative or benign mammogram and negative or benign CBE of the study breast are required within 90 days prior to the MRI, and there must be no new breast symptoms for which further evaluation is recommended in order for the patient to be eligible for the study.
- No history of breast biopsy (including FNA) of the study breast within 6 months prior to the MRI.
- No current or recent (6 months prior to the MRI) history of chemotherapy for cancer.
- Signed study-specific informed consent prior to registration.
- No contraindications to MRI examination.
- No current history of receiving hormonal therapy, tamoxifen, and or aromatase inhibitors for therapeutic measures.
- No prior MRI of study breast within the 12 months prior to the study MRI.
- No initial biopsy-proven breast cancer diagnosis, including FNA in either breast, greater than 60 days prior to the MRI.

Required Sample Size: 1000; maximum of 200 per site

1.0 ABSTRACT

The primary aim of this study is to determine the cancer yield of MRI in the contralateral breast of women with a recent breast cancer diagnosis and no known disease by mammography or clinical breast exam in the contralateral breast. A total of 1,000 women with a recent breast cancer diagnosis will be enrolled into the trial at 21 centers in the US, Canada and Germany. Women with a history of breast cancer, negative or benign mammogram, and negative or benign clinical breast exam of the contralateral breast within 90 days prior to the MRI will be invited to participate. All women will undergo MR evaluation of the contralateral breast. Truth regarding breast cancer status will be determined through the results of a breast biopsy, if that occurs, or as a result of a 24-month follow-up without clinical evidence of disease.

Secondary aims include assessing sensitivity, specificity and positive predictive values (PPV for call back/additional imaging and PPV for biopsy recommendation) and ROC curves of MRI in evaluating the contralateral breast of women with recent diagnosis of breast cancer. In addition, preliminary evaluation of the influence of breast density, age, and tumor histology on the yield of MRI will be performed.

2.0 BACKGROUND AND SIGNIFICANCE

Until breast cancer can be prevented, early detection and intervention offer the best chance of survival. Although mammography is the current standard screening study for breast cancer, it has difficulty in demonstrating cancers in radiographically dense breasts and in demonstrating some types of cancer (e.g., invasive lobular cancers) in women of all breast density types. These limitations have stimulated exploration of alternative or adjunctive imaging techniques such as Magnetic Resonance Imaging (MRI). Single institution pilot studies have reported that MRI can detect disease that is occult on mammography, ultrasound, and physical exam.

The ability to improve cancer detection would make MRI a good screening tool for breast cancer, yet its cost and its variable specificity prohibit its routine use to screen for breast cancer in general populations. However, it may be efficacious and cost effective for screening women determined to be at particularly high risk for breast cancer. Women with a current diagnosis of breast cancer have a significantly increased risk of cancer in the contralateral breast. Unfortunately, this contralateral breast cancer is not always diagnosed at the same time as the known cancer.

A personal history of breast cancer places a woman at a 2- to 6-fold increased risk of breast cancer in the contralateral breast compared to women in the general population of developing a first breast cancer (Li, 2001; Kollias, 2001; Fowble, 2001). Fowble et al found a 3% and 7% cumulative incidence of contralateral breast cancer at 5 and 10 years post initial cancer diagnosis. These contralateral cancers are often present, but not necessarily detected, at the time of the original breast cancer diagnosis. Barlow et al studied women with a known unilateral cancer who underwent bilateral mastectomy. In this study, 2.4% of women had incidental cancers found in the contralateral mastectomy specimen (personal communication, Barlow).

Recent preliminary results suggest MRI can improve cancer detection, compared to mammography, in the contralateral breast of women with known breast cancer at the time of their initial cancer diagnosis (Slanetz, Edmister, Yeh, Talele, Kopans 2002). Fischer (Radiology 1999) found synchronous contralateral cancers in 19 of 463 (4%) patients scanned. In the Slanetz study, 4 of 17 patients with invasive cancer had contralateral cancers detected on MRI that were occult to CBE, mammography, and ultrasound. In a separate study (Lee, Orel, Woo et

al, Radiology, 2003) the cancer yield of MRI in women with a recent cancer diagnosis and negative contralateral mammogram was found to be 3.8%. In a report by Kuhl et al, MRI revealed suspicious or equivocal lesions in the asymptomatic, contralateral breast in 91 out of 710 patients scanned. Of these 91 women, 45 were determined to have incidental foci of invasive and/or intraductal breast cancer in the clinically and conventionally asymptomatic breast – a cancer yield of 6.3%. This work led to the recent opening of a pilot study through the International Breast MRI Consortium (PI: Schnall) of 100 women with a current cancer diagnosis. It is anticipated that the current proposal to ACRIN for a definitive study of approximately 1000 women with a current cancer diagnosis will provide conclusive recommendations for the clinical utility of contralateral MR imaging in this important patient population.

In summary, exciting preliminary results demonstrate we have imaging tools that can detect breast cancers that are occult on both clinical exam and mammography. MR may detect occult cancer in the opposite breast of 1 in 20 women with a current breast cancer diagnosis. A large multi-institutional clinical trial of women with a current breast cancer diagnosis is needed before definitive recommendations for optimal clinical care of these women can be made.

3.0 SPECIFIC AIMS OR OBJECTIVES

3.1 PRIMARY SPECIFIC AIM

To assess the diagnostic yield of magnetic resonance imaging (MRI) in evaluating the contralateral breast of women with a recent unilateral diagnosis of breast cancer and a negative contralateral mammogram and clinical breast exam.

We will study a distinct population of women at high risk for breast carcinoma: women with a recent (within 60 days) personal diagnosis of breast cancer. In this group, the breast contralateral to the breast diagnosed with cancer will be scanned prior to initiation of chemotherapy and within 90 days of a negative mammogram of the study breast. A recent (within 90 days) negative or benign mammogram (defined by final BIRADS category 1 or 2) and negative or benign clinical breast exam of the study breast will be required for entry into the study.

3.2 SECONDARY SPECIFIC AIMS

To assess the sensitivity, specificity, and positive predictive values (PPV for call back/additional imaging and PPV for biopsy recommendation) and ROC curves of MRI in evaluating the contralateral breast of women with recent personal diagnosis of breast cancer.

Although MRI has been shown to detect cancers occult on mammography, the reported performance of MRI varies across published single site reports. Please refer to Appendix III for detailed definitions of the above descriptive variables.

3.2.1 To determine the effect of the following participant related factors: age (> = 50, < 50), breast parenchymal density (fatty vs. non fatty breast), and tumor histology (invasive lobular vs. invasive ductal, invasive vs. in situ) on the performance of MRI (cancer yield, sensitivity, specificity, and PPV).

The results from this study will be used to determine if the relative contributions of the imaging modalities differ based on the above patient and tumor related factors.

4.0 STUDY OVERVIEW

The primary aim of this multi-institutional study is to assess the performance of breast MRI in detecting clinically and mammographically occult disease in the contralateral breast of women with a current breast cancer diagnosis. This is a cohort study in which all women with a recent breast cancer diagnosis and no suspicion of malignancy in the contralateral breast (as defined by recent negative or benign CBE and negative or benign mammogram (BIRADS 1 or 2)) will receive an MRI of the contralateral breast. For study entry, "recent" is defined as the 60 days prior to the MRI for the diagnosis and 90 days prior to the MRI for the mammogram and CBE. In this study, performance of MR is defined by cancer yield (cancers/women screened), sensitivity, specificity and positive predictive value for call back for additional imaging and positive predictive value for recommendation for biopsy. All MR exams will be assigned an initial and a final assessment and recommendation based on the ACR MRI Breast Lexicon Classification Form (Appendix IV). All category 4 and 5 lesions will be biopsied. A 5-point Likert scale rating will be used to assess each MR for purposes of ROC analyses.

Women with a personal history of breast cancer will have the contralateral breast evaluated with MRI. These women will receive only one MR examination. This evaluation of the contralateral breast will be performed within 60 days of their cancer diagnosis and before initiation of chemotherapy. A subset of women may receive a short interval follow up MRI, depending on the recommendation at the initial MR scan. All women will be contacted 12 months and 24 months after the initial study MR to collect follow up data including any imaging, breast examinations, and or biopsies performed in the 12 months or 24 months following the study MRI. For any studies within the 12 months or 24 months that are not negative or benign, additional information will be collected to complete the follow up assessment. For example, if an abnormal mammogram is obtained during the 12 months or 24 months after the MRI, follow-up information to complete the abnormal assessment (including additional imaging and/or pathology information) will be collected up to 30 months after the MRI.

4.1 Possible Outcomes

The anticipated outcome is that women who undergo MRI evaluation of the contralateral breast will have otherwise occult cancer detected by the MRI. Since at this time early detection is our best method to reduce breast cancer morbidity and mortality, increased cancer yield is a successful outcome.

5.0 PATIENT SELECTION

Patients of all races and ethnic backgrounds at least 18 years old will be considered eligible for this study. Subjects will be recruited from those patients presenting at participating institutions with a recent diagnosis of breast cancer.

Each patient entered into the study will have had a physical examination and thorough medical history including hormonal medications, family and personal history of breast disease, family and personal history of other cancers, obstetrical history, phase of menstrual cycle, and results of prior breast cancer screening.

All patients will have a negative or benign mammogram (BIRADS 1 or 2) and negative or benign CBE of the study breast within 90 days prior to the MRI.

5.1 Inclusion Criteria

5.1.1 Women with a recent history of breast cancer (DCIS or invasive cancer in the breast).

5.1.2 Initial biopsy proven cancer diagnosis, including FNA, within 60 days prior to the MRI.

5.1.3 A negative or benign mammogram (diagnostic or screening with a final BIRADS assessment 1 or 2) and a negative or benign clinical breast exam of the study breast within 90 days prior to the MRI.

5.2 Exclusion Criteria

5.2.1 Pregnant patients (gadolinium is not approved for this population) and patients with other contraindications to MRI examination. Patients with contraindications include those with a pacemaker, magnetic aneurysm clip or other implanted magnetic device, or severe claustrophobia**.**

5.2.2 Patients less than 18 years of age.

5.2.3 Patients with psychiatric, psychological, or other conditions, which prevent a fully informed consent.

5.2.4 Patients with a previous biopsy, including FNA, of the study breast within 6 months prior to the MRI.

5.2.5 Patients with current or recent history (6 months prior to the MRI) of chemotherapy for cancer.

5.2.6 Patients are not eligible if they are receiving hormonal therapy, tamoxifen, and/or aromatase inhibitors for therapeutic measures. *Note: Patients are not excluded if receiving these therapies for preventive measures.*

5.2.7 Patients who have had an MR exam of the study breast within the 12 months prior to the study MRI.

5.2.8 Patients who have a remote history of breast cancer, as defined by an initial biopsy-proven breast cancer diagnosis, including FNA in either breast, greater than 60 days prior to the MRI.

5.2.9 Patients with new breast symptoms within the past 60 days for which further evaluation is recommended.

6.0 SITE SELECTION

6.1 Institution Requirements

Three items must be received and reviewed by ACRIN headquarters before an institution may submit a protocol to its IRB. All institutions must submit 1) a General Qualifying Application (GQA) to be approved by ACRIN headquarters, 2) a Protocol Specific Application (PSA, Appendix V) to be approved by ACRIN headquarters, and 3) a federal-wide assurance (or other assurance from the OHRP) to be filed at ACRIN headquarters. The GQA and the PSA should be e-mailed, faxed, or mailed to ACRIN administration at the address found on the PSA; the federal-wide assurance should be faxed to the ACR Regulatory Department at 215-574-0300. The PSA requires submission of sample patient images demonstrating MR-guided biopsy capability. Both MR-guided core needle biopsy and MR-guided wire localization are acceptable methods of tissue sampling. While a grid approach is encouraged, a free-hand approach will be accepted. The images will be reviewed before the site is allowed to open to accrual. The MR images should be sent to ACRIN.

6.2 IRB Approval and Informed Consent

All institutions must have study-specific IRB approval. RAs must follow OHRP-approved consent procedures, as well as those set by the Institutional Review Board (IRB) at the institution. A copy of IRB approval and the sample institutional study-specific consent form must be on file at ACRIN Headquarters (fax 215-574-0300) prior to registering your first patient.

7.0 ONLINE REGISTRATION AND RANDOMIZATION SYSTEM

7.1 Using the Online Registration System

7.1.1 Once the RA has completed the eligibility form (Appendix II) and the patient has been found to be eligible, the patient may be consented. The RA will register the patient by logging onto the ACRIN web site **(www.acrin.org)** and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist and the date the study-specific informed consent form was signed. **Eligible patients can be registered no more than two business days after completion of the MRI scan.**

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

7.2 Unsuccessful Registrations

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

7.2.2 In the unlikely event that the ACR web registration site is not accessible, participating sites may still register a patient by faxing the completed eligibility checklist to the DMC at the ACR (215-574-0300, ATTN: PATIENT REGISTRATION). ACR staff will fax a response to the registering site with the confirmation of registration and patient case number and randomization as soon as possible.

8.0 DATA COLLECTION AND MANAGEMENT

8.1 General

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

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

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

8.2 Clinical Data Submission

8.2.1 As soon as a patient has been registered, the RA may download the patient's data submission calendar, which lists all forms and/or designated reports required by protocol, along with the date that each form is due at the DMC. These calendars will be updated as the study proceeds to reflect data that has been received, reply deadlines for queries about unclear data, deadlines for follow-up reports of adverse events, or changes in the protocol which might change the data being collected or their timing.

Updated calendars for each patient can be obtained 24 hours a day from the ACRIN website.

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

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

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

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

8.3 Data Security

The registration system has built-in security features which encrypt all data for transmission in both directions preventing unauthorized access to confidential patient information. Access to the system will be controlled by a sequence of identification codes and passwords.

8.4 Electronic Data Management

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

for unexpected patterns in data, and other summaries needed for study monitoring. Any errors found at the BC will be reported to the DMC RA for resolution.

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

8.5 Missing and Delinquent Data Submission

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

8.6 Data Quality Monitoring

8.6.1 The BC at Brown University will maintain a study database at its site for monitoring data quality and for performing interim analyses. These data will be drawn directly from the DMC's permanent database using a PowerBuilder utility that allows BC staff to log onto the DMC computer and select needed data. This analysis database will be maintained in permanent SAS (Statistical Analysis System software) format on the BC's ACRIN server and updated on a scheduled basis, usually monthly once the study is in its steady state. Any discrepancies and other data quality issues will be referred to DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.

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

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

8.6.4 CASE REPORT FORMS

Data Items	Submitted from	Submitted to	Time of Submission
Eligibility Checklist **(Appendix II/A0)**	Clinical Site	ACR	at registration
Initial Evaluation Form **(I1)**	Clinical Site	ACR	within 2 weeks of registration
Mammogram Report [c] **(I2)**	Clinical Site	ACR only	within 2 weeks of registration
Initial Mammogram Assessment Form **(IA)**	Clinical Site	ACR	within 2 weeks of registration
Post-MRI Mammogram Assessment Form **(IM)**	Clinical Site	ACR	*as needed*, site will be notified of addition to case calendar
Mammogram Images **(C4)** *as needed*	Clinical Site	ACR only	*as needed*, site will be notified of addition to case calendar
Ultrasound Form **(IS)** *as needed*	Clinical Site	ACR	*as needed*, site will be notified of addition to case calendar
Ultrasound Report[c] **(DR)** *as needed*	Clinical Site	ACR	*as needed*, site will be notified of addition to case calendar
Ultrasound Images **(H1)** *as needed*	Clinical Site	ACR	*as needed*, site will be notified of addition to case calendar
Initial MRI Assessment Form **(M3)**	Clinical Site	ACR	within 2 weeks of registration
MRI Short Interval Imaging Form **(M4)**	Clinical Site	ACR	*as needed*, site will be notified of addition to case calendar
MRI Finding Tracking Diagram[c] **(B2)**	Clinical Site	ACR	*as needed*, site will be notified of addition to case calendar
MRI Report [c]**(ME)**	Clinical Site	ACR	within 4 weeks of registration and as otherwise specified for short interval imaging
MRI Digital Image **(MR)**	Clinical Site	ACR	within 4 weeks of registration

Biopsy Procedure Form **(AB)**	Clinical Site	ACR	*as needed,* within 4 weeks of biopsy/surgical procedure
Follow-up Assessment **(F1)**	Clinical Site	ACR	at 12-16 months and 24-30 months following the initial study MRI
Pathology Report [c] **(P1)**	Clinical Site	ACR	*as needed,* within 4 weeks of biopsy/surgical procedure
Surgical Report[c] **(S2)**	Clinical Site	ACR	*as needed,* within 4 weeks of biopsy/surgical procedure
Surgical Pathology Report[c] **(S5)**	Clinical Site	ACR	*as needed,* within 4 weeks of biopsy/surgical procedure
Pathology Evaluation Forms: Excisional **(PA)** Core Needle Biopsy **(PE)** Mastectomy **(PD)**	Clinical Site	ACR	Within 4 weeks of biopsy/surgical procedure
MRI Quality Assessment Form **(QA)**	QC Committee Reader	ACR	Per Section 12.2.2
Re-Reader Mammogram Form **(XC)**	QC Committee Reader	ACR	*as needed* per Section 13.3
Protocol Variation Form **(PR)**	Clinical Site/DMC	ACR	*as needed*, site will be notified of addition to case calendar

a. Maintain onsite and available for audit
b. FAX 215-717-0936
c. Non Web/**reports

8.6.5 All standard form items will be submitted through the ACRIN website at www.acrin.org. Before a form can be submitted, the user must complete all required information for that form including the study number (6667), the case number, patient initials, and the institution's ID number.

9.0 INSTITUTIONAL AUDITS

9.1 Institutions will be eligible for on-site audit as soon as they accrue 25 participants. If an audit is acceptable, a subsequent audit will be scheduled 12 months after the initial audit date. If an audit is unacceptable, a follow-up audit will be scheduled as per the ACRIN Audit Manual guidelines. Auditors will follow procedures established by the Cancer Imaging Program (CIP) of the NCI. Instructions for preparing for the audit will be sent to sites in advance of the audit date. With these instructions, the auditors will specify which case records will be reviewed during the audit. Auditors will review on-site records against the reviewed data, and they will record their findings on specially prepared questionnaires. Major discrepancies will be forwarded to the appropriate oversight body within ACRIN. IRB procedures, approvals, and consent forms will be also reviewed at the audit.

9.2 To help sites prepare for audits and assure that clinical RAs maintain records appropriately, ACRIN staff will offer training. This training will cover all aspects of data collection, but will include special instructions for finding and filing the kinds of source documentation needed to verify the accuracy of submitted data for this trial.

9.3 **Source documentation**: Data elements that are expected to be extracted from the medical record (patient history, official clinical interpretations of images, pathology or surgery results) and recorded on the case report forms (CRFs) will be audited against the appropriate component of the medical record. Data elements gathered from signed patient questionnaires may be documented on the CRF. The image interpretation data beyond that documented in the radiology report may be recorded on the CRF and is accepted as source documentation if signed by the MD. At the time of audit, the auditor will verify the occurrence of the imaging examination, the reader, and the date on which the exam took place from the medical record. Any use of an approved CRF as source documentation requires that the CRF be signed and dated and refer to the source of the information (patient questionnaire, CT, MR, etc.). Section 9.7 includes a listing of study-specific forms and the source documentation that will be accepted at the time of the audit. Any use of CRFs as source documentation where it is designated the information will be audited against the medical record will be considered a discrepancy.

9.4 **Institutional Review Board:** Sites must have on hand documentation of IRB approval prior to subject registration, including a copy of IRB approval of initial application, a copy of IRB approval of modifications, and copies of annual renewal(s).

9.5 **Equipment Safety or Service Reports**

These records will be audited only if deemed necessary by the Principal Investigator or by the Quality Control Committee.

Mammography: Obtain copies of *Mammography Physicist Reports* for the previous 18 months or the duration of the study (whichever is less) for review at the time of the audit. Physicist reviews must be *performed annually per ACR guidelines* and reports are maintained by the facility. Sites must have Mammography Physicist Reports documenting annual review.

MR Scanner: Obtain copies of *MRI Preventive Maintenance Reports* for the previous 18 months or the duration of the study (whichever is less) for review at the time of the audit. Preventive maintenance is usually performed at least once every 3 months by the scanner manufacturer's service engineer and reports may be maintained by the facility or the manufacturer. Sites must have MR Preventive Maintenance Reports documenting quarterly service.

9.6 **Research Records:** Maintain *source documentation* for each case that substantiates the data reported to ACRIN.

Source documentation includes the following:

- hospital chart or legible copies
- clinic chart or legible copies
- surgery reports or legible copies
- pathology reports or legible copies
- mammography reports or legible copies
- MRI reports or legible copies
- ultrasound reports or legible copies
- forms signed and dated by the subject
- follow-up form from phone interview signed and dated by the research assistant
- ACRIN case report forms signed by the physician
- worksheets signed by the physician which are used by research staff to submit the data on case report form(s)
- verification of receipt of submitted case report forms (mailed or emailed from ACRIN to site)

Source documentation must verify the eligibility criteria and data submitted on all case reporting forms. If an item is *not mentioned* (e.g., history and physical with no mention of a psychological condition) it will be assumed it is *not present*.

It is suggested that the research record for each case contain copies of the source documentation for the data reported to ACRIN. Copy the source documentation as you abstract the data from the primary record. This will prevent a discrepancy and inability to document the data reported when reviewed by auditors.

9.7 Audit/Source Documentation

Case Reporting Form	Data Items	Source Documentation
Eligibility Checklist **(A0)** (Patient registration must occur within 2 business days of initial MRI scan)	**Recent biopsy confirmed breast cancer**	Path report (P1)**
	Negative or benign mammogram	Mammogram report (I2)**
	Negative or benign CBE	Hospital or clinic chart or legible copy of A0 form completed, signed, and dated by subject **and** signed and dated by RA
	Treatment plan, treatment	
	Exclusion criteria	
Initial Evaluation Form **(I1)**	**Patient history** (menopausal status, date of last period, # of full term pregnancies, age at menarche, age at menopause, breast implant, history of hormone use, history of prior biopsy in study breast)	Hospital or clinic chart or legible copy of I1 form completed, signed, and dated by subject **and** signed and dated by RA
	Breast cancer diagnosis (histology, date of diagnosis, laterality)	Path report **(P1)****
Initial Mammogram Assessment Form **(IA)**		Mammogram Report **(I2)**** **and** IA form*** completed, signed, and dated by RA **or** MD
Ultrasound Form **(IS)** *as needed*		Ultrasound Report **(DR)**** **and** IS form*** completed, signed, and dated by RA or MD
Ultrasound Report **(DR)**		Ultrasound Report (DR) **
Initial MRI Assessment Form **(M3)** (Patient registration must occur within 2 business days of initial MRI scan)		MRI Report **(ME)**** signed and dated by study MD **and** completed M3 form*** signed and dated by RA or MD **OR** MRI Report (ME)** signed and dated by non-study MD and completed M3 form*** signed and dated by study MD
Biopsy Procedure Form **(AB)** *as needed*	If biopsy, excision, mastectomy or other surgery is performed on contralateral (study) breast	Pathology Report **(P1)**** *as needed* **and** Biopsy Procedure Form (AB)***, completed, signed, and dated by RA or MD
Post-MRI Mammogram Assessment Form **(IM)**		Mammogram Report **(I2)**** **and** IM form*** completed, signed, and dated by RA or MD

MRI Short Interval Imaging Form **(M4)**		MRI Report **(ME)**** signed and dated by study MD **and** completed M4 form*** signed and dated by RA or MD **OR** MRI Report (ME)** signed and dated by non-study MD and completed M4 form*** signed and dated by study MD
Pathology Evaluation Form **(PA, PD, PE)** *as needed*	If biopsy, excision, mastectomy or other surgery is performed on contralateral (study) breast	Pathology Report **(P1)** ** *as needed* PA, PD, and PE Forms completed, signed, and dated by RA or MD
Protocol Variation Form **(PR)**	Reviewed for cases in which a variation has been found.	Completed, signed, and dated by RA
F1 Follow-Up Assessment Form **(F1)** To be collected 12 to 16 months after initial study MRI and 24-30 months after the initial study MRI*	If CBE is performed on contralateral (study) breast 0-16* months following initial MRI	Hospital or clinic chart or legible copy of F1 form*** completed, signed, and dated by RA or MD
	If Mammogram, Ultrasound, or MRI is performed on contralateral (study) breast 0-16* months following initial MRI	Mammogram Report **(I2)**** Ultrasound Report **(DR)**** MRI Report **(ME)**** *as needed* **and** F1 Form*** completed, signed, and dated by RA or MD
	If biopsy, excision, mastectomy or other surgery is performed on contralateral (study) breast 0-16* months following initial MRI	Pathology Report **(P1)**** *as needed* **and** F1 Form*** completed, signed, and dated by RA or MD

Follow-up information after 12 and 24 months post the study MRI will only be obtained in the subset of participants with an abnormal finding identified at the initial 12 and 24 month follow-up evaluation. In this group of patients with abnormal findings identified in the 12 and 24 months post MRI, any information from studies (CBE, imaging, pathology) resulting from the abnormal finding at 12 and 24 months will be collected up to 16 months post the initial study MRI. In addition, abnormal findings identified at the 24-month follow-up evaluation will be collected up to 30 months post the initial study MRI.

** Clinical reports identified as source documentation must include patient's name, date of imaging or procedure, the clinical information, and the signature of the examiner/reader.

***The image interpretation data beyond that documented in the radiology report may be recorded on the CRF and is accepted as source documentation if signed by the MD (see Section 9.3).

10.0 IMAGE COLLECTION

10.1 The following images are required to be submitted to ACRIN Image Archive (see address below): 1) all MR images and 2) original mammogram and sonogram ONLY for cases in which cancer has been identified.

10.1.1 When digitizing and direct transfer or electronic media (CD, disk, tape) of any required film images are not available, original films must be submitted via mail for digitization at the DMC and subsequent entry to the image archive. All original mammograms will be digitized and returned by overnight courier within 48 hours. While it is the preference of ACRIN that all patient identifiers be removed from the films to be submitted, we recognize that MQSA requirements may prevent you from doing so. If films are submitted with patient identifiers, they will be masked during the scanning process in order to maintain future patient anonymity. Mailed film images or images on CD should be addressed and sent as follows:

ACRIN Image Archive
ACRIN 6667 Images
American College of Radiology
1101 Market Street, Suite 1400
Philadelphia, PA 19107
Attn: Anita Murray

10.1.2 Where required, images stored in the ACRIN Headquarters image archive may then be routed to other sites involved, using either FTP or CDROM where appropriate, for purposes of secondary review.

11.0 IMAGE INTERPRETATION

11.1 Mammography

Mammograms will be interpreted at the host institutions and coded according to the ACR BI-RADS™ Lexicon. This coding system includes: 1.) breast composition, 2.) findings, and 3.) overall assessment and recommendations. The overall assessment will be performed according to a 5 point scale as indicated in the ACR BI-RADS Lexicon.

11.2 MRI Examination

MR images will initially be searched for the presence of enhancing lesions after contrast administration. The interpretation scheme has been proposed by a task force of the ACR (Debra Ikeda, MD, Chair and Nola Hylton, PhD, Co-Chair) and is included as Appendix IV**.** This includes a classification of lesion type, shape, lesion borders, lesion distribution and internal architecture. Lesions that demonstrate malignant features will undergo further evaluation, which may include repeat MRI, US, and/or biopsy under MRI or US guidance. All other cases will be followed according to protocol. Features that will be considered suspicious for malignancy include:

1. ductal enhancement
2. area enhancement in a segmental distribution
3. focal mass enhancement greater than 5 mm with
    a. irregular or spiculated margins
    b. lobulated margins without nonenhancing septations
    c. any solid enhancing focal mass with rim enhancement

It will be possible to recommend additional imaging (US, mammography or repeat MR) based on the MR findings. In these cases, both an initial assessment of "0, additional imaging recommended" and a final assessment (1-5) after the ultrasound, mammography or repeat MRI will be recorded. It will be possible to recommend short interval follow up based on the MRI. In these cases, both the initial "3, probably benign short-interval follow up" assessment and recommendation and the final assessment and recommendation within 1, 3 or 6 months post initial MRI will be recorded. At the time of the short interval follow-up MRI, a definitive negative/benign or suspicious-recommend biopsy assessment must be given. Continued short interval follow up MRIs will not be an option after the first short interval MR exam.

12.0 METHODS

12.1 Mammograms

All study participants will have a negative or benign mammogram (BIRADS 1 or 2) of the study breast prior to entry and within 90 days of the MRI. If a unilateral mammogram is performed of the study breast, the study breast must be stated to be negative or benign (BIRADS 1 or 2). Separate assessments of each breast are not required in a bilateral mammogram; therefore, if a bilateral mammogram is performed with no mention of any abnormality of the study breast, the study breast is negative. (Example of a study-eligible mammogram report without mention of the study breast: bilateral mammogram, Impression: Highly suspicious mass in the right breast; biopsy recommended.) Either a screening or diagnostic negative or benign mammogram of the study breast is acceptable. Mammograms will be interpreted and coded according to criteria described below:

1) All sites will perform mammography in accordance with the standards set by the American College of Radiology (ACR).
2) All mammographic studies will consist of a cranio-caudal and medio-lateral oblique view. Additional views are allowed as needed to include all breast tissue.
3) Appropriate use of spot magnification views will be performed prior to final assessment and recommendation.

12.2 MRI Examinations

12.2.1 There are many acceptable methods of performing breast MRI. While multiple methods of MR acquisition will be accepted in this study, the following minimum standard criteria must be met for participation:

- 1.5T or greater magnet and dedicated breast surface coil
- Minimum of one pre-contrast and two post-contrast enhanced 3D T1 weighted gradient echo sequences (TR<60 msec; TE<20 msec)
- Initial post-contrast images of the study breast must be obtained within 4 minutes of contrast injection with the second post-contrast scan ending no later than 8 minutes following injection. Additional post-contrast scans beyond 8 minutes are acceptable at the site's discretion.
- Both bilateral and unilateral scans, using a 3 mm slice thickness, will be accepted providing the minimum resolution requirements are met:
    - Voxel sizes less than 0.9 mm in the frequency encoding direction, less than 1.8 mm in the phase encoding direction, and less than or equal to 3 mm in the slice direction, providing full coverage of the breast of interest. This might be achieved in one of the following ways:
    - Bilateral in axial or coronal planes: FOV 36 cm or less with 256x512 matrix. Only in cases in which the recommended FOV of 36 cm is not sufficient to cover the full area of breast tissue, the FOV may be increased to 40 cm.
    - Unilateral in axial or coronal planes or bilateral in sagittal plane: FOV 20 cm or less with 128x256 matrix. Only in cases in which the recommended FOV of 20 cm is not sufficient to cover the full area of breast tissue, the FOV may be increased to 22 cm.
- Acceptable method of fat suppression, including available software to suppress fat signal and/or subtraction methods.

12.2.2 A detailed description of the individual site's specific methods of performing breast MRI (part II of the Protocol-Specific Application; see section 6.1 and Appendix V) will be submitted and reviewed prior to site enrollment. A quality assessment will be performed on a subset of study subject MR scans performed at each participating site. The first

study scan performed by each site will be reviewed as well as a random sampling of the remaining cases. This assessment will be performed under the direction of the Study QC Committee (R. Edward Hendrick, Chair).

12.3 Ultrasounds

All study participants will have a negative or benign mammogram (BIRADS 1 or 2) of the study breast at entry. Subjects may or may not have an ultrasound performed prior to study entry. This information will be recorded on the initial imaging review form. If subsequent additional imaging by ultrasound is recommended based on MRI findings, ultrasound will be performed by a radiologist in accordance with the standards set by the American College of Radiology (ACR).

12.4 Biopsy

12.4.1 All lesions identified as suspicious or highly suggestive of malignancy on MR during initial or final assessment (category 4 or 5) will undergo biopsy. Biopsy of lesions may be in the form of a core needle biopsy or excisional biopsy. Excisional biopsy will be required in all cases that needle biopsy does not yield a positive or concordant benign biopsy.

If the same lesion is detectable on multiple modalities (for example, US and MRI) the biopsy will be guided by the most convenient method. If the lesion is identified on only one study, that study must be used to guide the biopsy. Therefore, mammographically, sonographically, and clinically occult enhancing lesions that are identified as suspicious by MRI require biopsy under MR guidance. Excisional biopsy will be required in all cases that core needle biopsy does not yield a positive or concordant benign biopsy.

12.5 Pathology

Pathologic samples will be processed and interpreted according to the protocol described below. Histology will be recorded from specimen processing at the originating institutions. A core pathology site is not proposed in this study. This was determined based on findings from the International Breast MRI Consortium studies where high correlation between site-specific pathology and core pathology findings were found. In addition, Dr. Stuart Schnitt and colleagues (Collins, 2000) recently reported a high correlation between findings from site-specific pathology readings and core pathology institution readings. In their study they report that the core central diagnosis and local site diagnosis were concordant in 1,925 core needle biopsy cases (86%). The core central diagnosis was in agreement with the local site diagnosis in 99% of benign cases, 97% of invasive cancer cases, 84% of DCIS cases, 64% of ADH cases, and 58% of ALH/LCIS cases. This level of agreement was comparable to that observed among 552 open surgical biopsies obtained from patients in this study and subjected to central pathology review. Thus, the expense and risks associated with tissue transportation and core pathology site readings are not considered justified for this study.

12.5.1 *Specimen Processing at Originating Institution*

An English translation of the final diagnosis must be submitted with any pathology report originating in a language other than English.

12.5.2 *Core Needle Biopsies*

Core biopsies should be processed according to the routine at the individual institutions.

12.5.3 *Excision Specimens*

Excision specimens should be oriented by the surgeon and inked by the pathologist prior to sectioning. Application of inks of different colors to the various margins is recommended in order to help maintain orientation of the tissue sections through processing. The specimens should then be processed according to the routine at the

individual institutions. At a minimum, sections for histological examination should include all radiographically and macroscopically abnormal areas as well as random sections of grossly benign breast tissue adjacent to the abnormalities.

12.5.4 *Mastectomy Specimens*

All specimens will be labeled in the 12:00 axis by the surgeon and transported to pathology by the normal mechanism. After arriving in pathology, the deep margin of the specimen will be inked, then the specimen will be chilled until the fat solidifies. The specimens will then be placed on a mechanical slicer and sliced at 5 mm intervals in the sagittal plane from lateral to medial. The slices will be displayed for gross examination. The radiologist and pathologist will jointly examine the gross specimens guided by the MRI studies. Each lesion in the MRI examination will be located in the specimen. It will be indexed and measured in all 3 planes. A description of the location of the lesion that includes the quadrant and distance from the nipple will be recorded. The lesion will then be sampled and submitted for histologic analysis. After all MRI visible lesions are sampled, the specimen will be examined for the presence of additional lesions. All additional lesions will also be indexed and measured and sampled for histologic analysis.

12.5.5 *Section Classification*

Sections will be classified as benign, atypical, in situ cancer, or invasive cancer.

12.5.6 *Invasive Cancer*

Invasive cancer will be graded and described according to its histologic type: Infiltrating ductal carcinoma NOS, Infiltrating lobular carcinoma, Infiltrating carcinoma with ductal and lobular features, Tubular carcinoma, Mucinous carcinoma, or Medullary carcinoma.

12.5.7 *In Situ Cancer*

In situ cancer will be described by its histologic type: Lobular, Ductal and Lobular, and Ductal. It will also be described by its growth pattern: Comedo, small areas of necrosis, Cribriform, Solid, Micropapillary, and papillary.

12.5.8 *Benign Lesions*

Benign lesions will be described as Benign, non atypical, NOS; Fibroadenoma, Radial scar; or other.

12.5.9 *Atypical Lesions*

Atypical lesions will be described as demonstrating lobular or ductal features.

12.6 Patient Clinical Follow-up

All participants may be contacted to obtain interim information at 12 months and at 24 months after initial imaging that will include questions regarding any breast procedures (CBE, imaging and/or interventions) performed in the months since the initial study MRI and their dates and results. For all procedures that were not negative or benign, additional follow up to 30 months will be collected, including additional imaging and any pathology resulting from abnormal findings during the months post the study MRI. This follow-up information may be collected from the patient in writing through a study-specific follow-up questionnaire or through telephone or in-person interview. All information obtained through a questionnaire or telephone or in-person interview will be recorded on the Follow-up Assessment Form (F1) and submitted to the ACR.

13.0 ORGANIZATION AND MANAGEMENT

13.1 Data and Statistics Center

The Data and Statistics Center will be headquartered at Brown University under the Direction of Dr. Constantine Gatsonis who will be responsible for the establishment of methods for data collection, management, analysis, and monitoring. The Data and

Statistics Center will be composed of a **Statistics Center** at Brown and a **Data Management Center** at the Philadelphia Offices of the American College of Radiology. The functions of the Statistics Center include protocol design and monitoring, performance of interim and final analyses, and preparation of reports on the results of these analyses. The Statistics Center is actively involved in protocol and data forms development, working with the principal investigator and other study co-investigators in defining important research questions and ensuring that the necessary data will be collected in order to fully address and analyze these questions. The Statistics Center will evaluate any proposed changes in the way data will be collected in order to fully address and analyze these questions. The Statistics Center will evaluate any proposed changes to the protocol once it has been opened to accrual.

13.2 The Data Management Center

The Data Management Center at the ACR will participate in development and implementation of the protocol and will be responsible for forms development; patient registration; data collection, review, and entry; transmission of data to the Statistics Center; and assisting in meeting management. It will also implement a system of data monitoring including IRB and assurance approvals and on-site audits. The Data Management Center will also house the database for this study, including the digital images database and the case report form database.

13.3 A Quality Control Committee

A Quality Control Committee will be established for the protocol in order to make certain all participating institutions adhere to the imaging guidelines and that the quality of imaging is maintained across institutions. The Committee will include the protocol statistician, Dr. Lehman, Dr. Schnall, and Dr. Hendrick. In addition, imaging physicists from the manufacturers of the MRI instruments represented in the consortium will be available as consultants to the Quality Control Committee. This is critical in order to accurately assess the ability of a particular instrument to meet protocol requirements, address image quality issues at individual sites, and ensure the integrity of image translation into the digital image database. The principal investigator at each institution will be responsible for checking the quality of images at his or her own institution. The Quality Control Committee provides a means of further assuring adherence to the agreed upon imaging methodology as set forth in the study protocol.

As Chair of the QC Committee, Dr. Hendrick will coordinate image reviews. Prior to opening, a site must submit an MR-guided patient biopsy case to ACRIN for review and approval by Dr. Hendrick; subsequent to opening, the first enrolled case will also be sent to Dr. Hendrick via ACRIN for review. This will allow deviations from protocol and poor quality studies to be discovered at the earliest possible time. Studies that do not meet quality standards will result in notification of the Chair of the Quality Control Committee and the study PI. The site PI and RA will be notified by either the QC Committee Chair or the study PI and asked to submit plans to rectify any systemic problem. In addition, there will be an overread of mammography, sonography, and MRI (if performed because of a cancer identified during the study).

13.4 Data and Safety Monitoring Committee (DSMC)

The Data and Safety Monitoring Committee (DSMC) will include experts in breast cancer imaging and treatment and a statistician. The DSMC will be identified early in the

study and will convene at regular intervals (1 year) to review progress in the key elements of the study, including accrual, interim results, modifications to the protocol, and study termination. It will serve to protect patient safety, scientific ethics, and data impartiality.

14.0 ADVERSE EVENT REPORTING

14.1 Definition of Adverse Event

An **Adverse Event (AE)** is any untoward, undesired, and unplanned medical occurrence in a patient that does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or physiological observation), symptom or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Any symptom, sign, illness, or experience that develops or worsens in severity during the course of the study, including intercurrent illnesses or injuries, should be regarded as an adverse event. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- Results in study withdrawal
- Is associated with a serious adverse event
- Is associated with clinical signs or symptoms
- Leads to additional treatment or further diagnostic tests
- Is considered by the investigator to be of clinical significance

14.2 Definition of Serious Adverse Effect

Adverse events are classified as serious or non-serious. A **Serious Adverse Event (SAE)** is defined as any untoward medical occurrence/AE that is:

- Death.
- Life-threatening (refers to any adverse event that places the subject at immediate risk of death from the event as it occurred; life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death, but as it actually occurred did not create an immediate risk of death).
- Inpatient hospitalization and/or prolongation of an existing hospitalization (*hospitalization* refers to an overnight admission). Emergency room visits are not considered serious until one of the above criteria is met. Any elective hospitalization for a pre-existing condition that has not worsened does not constitute and SAE.
- Persistent or significant disability or incapacity (substantial disruption in a person's ability to conduct normal daily living activities).
- A congenital anomaly or birth defect.
- Other medically important event.

Important medical events are those based upon appropriate medical judgment that may not be immediately life-threatening, but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above.

A *pre-existing condition* is one that is present at the start of the study. A pre-existing medical condition is defined as an adverse event if the frequency, intensity, or character of the medical condition worsens during the study period. At the screening visit, any clinically significant findings/abnormalities should be recorded as a pre-existing

condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events. If there is any doubt whether the adverse event constitutes an SAE, it should be treated as serious.

14.3 Adverse Event Grading

Grade refers to the severity (intensity) of the adverse event:

1—Mild: AE is noticeable to the participant but does not interfere with routine activity.

2—Moderate: AE interferes with routine activity but responds to symptomatic therapy/rest.

3—Severe: AE significantly limits the subject's ability to perform routine activities despite symptomatic therapy.

4—Life-threatening or disabling.

5—Fatal.

14.4 Expected Adverse Events from MRI

Hemorrhage (hematoma at the injection site)

Infection (catheter related infection) at the injection site

14.5 Expected Adverse Events from Contrast Agent (gadolinium)

Nausea

Headache

Hives

Temporary low blood pressure

Allergic reaction

14.6 Expected Adverse Events from Needle Placement

Minor discomfort

Bleeding

Infection

Bruising

14.7 Reporting of Adverse Events

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

14.8 When to Report

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

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

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

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

14.9 How to Report

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

14.9.2 Completed expedited reports should be sent to:

NCI
Program Director
Re: Adverse Event Report
Cancer Imaging Program
6130 Executive Blvd., MSC 7412
Bethesda, MD 20892-7412

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

14.9.3 A copy of all expedited adverse event reports should be sent to **ACRIN** by fax at **(215)-717-0936.** All fatal adverse events should be reported by telephone within 24 hours of the event. To make a telephone report to ACRIN, call **(215)-717-4763**, available 24 hours a day (recorder after hours from 5 PM to 8 AM Eastern Time).

14.9.4 All expedited adverse event reports should be sent to your local Institutional Review Board (IRB). Adverse events not requiring expedited reporting are normally reported to your local IRB in an annual report and/or continuing review. Please refer to your local institution's policies regarding AEs, SAEs, and safety reports.

15.0 STATISTICAL CONSIDERATIONS

REMOVED FROM WEB VERSION

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APPENDIX I

SAMPLE CONSENT

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6667

MRI Evaluation of the Contralateral Breast in Women with a Recent Diagnosis of Breast Cancer

LIST INVESTIGATORS AND STAFF INVOLVED IN CONSENT PROCESS:
NAME, M.D., Ph.D., Associate Professor, Dept. of Radiology, *phone number*
NAME, M.D., Assistant Professor, Dept. of Medicine/Oncology, *phone number*
NAME, MRI Technologist, Dept. of Radiology, *phone number*
NAME, Research Coordinator, Dept. of Radiology, *phone number*

Emergency Number: Hospital, *phone number*

INVESTIGATOR'S STATEMENT

We are asking you to be in a research study. The purpose of this consent form is to give you the information you will need to help you decide whether to be in this study. Please read this form carefully. You may ask questions about the purpose of the research, what we will ask you to do, the risks, the benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all of your questions, you can decide if you want to be in this study or not. This process is called "informed consent." We will give you a copy of this consent form for your records.

You have been selected for participation in this study because you have been diagnosed with breast cancer within the past 60 days and have not been treated with hormonal therapy or chemotherapy. This study involves the breast without cancer. Women with a previous diagnosis of cancer in one breast are at risk of developing cancer in the other breast. Your physical exam and mammogram have indicated that your breast without cancer is normal. This study involves performance of an MRI on the breast without cancer to determine if MRI is able to detect cancers that are not detectable by clinical breast exam or mammogram.

This study involves [*a research MRI and*] the collection and review of health care information. This includes information from your medical record, questions about your hormonal and family history, the review of your mammograms, MR images, and pathology slides if you have biopsies or other surgery of the breast without cancer. To participate in this study, you are being asked to [*have a breast MRI,*] give your permission for study personnel to document your medical and family history, review and copy portions of your medical records, and submit films, computer images, and reports from your mammogram, MRI, and biopsies of your breast without cancer. Data, copies of reports, mammogram films and MR images will be sent to the American College of Radiology (ACR) in Philadelphia, PA.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

You will be one of approximately 100 women to be enrolled in this research study at [*institution*]. This study is sponsored by the American College of Radiology Imaging Network (ACRIN) and involves multiple institutions. Approximately 1,000 women will be enrolled in this study nationwide.

PURPOSE

The purpose of this study is to investigate the usefulness of high resolution MRI (magnetic resonance imaging) in evaluating patients who have a recent breast cancer diagnosis and no known disease by mammography or clinical breast exam in the breast without cancer.

DESCRIPTION OF THE MRI PROCEDURE

You will receive an MRI of your breast tissue. In magnetic resonance imaging (MRI), a magnet linked to a computer creates detailed pictures of areas inside the body without the use of radiation. For the MRI examination you will change into a hospital gown and lie on your stomach on the scanning table with your breasts suspended through an opening in the table. Wire coils will be placed on either side of your breast to receive the very weak radio signals from the breast. The table will slide into a tube-like machine that contains the magnet. Gentle compression will be applied to the breast. This is less than that used in a mammogram and usually results in no discomfort. A computer attached to the MRI machine will process the radio signals into a picture and spectrum of the breast. The spectrum gives your doctors information about the chemical composition of the breast.

Approximately 20 minutes into the procedure, an MRI contrast agent called Gadolinium will be injected into a vein in your arm and additional images will be taken. Although the placement of the needle may cause discomfort, gadolinium is considered safe and is routinely used for examinations of the breast as well as other parts of the body. This contrast agent helps to improve the images of your breast by making breast tumors easier to see.

The entire MRI procedure will take 30-40 minutes and will be performed by a technician. A physician will be available throughout the study. You will have to lie still during this time. A padded table will be used to keep you from becoming too uncomfortable.

ADDITIONAL PROCEDURES

If a suspicious area is noted on your MRI, additional studies may be performed, including mammography, ultrasound and or additional MR examinations. In addition, a biopsy may be recommended for certain types of lesions.

ADDITIONAL INFORMATION

Approximately 12 months after your initial study MRI, and again approximately 24 months after your initial study MRI, you will be contacted by a study coordinator or other staff members. Information regarding any breast imaging, biopsies, clinical exams, or other procedures you have had since your initial study MRI will be collected at that time. You will be asked for permission to borrow any imaging studies that have been obtained since your initial study MRI.

HOW LONG WILL I BE IN THE STUDY?

You will receive an evaluation of the breast without cancer within 60 days of being diagnosed with breast cancer and starting chemotherapy. It is possible you will receive a 6-month follow-up MRI (magnetic resonance imaging) test, depending on the recommendation of your initial screening. You may be contacted approximately 12 months and 24 months after the initial study MRI to collect follow-up data including any imaging (for example, mammogram, ultrasound and MRI), breast biopsies, and

pathology results**.** Depending on the results of examinations you have had during the 12 months and 24 months since the MRI, you may be contacted again for additional information for up to 30 months after the MRI. **Your participation in this study will not exceed thirty months.**

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for side effects. You should discuss possible side effects with the researcher and/or your regular doctor. Many side effects go away shortly, after the MRI and gadolinium contrast is stopped, but in some cases side effects can be serious or long-lasting. This study may cause all, some, or none of the side effects listed below. In addition, there is always the risk of uncommon or previously unknown side effects occurring.

It is also possible that your MRI may detect an abnormality not previously detected by mammography or physical examination. That is, mammography and palpation may not be sensitive enough to detect lesions an MRI would find. It is also possible that the MRI may be too sensitive and will detect changes in the breast that are not malignant. These may require biopsy to prove that they are not malignant and this could cause you unnecessary worry, surgery, and expense. Your physician may recommend that you have that area biopsied under MRI or ultrasound guided needle localization. Although it is possible that an abnormality may represent cancer, it may also be benign.

In addition, some of the questions you are asked may be personal and embarrassing to you. You may refuse to answer any of the questions. Although we will make every effort to keep your information confidential, no system for protecting your confidentiality can be completely secure.

Risks Associated with MRI (Magnetic Resonance Imaging)

While there are no significant risks from MRI, you may be uncomfortable due to the loud noise and/or feelings of claustrophobia during the MRI. If you experience a sensation of claustrophobia while in the magnet, the MRI will be immediately stopped. Being pregnant or having a pacemaker or other electromagnetic device or vascular clip in your head excludes you from this study. No serious biological effects have been reported from the magnetic fields used in clinical MRI.

Likely
The MRI unit is noisy.
Some patients feel claustrophobic in the MRI magnet.

Risks Associated with Gadolinium

Approximately two percent of patients experience some side effects with the use of Gadolinium; however, they are mostly mild (nausea, headache, hives, temporary low blood pressure). Serious side effects are very rare.

Less likely
Headaches and nausea

Less likely, but Serious
Allergic reaction

Risks Associated with Intravenous Catheter Placement

Likely
Minor discomfort

Less likely
Low risk of bleeding, infection, and bruising

Risks Associated with Biopsies

Likely
Minor discomfort

Less likely
Low risk of minor pain and bleeding
Infection
Bruising
Collection of air or gas in the chest cavity (pneumothorox)

Reproductive risks
You must not be pregnant when you join this study. Talk with your physician about the risks associated with pregnancy during your cancer treatment.

BENEFITS
There will be no direct benefit to you from being in this study. We hope that the results of this study may help patients with breast disease in the future.

PAYMENT
You will receive no payment for taking part in this study.

COSTS
Taking part in this study may lead to added costs to you or your insurance company. Please ask about any unexpected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

ALTERNATIVES
If you choose not to participate in this study, your care will not be affected. You will have an MRI and further evaluation as recommended by your radiologist and primary health care provider.

WITHDRAWAL
Your participation in this study is *voluntary*. If you do not participate, you will not be contacted again about this study. You may withdraw from this study at any time. You will continue to receive your usual medical care whether or not you decide to participate in this study. Questions about this study

and/or your participation in the study may be addressed to *principal investigator*, your doctor, or research study staff.

CONFIDENTIALITY

We will keep your identity as a research subject confidential. The information about you will be numbered and linked to your name on a master list that will be kept indefinitely. The master list and your study charts will be kept indefinitely for the purpose of analysis and will be destroyed at the close of the study when analysis is complete. Only the researchers, the NCI, the Institutional Review Board, the American College of Radiology, and the Statistical Center at Brown University in Providence, RI will have access to information about you.. The information reported about you will be identified by a study ID#. **Your name will never be used in any reports of the results of these studies.**

Your records will be identified only by a study identification number at the headquarters of the American College of Radiology in Philadelphia, PA and at the Statistical Center at Brown University in Providence, RI. The confidentiality of the central computer records is carefully guarded. During their required reviews, representatives of the National Cancer Institute (NCI), American College of Radiology (ACR), Institutional Review Board, or other organizations that have a role in the conduct of this study may have access to medical records which contain your identity.

Your mammograms may be requested for the study. If so, your name and other identifiers will be masked and the films, identified by your study identification number, [*will be copied and sent to the American College of Radiology*] *or* [*will be sent to the American College of Radiology*] to be copied onto a computer. These computer copies are referred to as "digitized" films. After the films have been digitized the original films will be returned.

MR images are stored on a computer. Your name and other identifiers will be replaced by your study identification number before copies of the images are sent to the American College of Radiology.

OTHER INFORMATION

The data and images you provide, identified only by your study identification number, will be retained indefinitely by the American College of Radiology and may be used in other studies.

CONTACT PERSONS

For more information concerning the research and research-related risks or injuries, contact Dr. XXX, the investigator in charge at *(###) ###-####* or XXX, Research Coordinator, at *(###) ###-####*. In addition, you may contact the Institutional Review Board at *(###) ###-####* for information regarding patients' rights in research studies.

Signature of Researcher _____

Printed Name of Researcher _____ Date _____

SUBJECT'S STATEMENT

This study has been explained to me. I volunteer to take part in this research. I have had a chance to ask questions. If I have questions later about the research, I can ask one of the researchers listed on the first page. If I have questions about my rights as a research subject, I

can call the Institutional Review Board at *(###) ###-####*. I will receive a copy of this consent form.

I give permission to the researchers to use my medical records as described in this consent form.

Signature of Subject _____

Printed Name of Subject _____ Date _____

Witness _____Date_____

APPENDIX II

ACRIN 6667 MRI Evaluation of the Contralateral Breast in Women with a Recent Diagnosis of Breast Cancer

Inst.# _____ **Eligibility Checklist**

Case # _____ **(page 1 of 3)**

Eligibility Requirements (a response coded other than that prompted renders a patient ineligible for enrollment).

_____(Y) 1. Has the patient had a diagnosis of DCIS or invasive cancer in the non-study breast?

_____ (Y) 2. Will the study MRI be performed within 60 days of the initial biopsy proven (including FNA) cancer diagnosis?

___/___/____ 3. Date of initial biopsy demonstrating DCIS or invasive cancer in the non-study breast. (mm/dd/yyyy)

_____(Y) 4. Has the patient had a negative or benign mammogram and a negative or benign clinical breast exam of the study breast within 90 days of the MRI?

_ _/___/____ 5. Date of negative or benign mammogram (mm/dd/yyyy)

___/___/____ 6. Date of negative or benign clinical breast exam (mm/dd/yyyy)

___/___/____ 7. Scheduled Date of MRI (mm/dd/yyyy) [MRI must be within 90 days of CBE and mammogram, and within 60 days of biopsy of initial diagnosis.]

Eligibility Requirements: Exclusion Criteria (a response coded other than that prompted renders a patient ineligible for enrollment).

_____(N) 8. Are there any contraindications to the MR imaging outlined in Section 5.2.1 of the protocol?

_____(N) 9. Is the patient pregnant? (Gadolinium has not been approved for this population.)

_____(N) 10. Is the patient less than 18 years of age?

_____(N) 11. Are there psychiatric or psychological or other conditions which prevent a fully informed consent?

_____(N) 12. Has there been a previous breast biopsy in the study breast within the past 6 months, including FNA?

_____ (N) 13. Has the patient had an MR exam of the study breast within 12 months prior to the study MRI?

_____ (N) 14. Does the patient have current or recent history (within 6 months prior to the MRI) of adjuvant chemotherapy for cancer? (Patients receiving adjuvant hormonal therapy, tamoxifen, and/or aromatase inhibitors for **preventative** measures, not **therapeutic** measures, are eligible.)

_____(N) 15. Does the patient have a remote history of breast cancer as defined by biopsy-proven breast cancer diagnosis greater than 60 days prior to the study?

The following questions will be asked at Study Registration for enrollment onto 6667:

_____ 1. Institution person registering the case

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

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

____/____/____ (mm / dd / yyyy) 4. Date the study-specific Consent Form was signed (must be prior to study entry)

_____ 5. Patient's Initials (Last, First) (L, F)

_____ 6. Verifying Physician

_____ 7. Patient ID # (optional; this is an institution's method of internally tracking a patient to a protocol case number; may code a series of 9s)

____/_____/____ 8. Birthdate (mm/dd/yyyy)

_____ 9. Ethnic category

1 Hispanic or Latino
2 Not Hispanic or Latino
9 unknown

_____ 10. Race (check all that apply):

- ❑ American Indian or Alaskan Native
- ❑ Asian
- ❑ Black or African American
- ❑ Native Hawaiian or other Pacific Islander
- ❑ White
- ❑ Unknown

_____ 11. Gender (N/A)

_____ 12. Patient's country of residence (if country of residence is **other, complete Q18)**

1 United States
2 Canada
3 Other
9 Unknown

_ _ _ _ _ _ 13. Zip Code (5 digit code)

_____ 14. Patient's insurance status

1 Private insurance
2 Medicare
3 Medicare and Private insurance
4 Medicaid
5 Medicaid and Medicare
6 Military or Veterans Administration
7 Self-pay
8 No means of payment
9 Unknown/decline to answer
0 Other

_____ 15. Will any component of the patient's care be given at a military or VA facility?

1 No
2 Yes
9 Unknown

_____/_____/_____ 16. Calendar base date (date of registration)
(mm / dd / yyyy)

_____/_____/_____ 17. Date of Registration (must be within <u>two</u> business days after completion of MRI scan)
(mm / dd / yyyy)

_____ 18. Other country, specify (completed only if Q12 is coded *other*)

Completed by_____ Date form completed: ___/____/_____

Patient Signature _____

Signature of person entering data onto the Web _____

APPENDIX III
Definitions of Performance:

Whether the MR is positive or negative will be based on the BI-RADS assessment given to the exam. In the proposed study design, both an initial and final assessment are possible. For calculations of endpoints, the following definitions will be used:

Initial Negative MR: BI-RADS 1, 2, 3
Initial Positive MR: BI-RADS 0, 4, 5
Final Negative MR: BI-RADS 1, 2, 3
Final Positive MR: BI-RADS 4, 5

Note: Patients with recommendations for short interval follow up will have two "final" assessments and recommendations, one at the initial evaluation and the second at the short interval follow up evaluation. Continued short interval follow up will not be an option in this study. In other words, at the short interval follow up MRI, a final recommendation of biopsy or annual follow up will be made (assessment of 1, 2, 4 or 5).

The subset of probably benign lesions, including the initial and follow up MRI will be reported in detail descriptively in the final report. The percent of category 3 lesions that were recommended for biopsy after a short interval follow up MRI will be reported as well as the pathology from these biopsies.

True Positive: Final positive MR (BIRADS 4,5) associated with cancer diagnosis from biopsy recommended by MR finding

False Positive: Final positive MR (BIRADS 4, 5) with no known cancer diagnosis within 12 and 24 months, follow up at 12 and 24 months documents no interval biopsies or abnormal CBE, mammography, ultrasound or MRI findings during the 12 and 24 months since the initial study MRI. Please note that a definitive (e.g., fibroadenoma) benign biopsy result is mandatory to avoid excisional biopsy after negative core needle biopsy in this study. Note that initial category 0 MRIs are not included as false positives. However, the results from call back recommendations (BIRADS 0) will be reported in the PPV1 described below.

True Negative: Final negative MRI (BIRADS 1, 2) with no known cancer diagnosis within 12 and 24 months post initial study MRI (follow up at 12 and 24 months documents no interval biopsies since MRI in study)

False Negative: Final negative MR (BIRADS 1, 2) with cancer diagnosis confirmed within 12 and 24 months of study MRI.

Cancer Yield of MRI: Patients with true positives/all patients

Sensitivity of MRI: TP/all cancers diagnosed within 12 and 24 months of study MR (TP+FN)

Specificity of MRI: TN/FP+TN

PPV1 for call backs/additional imaging: TP/ BIRADS 0, 4, 5
PPV2 for biopsy: TP/BIRADS 4, 5

APPENDIX IV: ACR–BI-RADS®–MRI Lexicon Classification Form

For each of the following categories, select the term that best describes the dominant lesion feature.
Wherever possible, definitions and descriptions used in BI-RADS® for mammography will be applied to MRI of the breast. This form is for data collection and does not constitute a written MRI report.

LESION TYPE (select one)

A. Focus/Foci (Tiny spot of enhancement, < 5 mm) if only finding, *GO TO SECTION E*

B. Mass (Three-dimensional space-occupying lesion that is one process, usually round, oval, or irregular in shape).

Shape *(select one)*	**Description**
❑ Round	Spherical or ball-shaped
❑ Oval	Elliptical egg-shaped
❑ Lobular	Undulating contour
❑ Irregular	Uneven shape (not round, oval, or lobulated)

Margin *(select one)*	**Description**
❑ Smooth	Well-circumscribed and well-defined margin
❑ Irregular	Uneven margin can be round or jagged (not smooth or spiculated)
❑ Spiculated	Characterized by radiating lines

Mass Enhancement *(select one)*	**Description**
❑ Homogeneous	Confluent uniform enhancement
❑ Heterogeneous	Nonspecific mixed enhancement
❑ Rim enhancement	Enhancement more pronounced the periphery of mass
❑ Dark internal septation	Dark nonenhancing lines within a mass
❑ Enhancing internal septation	Enhancing lines within a mass
❑ Central enhancement	Enhancement more pronounced at center of mass

C. Non-Mass-Like Enhancement (that is in an area that is not a mass)

Non-Mass-Like Enhancement *(select one)*	**Description**
❑ Focal area	Enhancement in a confined area, less than 25% of quadrant
❑ Linear	Enhancement in a line that may not conform to a duct
❑ Ductal	Enhancement in a line that may have branching, conforming to a duct
❑ Segmental	Triangular region of enhancement, apex pointing to nipple, suggesting a duct or its branches
❑ Regional	Enhancement in a large volume of tissue not conforming to a ductal distribution, geographic
❑ Multiple regions	Enhancement in at least two large volumes of tissue not conforming to a ductal distribution, multiple geographic areas, patchy areas of enhancement
❑ Diffuse	Enhancement distributed uniformly throughout the breast

Non-Mass-Like Enhancement (internal enhancement) *(select one)*	**Description**
❑ Homogeneous	Confluent uniform enhancement
❑ Heterogeneous	Nonuniform enhancement in a random pattern
❑ Stippled, punctate	Punctuate, similar appearing enhancing foci, sand-like or dot like
❑ Clumped	Cobblestone-like enhancement, with occasional confluent areas
❑ Reticular, dendritic	Enhancement with finger like projections extending

toward nipple, especially seen on axial or sagittal images, in women with partly fatty–involuted breasts

D. Symmetric or Asymmetric (Bilateral scans only)

Symmetric or Asymmetric *(select one)*	**Description**
❑ Symmetric	Mirror-image enhancement
❑ Asymmetric	More in one breast than in the other

E. Other Findings *(select all that apply)*

Other Findings ***(select all that apply)***

❑	**None apply**	❑	**Edema**
❑	**Nipple retraction**	❑	**Lymphadenopathy**
❑	**Nipple invasion**	❑	**Pectoralis muscle invasion**
❑	**Pre-contrast high ductal signal**	❑	**Chest wall invasion**
❑	**Skin thickening (focal)**	❑	**Hematoma/blood**
❑	**Skin thickening (diffuse)**	❑	**Abnormal signal void**
❑	**Skin invasion**	❑	**Cysts**

F. Kinetic Curve Assessment

Kinetic Curve Assessment	**Description**
❑ Initial rise	Slow, medium, rapid
❑ Delayed phase	Persistent, plateau, washout

G. Assessment Category *(select one)*

Assessment Category *(select one)*	**Description**
❑ **Category 0** – Incomplete: Need additional imaging evaluation	Finding for which additional evaluation is needed
Final Assessment	
❑ **Category 1** – Negative	No abnormal enhancement, no lesion found (routine follow-up)
❑ **Category 2** –Benign finding	Benign, no malignant features; i.e. cyst, (routine follow-up)
❑ **Category 3** – Probably benign finding	Probably benign finding (short interval follow-up)
❑ **Category 4** – Suspicious abnormality	Low to moderate suspicion for malignancy (biopsy should be considered)
❑ **Category 5** – Highly suggestive of malignancy	High probability of malignancy (appropriate action should be taken)
❑ **Category 6** – Known cancer	Known, biopsy proven malignancy diagnosis on the imaged finding prior to definitive therapy (appropriate action should be taken)

APPENDIX V, revised May 6, 2003

ACRIN PROTOCOL-SPECIFIC APPLICATION

ACRIN 6667 – MRI EVALUATION OF THE CONTRALATERAL BREAST IN WOMEN WITH A RECENT DIAGNOSIS OF BREAST CANCER

This application is in addition to the ACRIN General Qualifying Application that can be found on the ACRIN web page (**www.acrin.org)**.

Name of Institution _____

ACRIN P.I. Name _____

Address _____

Address _____

Telephone _____

Fax _____

E-mail _____

Research Associate's Name _____

Name(s) of Radiologist(s) interpreting study mammograms at your site _____

Name(s) of Radiologist(s) interpreting study ultrasounds at your site _____

Name(s) of Radiologist(s) interpreting study breast MRIs at your site_____

Number of breast MRIs interpreted by above radiologist(s) (in order listed above)*

_____ _____ _____

Name(s) of Radiologist(s) performing breast MR wire locs or biopsies at your site_____

Number of breast MR wire locs or biopsies performed by named radiologist(s) (in order listed)**

_____ _____ _____

Have you submitted clinical breast MR image data for a previous IBMC/ACRIN study? Yes ____ No ____
(If no, a clinical breast MR case must be submitted for review for participation in 6667.)

Have you submitted MRI biopsy qualifying data for a previous IBMC/ACRIN study? Yes ____ No ____
(If no, an MRI-guided biopsy patient case must be submitted for review for participation in 6667.)

Do you have Internet access? Yes No

* Minimum number of 50 per radiologist required for study participation.
** Minimum of 5 per radiologist required for study participation.

Institution_____ Date _____

MRI Scanner Used for Breast MRI:

Manufacturer _____ Model _____ Field Strength _____ Tesla Dedicated Breast Coil? ☐Unilateral ☐Bilateral

MR Pulse Sequence Used for Contrast-enhanced Imaging:

Acquisition Plane (Axial, Sagittal, or Coronal)	Sequence Name ---------- 2D or 3D? (please check one)	Slice Thick-ness (mm)	Unilateral or Bilateral (please check)	FOV	Matrix	Chemically-selective Fat Suppression Used? ---------- Subtraction Performed?	Basic Sequence Duration (i.e., time between end of contrast injection and end of initial post-contrast sequence)	Time between end of contrast injection and end of second post-contrast scan	TR (ms)	TE (ms)	Flip Angle (deg)
	---------- ☐2D ☐3D		☐Uni ☐Bilat			☐Yes ☐No _---------- ☐Yes ☐No					

Contrast Agent Used: _____ Dose:_____ Rate of Admin:_____ Saline Flush? ☐ Yes ☐ No. If yes, volume of saline used: _____

There are many acceptable methods of performing breast MRI. While multiple methods of MR acquisition will be accepted in this study, the following minimum standard criteria must be met for participation:

- 1.5T or greater magnet and dedicated breast surface coil
- Minimum of one pre-contrast and two post-contrast enhanced 3D T1 weighted gradient echo sequences (TR<60 msec; TE<20 msec)
- Initial post-contrast images of the study breast must be obtained within 4 minutes of contrast injection with the second post-contrast scan ending no later than 8 minutes following injection. Additional post-contrast scans beyond 8 minutes are acceptable at the site's discretion.
- Both bilateral and unilateral scans, using a 3 mm slice thickness, will be accepted providing the minimum resolution requirements are met:
  - Voxel sizes less than 0.9 mm in the frequency encoding direction, less than 1.8 mm in the phase encoding direction, and less than or equal to 3 mm in the slice direction, providing full coverage of the breast of interest. This might be achieved in one of the following ways:
  - Bilateral in axial or coronal planes: FOV 36 cm or less with 256x512 matrix. Only in cases in which the recommended FOV of 36 cm is not sufficient to cover the full area of breast tissue, the FOV may be increased to 40 cm.
  - Unilateral in axial or coronal planes or bilateral in sagittal plane: FOV 20 cm or less with 128x256 matrix. Only in cases in which the recommended FOV of 20 cm is not sufficient to cover the full area of breast tissue, the FOV may be increased to 22 cm.
- Acceptable method of fat suppression, including available software to suppress fat signal and/or subtraction methods.

Person Completing Form: _____ Telephone No.: _____ E-mail:_____

Please submit application to:
Electronic copies are preferred.

ACRIN Administrator, Attn. 6667 PSA
1101 Market Street, Suite 1400
Philadelphia, PA 19107
Fax: 215-717-0936
E-Mail: colson@phila.acr.org