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

Version Date: May 29, 2007
Activation Date: December 21, 2001
Amendments 1 - 3
# INDEX

## SCHEMA

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Eligibility (see Section 5.0 for details)
- Patients receiving neoadjuvant chemotherapy consisting of an anthracyclin based regimen only or followed by a taxane and enrolled in CALGB Correlative Science trial 150007.
- IRB approval/signed informed consent.
- Patient cannot be pregnant.
- Patient cannot have a ferromagnetic protheses.

Required sample size: 244 patients (Protocol Extension: additional 140 patients)

ACRIN 6657/CALGB 150007 SCHEMA (original)

<table>
<thead>
<tr>
<th>AC +/-</th>
<th>Paclitaxel +/-</th>
<th>Herceptin</th>
<th>Surgery</th>
<th>RT</th>
<th>Tamoxifen or Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextrazoxane</td>
<td>Wks 1-12</td>
<td>Wks 13-25</td>
<td>Week 27</td>
<td>Wks 31-38</td>
<td>Wks 39-78</td>
</tr>
</tbody>
</table>

MRI/Core biopsy
Core biopsy

MRI

<table>
<thead>
<tr>
<th>MRI₁</th>
<th>MRI₂ **</th>
<th>MRI₃ *, **</th>
<th>MRI₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>(within 4 wks prior to cycle 1 of AC)</td>
<td>(at least 2 weeks after the first cycle of AC and prior to the second cycle of AC)</td>
<td>(between AC &amp; paclitaxel)</td>
<td>(after paclitaxel and before surgery)</td>
</tr>
<tr>
<td>Core Biopsy</td>
<td>Core Biopsy**</td>
<td>(Core Biopsy)’ (optional)</td>
<td>Surgical Tissue (at Surgery)</td>
</tr>
<tr>
<td>Serum Sample</td>
<td>(24-96 hours after start of AC)</td>
<td>Serum Sample</td>
<td></td>
</tr>
</tbody>
</table>

Mammo
Ultrasound (optional)

*MRI₁ and Core Biopsy: between AC chemotherapy and taxane therapy if the patient continues to taxane therapy (Paclitaxel +/- Herceptin)

**The following changes will apply to the schema for ACRIN 6657 Protocol Extension: MRS will be performed in combination with each MRI exam; MRI₁ will be performed either 1) 20-28 hours or 2) 48-96 hours, after the first cycle of AC; the second core biopsy (24-96 hours after start of AC) will not be performed; MRI₃ will not be performed.
1.0 INTRODUCTION

The role of MRI in the management of breast cancer is an active area of investigation and may include differential diagnosis as an adjunct to conventional imaging, local staging of disease extent, and high-risk screening. Numerous studies have evaluated contrast-enhanced MRI for detecting, diagnosing, and staging breast disease. These studies have demonstrated that essentially all breast malignancies enhance with gadolinium and that contrast-MRI is highly sensitive to cancers in the breast as small as a few millimeters.\(^1\-\(^8\) Sensitivities have been reported in the range of 95-100%. The limitation has been low to moderate specificity with false positive enhancement occurring frequently in benign breast lesions.\(^2\,\,4\-\,6\,9\-\,17\)

MRI has shown promise as a staging tool and can accurately represent the extent of cancer when compared to pathology specimens.\(^18\) For local staging, MRI can be used to estimate the extent of disease prior to or following neo-adjuvant chemotherapy. Increasingly, Stage III patients are being treated with neoadjuvant chemotherapy, and MRI provides the additional value of quantifying the original extent of disease prior to treatment. Potentially, MRI could be used as a tool to predict response to therapy. In 1998 the U.S. Public Health Service’s Office on Women’s Health sponsored the International Working Group in Breast MRI to identify barriers and propose strategies to facilitate dissemination and clinical implementation of breast MRI. One of the outcomes of this effort was a meeting of MRI investigators and cooperative group leaders to consider the potential role of breast MRI in clinical trials. Staging of neoadjuvant treatment response emerged as a potentially important application.\(^19\)

ACRIN Study 6657 is designed to be one of two companion studies to look at imaging and tissue markers in women receiving neoadjuvant treatment for breast cancer. The goals of Study 6657 are to investigate the validity of breast MRI as a staging tool for patients undergoing neoadjuvant chemotherapy and to quantify early responses to therapy using MRI measurements of volume and contrast kinetics. The use of neoadjuvant therapy followed by surgical excision allows the assessment of pathologic response, which has been demonstrated to be an excellent surrogate endpoint to predict survival. Thus the neoadjuvant trials for breast cancer serve as an ideal setting to further develop and test MRI technology and its value in predicting response to therapy. The second companion trial, CALGB 150007, is designed to look at correlative tissue markers and will be conducted in collaboration with the NCI Specialized Programs on Research Excellence (SPORE) programs in breast cancer. The correlative tissue marker study will include analysis of tumor protein markers (Ki-67, ER, PR, apoptosis-related proteins), DNA markers (comparative genomic hybridization, CGH, at multiple loci) as well as specific mRNA induced by treatment over time and will allow the correlation of cellular and molecular analysis with imaging changes after therapy.

Women receiving neoadjuvant chemotherapy consisting of an anthracyclin based regimen only or followed by a taxane, will be eligible to enroll in both the Correlative Science trial (CALGB 150007) and the MR imaging protocol (ACRIN 6657).

The overall trial will therefore be a joint collaboration among three groups: the CALGB, the NCI SPOREs in breast cancer, and ACRIN. Both SPORE and ACRIN have a unique opportunity to leverage their resources through a companion study to the Stage III CALGB trial, which is a funded cooperative group trial. The introduction of MRI and correlative tissue marker studies as part of the CALGB Stage III protocol is opportune because of the overlap of Breast SPORE, CALGB, and ACRIN member institutions. The integration of the companion study with
the CALGB Stage III trial optimizes the use of resources because much of the necessary infrastructure is already in place, including patient recruitment, data forms, and follow-up procedures. The development of clinically relevant MRI strategies requires multidisciplinary commitment. The SPORE programs have the translational infrastructure necessary to more than exceed this requirement, as well as committed investigators who can facilitate the realization of the project’s potential to transform clinical management through the application of MR imaging technology to clinical care of Stage III patients.

2.0 BACKGROUND AND SIGNIFICANCE
A major purpose of studying MRI in patients with Stage III disease is to develop early predictors of response to chemotherapy by studying response after only one or two cycles of treatment. In addition, it would be valuable to know the conditional likelihood of response to a change in chemotherapy regimen. Stage III patients represent a group with poor prognosis in whom a meaningful follow-up can be realized over a shorter horizon. Strong predictors of response in this group of patients, which can be used as surrogate endpoints to test MRI, are available at the time of surgery. Additionally, MRI is particularly robust among Stage III (large) cancers for the capture of size and heterogeneity of the tumors. The richness and three-dimensional nature of MRI enables patterns of response to be studied in both anatomical and biological detail. It may allow areas of resistance to therapy to be identified and evaluated for response to second or third rounds of chemotherapy.

Decreased sensitivity of breast MRI following chemotherapy has been described in several studies. Rieber et al. reported underestimation of tumor extent in two patients and false-negative findings in four patients, out of a total of 13 patients, following four cycles of chemotherapy. All of the patients in these cases were “responders” according to clinical and MRI criteria, and responders exhibited a decreased contrast enhancement pattern after one cycle of chemotherapy. Changes in contrast dynamics may well have biologic significance, reflecting changes in vascularity or cellularity in response to chemotherapy. As a result, the diagnostic criteria used for MRI of treated tumors may be different from those of untreated tumors, requiring re-optimization. These are questions that will be investigated in the context of this multi-center study.

2.1 Association of Pathologic Response to Clinical Outcome in Stage III Patients Undergoing Neoadjuvant Therapy
Studies have shown that pathologic response after neoadjuvant chemotherapy predicts survival. Research from MD Anderson and other institutions suggests that complete pathologic response (elimination of tumor) following neoadjuvant therapy in patients with Stage IIIb and IIIId breast cancer is strongly predictive of an excellent long-term survival. In the MD Anderson series, which included 165 patients over 3 years, the patients with a complete pathologic response to chemotherapy had a 90% survival, whereas patients with less than a complete response to therapy had a poorer long-term survival (50%). In further analysis, Kuerer and colleagues found that those with less than 1 cm of invasive tumor remaining had an 80% survival rate and those that had greater than 1 cm of remaining invasive cancer had a 40% survival rate. Furthermore, 25% of the patients had a minimal response to therapy or progressive disease and a very poor outcome, regardless of therapy after surgery, with 30% and 10% survival, respectively. Those who had a complete clinical response had an 80% survival, and those with a partial
response had a 70% survival. Additional studies have shown that tumor size and lymph node status retain predictive value after neoadjuvant therapy.\textsuperscript{24-27} Thus it is reasonable to try to determine if comparison of serial MRI exams can predict which patients would be likely to have a good outcome, either a complete pathologic response or less than 1 cm of residual invasive tumor in the breast. Those with greater than 1 cm of residual tumor might be better served with a change in regimens or use of novel therapeutic agents as they become available.

These results suggest that those patients who do not have at least a partial response to chemotherapy will have a poor prognosis. Therefore, it would be of value to have a tool to quantify extent of disease and to predict response to therapy after 1-2 cycles of chemotherapy. The availability of such a tool should facilitate the identification of complete, partial, or minimal response to AC chemotherapy. Understanding whether response to the first chemotherapy regimen predicts response to a second chemotherapy regimen will provide very important information for the clinician. The companion study will also give us the opportunity to study the conditional probability of response to Taxol, based on response to AC. Because Stage III patients represent only a small fraction of overall breast cancer patients, it is necessary that this work be done in a collaborative setting among multiple sites.

2.2 MR Imaging in Stage III Patients

While data establishing the diagnostic accuracy of breast MRI are not yet conclusive, existing data support the usefulness of breast MRI for staging invasive carcinoma. The greatest diagnostic challenge for breast MRI lies in the spectrum of disease from atypia to non-invasive to low-grade invasive carcinoma. This spectrum produces the majority of false-positive and false-negative cases, which may have important implications for use of breast MRI in early detection. However, breast MRI has much greater accuracy in the diagnosis of higher-grade invasive carcinomas, which will be case for the stage III patients studied under this protocol. For this reason, this study is less an investigation of the optimal MRI method as a question of whether MRI can be effective in the clinical trials setting by providing non-invasive surrogate markers for treatment response. We have chosen a high-spatial-resolution, volumetric MRI technique because of the need to accurately assess extent of disease and quantify change with therapy. This emphasis on staging precludes the use of very-high-temporal-resolution, dynamic techniques that are generally proposed to maximize specificity. The demands for high specificity are not as stringent for evaluation of locally advanced breast cancer. We will adopt the same specifications for high resolution MRI established by the International Breast MRI Consortium (IBMC), a NCI-sponsored multicenter trial designed to evaluate the performance of breast MRI in characterizing lesions in patients with suspicious mammographic and clinical findings and in determining the extent of cancer within the affected breast.

2.3 \textsuperscript{1}H MR Spectroscopy of Breast Tumors

A number of studies have shown that total choline concentration [tCho] measured by \textsuperscript{1}H magnetic resonance spectroscopy (MRS), is useful for distinguishing benign and malignant breast tumors. Meisamy et al at the University of Minnesota have shown that change in [tCho] measured at 4 Tesla following a single course of chemotherapy is predictive of tumor response following the full regimen of treatment\textsuperscript{36}. This change
appears to precede measurable changes in tumor size. In an extension of ACRIN 6657 trial accrual, we will obtain preliminary data to investigate whether [tCho] measurement added to the early post-treatment MR imaging study can improve the ability of MRI to predict tumor response to treatment. Specifically, the protocol extension will address two important questions regarding \(^1\)H MRS, 1) whether the University of Minnesota results can be reproduced at the commercially-available field strengths 3.0 Tesla and 1.5 Tesla, and 2) whether post-treatment timing (24 hours versus 48-96 hours) is critical for the [tCho] measurement. This information is necessary to optimize \(^1\)H MRS measurement of [tCho] as a biomarker of response that can be used to evaluate treatment response in future clinical trials.

3.0 PRELIMINARY STUDIES
A group of 42 patients with stage III/IV breast cancer underwent MRI before and following a complete course (4 cycles) of adriamycin/cytoxan (AC) chemotherapy. Thirty-four of these patients have completed treatment and undergone surgery. Eighteen of the 34 patients also had one MRI exam following their first cycle of chemotherapy. The mean follow-up for the group of 34 patients was 17 months as of May 2000. As of that date, 6 patients had local recurrence, distant metastasis, or died. Of 9 patients showing a complete clinical response, 7 showed residual disease at pathology, and MRI agreed with pathology in all seven cases.

3.1 Qualitative Assessment of Patterns of Initial Presentation
Tumor classification by MRI pattern appears to correlate with clinical response and nodal status. Several distinct spatial patterns have been identified on MRI in the group of stage III and stage IV patients. We have classified these morphologically different patterns by which tumor enhancement is distributed in the breast according to the following descriptions (Table 1):

<table>
<thead>
<tr>
<th>Morphologic Pattern:</th>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Single uni-centric mass with well-defined margin</td>
<td></td>
</tr>
<tr>
<td>2 Multi-lobulated mass with well-defined margin</td>
<td></td>
</tr>
<tr>
<td>3 Area enhancement with irregular margins—without nodularity</td>
<td></td>
</tr>
<tr>
<td>4 Area enhancement with irregular margins—without nodularity</td>
<td></td>
</tr>
<tr>
<td>5 Septal spread; streaming</td>
<td></td>
</tr>
</tbody>
</table>

Examples of each of these patterns are shown in Figure 1. Our early observations suggest that tumors with the same pattern at presentation behave similarly in the pattern and rate of shrinkage with neoadjuvant chemotherapy, while tumors of different patterns show substantial differences. Figure 2 shows an example of response measurements for a large pattern 1 tumor.
Figure 1. Spatial patterns of enhancement on MRI distinguish tumor morphologies that may further characterize tumor type and predict responsiveness to therapy.
A pattern 1 tumor shows a significant decrease in peak SER after one cycle of treatment that is sustained through the end of treatment. Volume response is continual.

3.2 Results of Preliminary Analysis

For preliminary analysis, we have used the size of residual disease on pathology and number of positive axillary nodes as intermediate endpoints. Both of these measurements have been shown to predict patient outcome following neoadjuvant chemotherapy and surgery. MRI was found to accurately assess the extent of residual disease. In order to evaluate the ability of contrast-MRI to demonstrate disease extent following neoadjuvant chemotherapy, the longest diameter of disease measured by MRI was correlated with the longest dimension measured on pathology. MRI diameter was found to have a good correlation with pathologic residual disease diameter \((r^2 = .79)\) (Figure 3).

![Figure 3: Size of Residual Disease: Pathology vs. MRI](image)

When pathologic residual disease was classified as (a) \(\leq 1\) cm, (b) \(1\) cm – \(2.5\) cm, or (c) \(> 2.5\) cm, the correlation between percent change in diameter with treatment measured by MRI and pathologic disease was found to correlate significantly (\(p = .018\), Kruskal-Wallis test). Similarly, change in diameter was found to correlate with the number of positive nodes (\(p = .035\), Kruskal-Wallis test). When change in MRI diameter was categorized as less than or greater than 30% (corresponding to < or > 50% volumetric change standard according to the World Health Organization recommendations), a significantly greater proportion of patients with <30% change have had disease recurrence than those with > 30% change (100% versus 45%, respectively) (Figure 4).
Change in peak SER value was also significantly less in the group of patients with recurrence (23 vs. 37%, respectively; p=.053). Some interesting trends have emerged among groups of patients showing different patterns at initial presentation. The mean change in longest diameter differs markedly among groups 1, 2, 3, 4, and 5 (Figure 5). No patients with pattern 1 or 3 tumors have recurred to date; 50% of all recurrences have been pattern 4 tumors and 35% have been pattern 2 (Figure 6). The patient in Figure 7 demonstrated multi-focal disease with both pattern 2 and pattern 4. The response over treatment was dramatically different for the two types of disease.
**Figure 6**: % Recurrence by Imaging Pattern

<table>
<thead>
<tr>
<th>Pattern</th>
<th>No Evidence of Disease (n=28)</th>
<th>Recurrence/Metastasis (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>80%</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>60%</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>40%</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>20%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Figure 7**: Multifocal disease shows two distinct patterns of distribution with different rates and degree of shrinkage with neoadjuvant treatment

**4.0 OBJECTIVES**

**4.1 Overall Scientific Objectives of the ACRIN 6657/CALGB 150007 Companion Trials**

The overall shared goals of the MRI and biomarker studies in women undergoing preoperative (neoadjuvant) therapy is to identify surrogate markers of response to preoperative chemotherapy that are predictive of pathologic remissions and survival in Stage III breast cancer. We will use molecular and imaging characteristics to identify those patients likely to respond to novel therapeutic agents which could then be tested in the neoadjuvant setting. These studies enable us to gather sufficient preliminary data to estimate sample size for trials of novel therapeutics in the neoadjuvant setting for patients who fail to respond to standard chemotherapy regimens.

Based on recent published data showing that choline concentration [tCho] measured by 1H MRS at 4 Tesla 24 hours after the first cycle of neoadjuvant chemotherapy is...
predictive of tumor response, we will enroll an additional group of subjects under a protocol extension to investigate whether \([t\text{Cho}]\) measured early in treatment can add information beyond contrast-enhanced MRI. The ACRIN 6657 trial extension will obtain pilot data using \(^1\text{H} \text{MRS}\) to determine if similar results to the Meisamy study at 4 Tesla can be obtained at 3Tesla and 1.5Tesla, the field strengths of the vast majority of clinical MRI systems available today. The trial extension will also investigate whether the 24-hour post-treatment timing of the MRI/MRS exam is critical to the \([t\text{Cho}]\) findings, or whether less stringent timing requirements can be allowed. The aims of the ACRIN 6657 trial extension are described in Section 4.4 below.

4.2 Primary Aims of ACRIN 6657

Four MRI exams will be performed as part of the MRI companion study: pre-neoadjuvant therapy (MRI\(_1\)), after 1 cycle of AC therapy (MRI\(_2\)), between AC and paclitaxel (MRI\(_3\)), and after completion of neoadjuvant treatment and prior to surgery (MRI\(_4\)). MRI\(_1\) will serve as a baseline to characterize the pre-treatment breast. The purpose of MRI\(_2\) is to evaluate whether MRI changes early in treatment can predict overall response. MRI\(_3\) will allow us to address the question of whether the response to the second cytotoxic agent as measured by MRI is conditional upon response to the first. The final exam, MRI\(_4\), will be used to optimize criteria for detecting residual disease and evaluate the post-treatment sensitivity and specificity of MRI.

The Primary Aims to be addressed as part of the Imaging Component of the Stage III Trial are the following (corresponding specific aims in the statistical section 8.4.1):

4.2.1 Can MRI measurements of tumor response stratify patients with Stage III breast cancer demonstrating a partial or minimal clinical response to neoadjuvant chemotherapy, into groups with statistically different disease-free survival?

Tumor response measurements by MRI will include change in longest dimension, change in tumor volume and change in contrast enhancement kinetics represented by peak signal enhancement ratio (SER) and SER distribution.

**Aim 1:** Use MRI measurements of tumor response to uniquely identify two groups of participants who have statistically different three-year disease-free survival out of a group of participants with Stage III breast cancer who demonstrate a partial or minimal clinical response (as identified by physical examination) to neoadjuvant chemotherapy.

4.2.2 Can MRI measurements of tumor response measured after the first cycle of neoadjuvant chemotherapy predict which patients will ultimately have a poor clinical response?

**Aim 2:** Use MRI measured tumor response after the first cycle of neoadjuvant chemotherapy to identify patients who will ultimately have a poor response to chemotherapy.
4.3 Secondary Aims of ACRIN 6657
The Secondary Aims to be addressed as part of the Imaging Component of the Stage III Trial are the following (corresponding specific aims in the statistical section 8.4.2):

4.3.1 Can MRI predict the extent of residual disease as determined by histopathology more accurately than mammography?

**Aim 3:** Determine the accuracy of MRI measurements to assess the extent of residual disease following neoadjuvant chemotherapy, in comparison to measurement by mammography.

4.3.2 Do initial tumor characteristics (morphologic and vascular patterns) on MRI predict pathologic response and survival?

**Aim 4:** Determine if any initial MRI tumor characteristics, i.e., morphologic and vascular patterns, predict pathologic residual disease and/or survival.

4.3.3 What is the conditional probability of response to paclitaxel based on MR response to AC?

**Aim 5:** Estimate the conditional probability of response to paclitaxel based on MRI measured response to AC.

4.4 Aims of the ACRIN 6657 Protocol Extension

4.4.1 The objective of the ACRIN 6657 protocol extension is to investigate the usefulness of total choline concentration [tCho] measured by $^1$H MRS early in the course of treatment, for predicting pathologic response. Following completion of accrual to the original 6657 protocol, an additional group of patients meeting the same eligibility criteria as in the original protocol will be enrolled to the protocol extension. Three changes to the imaging protocol will be made: 1) addition of a single voxel $^1$H MRS acquisition and optional diffusion-weighted MRI acquisition to the MRI exam, 2) reduction of the number of (6657 study-related) imaging exams from 4 to 3 during the course of treatment, and 3) change of the timing of the post 1st cycle MRI/MRS exam.

4.4.2 The Primary Aim to be addressed as part of the ACRIN 6657 Protocol Extension is the following:
Is change in [tCho] measured in vivo in breast tumors after 1 cycle of chemotherapy predictive of overall response following a full regimen of chemotherapy as measured by pathologic response?
Aim 6: Determine whether change in [tCho] after 1 cycle of neoadjuvant chemotherapy, measured using a single voxel $^1$H MRS technique at 3T (or 1.5 T), is predictive of pathologic response and final change in tumor volume by MR imaging.

4.4.3 The Secondary Aims to be addressed as part of the ACRIN 6657 Protocol Extension are the following:

Is the association between change in [tCho], measured after 1 cycle of chemotherapy, and tumor response dependent on post-1 cycle timing?

Aim 7: Compare acute (within 20-28 hours post treatment) and persistent (48-96 hours post-treatment) change in [tCho] after 1 cycle, for association with pathologic response and final change in tumor volume by MR imaging.

Is the association between change in [tCho], measured after 1 cycle of chemotherapy, and tumor response dependent on field strength (1.5 Tesla or 3.0 Tesla)?

Aim 8: Compare acute change in [tCho] after 1 cycle measured at 1.5 Tesla and at 3.0 Tesla for association with pathologic response and final change in tumor volume by MR imaging.

How does early [tCho] change compare to early change in volume, SER and ADC for predicting pathologic response and final tumor response?

Aim 9: Compare early volumetric and functional measurements by MRI (ADC, SER) to [tCho] measurements for prediction of pathologic response and final tumor response.

5.0 PATIENT ELIGIBILITY

Inclusion criteria for ACRIN 6657 are patients receiving neoadjuvant chemotherapy consisting of an anthracyclin based regimen alone or followed by a taxane and enrolled in CALGB Correlative Science trial 150007.

5.1 Patients with T3 tumors will be eligible to participate in the Correlative Science and Imaging companion trials (ACRIN 6657/CALGB 150007) if they have at least a 3 cm tumor and choose to undergo neoadjuvant chemotherapy. The therapeutic regimen in this case will consist of adriamycin and cytoxan alone or followed by taxol.

5.1.1 IRB approval/Signed informed consent

5.2 Exclusion Criteria Specific to the MRI Study ACRIN 6657

5.2.1 Pregnancy

5.2.2 Ferromagnetic prostheses
6.0 DATA COLLECTION & MANAGEMENT

6.1 General

6.1.1 The ACRIN web address is www.acrin.org

6.1.2 Data collection and management will be performed by the Biostatistics and Data Management Center (BDMC) of American College of Radiology Imaging Network 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 ACRIN in Philadelphia.

6.1.3 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.

6.2 Clinical Data Submission

6.2.1 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 the ACRIN 6657 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.

6.2.2 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.

6.2.3 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. 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.

6.2.4 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
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.

### 6.3 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.

### 6.4 Electronic Data Management

#### 6.4.1 Data received from the web-based forms is electronically stamped with the date and time of receipt by the ACRIN server. The data is then entered into the database. A variable in the new record is set to “Unreviewed” until the data is reviewed at the DMC. A validation program is used to perform more extensive 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.

#### 6.4.2 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.

### 6.5 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 U.S. 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.
6.6 Data Quality Monitoring

6.6.1 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.

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

6.6.3 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.

6.7 Data Collection Table

<table>
<thead>
<tr>
<th>Forms</th>
<th>Data Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>A0 Registration Form</td>
<td>Completed by site RA and submitted at the time of registration via ACRIN web site.</td>
</tr>
</tbody>
</table>
| IA Mammography Interpretation Form | **Mammography protocol specific time-points:**  
Mammo 1- within 3 months before or 2 weeks after entry MRI but before start of treatment.  
Mammo 2-after the final chemotherapy treatment and before surgery.

**Data:** Completed by radiologist. Submitted by site within 2 weeks of each study mammogram via the ACRIN web site. If using prior mammogram at study entry, the IA is due before the start of treatment.
| C4 Mammography Images/Films | Mammo 1-Submitted by site within 4 weeks of registration.  
Mammo 2-Submitted by site within 2 weeks of mammogram. |
<table>
<thead>
<tr>
<th>Code</th>
<th>Form Description</th>
<th>Instructions and Data Collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>M3</td>
<td>MRI Form Pre-Treatment</td>
<td>MRI protocol specific time-point: MR 1-within 4 weeks before start of neoadjuvant treatment. Data: Completed by radiologist. Submitted by site within 2 weeks of the study entry MRI-1 exam via the ACRIN web site.</td>
</tr>
<tr>
<td>M4</td>
<td>MRI Form Treatment and Post-Treatment</td>
<td>MRI protocol specific time-points: MRI 2-at least 2 weeks after the first cycle and before the second cycle. MRI 3-between AC and paclitaxel regimens, if patient continues to paclitaxel. MRI 4-within 3 or 4 weeks after final chemotherapy treatment and before surgery. Data: Completed by radiologist. Submitted by site within 2 weeks of each study specific MRI-2, 3, 4 exams via the ACRIN web site.</td>
</tr>
<tr>
<td>MS</td>
<td>MRS Form Pre-Treatment, Treatment and Post-Treatment</td>
<td>MRI/MRS protocol specific time-points: MRI/MRS 1-within 4 weeks before start of neoadjuvant treatment. MRI/MRS 2-at least 2 weeks after the first cycle and before the second cycle. MRI 4-within 3 or 4 weeks after final chemotherapy treatment and before surgery. Data: Completed by Research Associate. Submitted by site within 2 weeks of each study specific MRI/MRS-1, 2, 4 exams via the ACRIN web site.</td>
</tr>
<tr>
<td>ME</td>
<td>MRI Report</td>
<td>MRI 1-Submitted by site within 4 weeks of registration via mail or fax. MRI 2, 3, 4-Submitted by site within 2 weeks of MRI exams via mail or fax.</td>
</tr>
<tr>
<td>MR</td>
<td>MRI Images</td>
<td>MRI 1-Submitted by site within 4 weeks of registration. MRI 2, 3, 4-Submitted by site within 2 weeks of MRI exams.</td>
</tr>
</tbody>
</table>

Mammo 1-Submitted by site within 4 weeks of registration via mail or fax. Mammo 2-Submitted by site within 2 weeks of mammogram via mail or fax.


Data: Completed by radiologist. Submitted by site within 2 weeks of the study diagnostic ultrasound, if performed, via the ACRIN web site.
6.8 **Image Submission**

All image data will be sent to the ACRIN Image Management Center (IMC). It is essential that all MRI data be collected in the digital format DICOM v. 3.0 due to the quantitative requirements of this study. Digitally generated images for MRI and scanned film diagnostic images for the mammograms can be transmitted to the IMC via FTP directly to the image archive. Plain film mammograms can be sent to the IMC to be digitized and will be returned (see Section 6.8.3 below). The FTP site is located at ftp://xray.acrin.org or ftp://206.137.103.34. For each transmission a new folder for each institution and sub-folders for each corresponding exam must be created. Images are then transferred into those folders. An e-mail verifying the transfer and its contents including the name and number of exams as well as image count for each will be sent to both alevering@phila.acr.org and rwels@phila.acr.org. Transmission will be verified by examining the folders to make certain that all the images were received.

6.8.1 The header recorded on DICOM formatted image data, which often contains information identifying the patient by name, MUST be scrubbed before the image is transferred. This involves replacing the Patient Name tag with the Institution ID or number, replacing Patient ID tag with the ACRIN case number and the study number should be put on the Other Patient ID tag. This can either be done by software present at the institution or software available from the ACRIN IMC. Please contact Rex Welsh (215-574-3215) for further information regarding scrubbing patient identifiers from the DICOM files.

6.8.2 In the event that either DICOM capability or transfer of scrubbed image headers is not available, images may also be sent on a CD or other electronic medium for the ACRIN IMC (rwels@phila.acr.org) to transfer to the image archive. Please contact the ACRIN IMC prior to sending the media to confirm compatibility.

6.8.3 Mammography plain film images should be sent via mail for digitization and subsequent entry to the image archive (ultrasound images will not be collected). ACRIN will digitize them and return the originals. Mailed plain film images or images on CD should be addressed and sent as follows:

```
ACRIN 6657 Films
American College of Radiology
Diagnostic Studies Film Library
1818 Market Street, Suite 1600
Philadelphia, PA 19103
ATTN: Anthony Levering
```

6.8.4 Images stored on the ACRIN IMC image archive will then be routed to other sites involved using either FTP or CD-ROM where appropriate for purposes of secondary interpretation.
6.9 Imaging Equipment Safety or Service Reports

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.

7.0 STUDY DESIGN

7.1 Overview

The study will be carried out at 9 institutions that are currently participating in ACRIN 6657 and are also participating in the CALGB trial: UCSF, University of Pennsylvania, UNC at Chapel Hill, Georgetown University, University of Alabama, Memorial Sloan-Kettering Cancer Center, University of Texas, Southwestern, University of Washington and University of Chicago. University of Minnesota will be added as a site for the protocol extension. Additional sites may continue to be added, depending on expertise, patient accrual projections, interest, and resources. The original 6657 study assumes an accrual rate of 244 patients over 3 years; an additional 140 patients will be accrued as part of the protocol extension. The therapeutic regimen is outlined in the schema included in this protocol.

7.2 Patient Enrollment

Patient recruitment and enrollment will be conducted through the CALGB 150007 study. Patients who enroll directly in CALGB 150007 will also participate in the ACRIN 6657 imaging study and will be referred to the ACRIN 6657 study coordinator at the host institution. The CALGB registration form and signed informed consent will be faxed to the ACRIN 6657 study coordinator within 5 days of subject enrollment. The subject will subsequently be registered on the ACRIN 6657 website. The MRI study coordinator will screen each patient for MRI-specific inclusion/exclusion criteria. A projected timeline of treatments and procedures will be generated at the time of enrollment for each patient to allow adequate time to pre-schedule MRI scan times. The maximum number of days allowed between registration and start of chemotherapy will be 30 days if the patient enrolls through CALGB 150007.

7.2.1 Using the ACRIN Online Registration System for ACRIN 6657

Once the MRI study coordinator (RA) has reviewed the eligibility criteria and the patient has been found to be eligible, 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.

7.2.2 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.

7.3 Unsuccessful Registrations

7.3.1 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.

7.3.2 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 (215-717-0936, 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.

7.4 Imaging Procedures

7.4.1 MRI

Four MRI procedures are to be performed for each patient. The MRIs will be performed at the following points:

MRI<sub>1</sub>: (baseline) within four weeks prior to start of neoadjuvant treatment. (Must have been performed using the same imaging parameters/protocol as the study MRI protocol. Baseline MRIs performed under other imaging protocols must be repeated using the study MRI protocol.)

MRI<sub>2</sub>: At least 2 weeks after first cycle of AC and prior to second cycle of AC

MRI<sub>3</sub>: between AC and paclitaxel regimens, if the patient continues to paclitaxel.

MRI<sub>4</sub>: 3-4 weeks after final chemotherapy treatment and prior to surgery (4-6 weeks after final chemotherapy unless there are medical complications [e.g., infection, significant bone marrow suppression]). Thus, MRI will usually precede surgery by 1-2 weeks.

Following completion of patient accrual to the original 6657 protocol, an additional 140 patients will be accrued as part of a protocol extension to study the usefulness of [tCho] measurement by 1 H MRS in breast tumors for predicting response to treatment. For the protocol extension the MRI procedures will be modified by 1) eliminating the MRI exam between treatment regimens (MRI<sub>3</sub>...
above), and 2) changing the timing of MRI. The MRI’s for the protocol extension will be the following:

MRI1: (baseline) within four weeks prior to start of neoadjuvant treatment. (Must have been performed using the same imaging parameters/protocol as the study MRI protocol. Baseline MRIs performed under other imaging protocols must be repeated using the study MRI protocol.)

MRI2: In 1 of 2 treatment time windows following the first cycle of AC: 20-28 hours or 48-96 hours.

MRI3: no MRI will be performed

MRI4: 3-4 weeks after final chemotherapy treatment and prior to surgery (4-6 weeks after final chemotherapy unless there are medical complications [e.g., infection, significant bone marrow suppression]). Thus, MRI will usually precede surgery by 1-2 weeks.

Sites will be asked to perform the study using a 1.5 Tesla scanner, 3.0 Tesla scanner, or both scanners, depending on the availability of equipment at their site. Initial survey of the participating sites indicates that equal enrollment at the two field strengths will be straightforward. Enrollment will be monitored to ensure that accrual to both field strengths is approximately balanced. If an imbalance is identified, sites with both field strengths available will be asked to temporarily direct all new studies to the field strength with lower accrual until a balance is reestablished.

Each site will be asked to alternate between the 20-28 hour and 48-96 hour post-treatment time points for MRI. Enrollment will be monitored to ensure that accrual to both post-treatment time points is balanced. If an imbalance arises, the highest accruing sites will be asked to enroll at one time point only until the imbalance is corrected.

In order to examine reproducibility of the MRS [tCho] measurement, enrolled patients will be asked to volunteer for an additional baseline MRI/MRS exam to be performed within 72 hours of each the original baseline exam, and prior to start of treatment. Volunteers will be recruited until a total of 30 patients are reached. These patients would receive monetary compensation for their effort and time.

7.4.2 Mammography
Mammography exams will be performed to coincide with first and last MRI (baseline and prior to surgery). The first mammogram will be obtained within 3 months prior to or 2 weeks after MRI1 but before start of treatment. The second mammogram will be obtained after the final chemotherapy treatment and before surgery, preferably 1-2 weeks prior to surgery.

7.4.3 Core Biopsy
Core biopsies will be obtained as part of companion trial CALGB 150007. One core biopsy (baseline) will be performed at entrance, prior to the start of AC. If possible, the baseline core biopsy should be performed after the baseline MRI to
avoid biopsy-related image artifacts. (This scheduling may not always be possible.) Two additional study-specific core biopsies will be performed as part of the Correlative Science trial: 1) 24-96 hours after the first cycle of AC, and 2) at the end of AC chemotherapy and prior to start of taxane, if the patient continues on to taxane therapy. Surgery at the completion of neoadjuvant therapy will provide final histopathology. Tissue processing of core biopsies will be done by the SPORE Pathology cores at the respective institutions. Histopathologic data will be available for imaging/histopathologic correlation. The use of MR-directed core biopsies will be acceptable but not required and will depend on capabilities and expertise available at individual institutions. The scheduling and specifications for performing and processing core biopsies are described in detail in protocol CALGB 150007. For the protocol extension, the 24-96 hour core biopsy will no longer be performed.

7.4.4 **Ultrasound (Optional)**

If ultrasound is used for diagnostic purposes as part of standard care or decision of the physician, ultrasound will be read by the study radiologist and the Ultrasound Interpretation Form will be completed. Only ultrasound exams corresponding to the first and/or last MRI exams will be reported.

7.5 **MRI Technique**

MRI studies will be performed on a 1.0 Tesla or higher whole body scanner using a dedicated breast radiofrequency coil. Patients will be imaged in the prone position with an intravenous catheter inserted prior to the start of imaging. The MRI exam should include a localization scan and a T2-weighted sequence, followed by the contrast-enhanced T1-weighted series. For T2-weighted imaging, a fast spin echo sequence with fat-suppression should be performed in the sagittal orientation over the symptomatic breast only. The following parameters should be used for T2-weighted imaging: 2D, spin echo, field of view (FOV) 16-20 cm, 3 mm slice thickness, skip 0.5 mm, 512x192 matrix, frequency A/P, 2 NEX, no phase wrap, fat-sat, echo train length 8-16, 1 echo, effective TE 80-140 ms, TR 4000-6000 ms. The pulse sequence specifications for high resolution, contrast-enhanced MR imaging will be comparable to those used by the NCI-funded multi-center Breast MRI trial (IBMC). For patient enrollment under the original protocol aims, the following image acquisition methods will be used: High resolution (≤ 1 mm in-plane spatial resolution), three-dimensional, fat-suppressed, T1-weighted imaging of the symptomatic breast will be performed. One data set will be acquired before injection of Gd-DTPA and at least two times immediately following injection. Gd-DPTA will be administered at a dose of .1 mmol/kg body weight over 15 seconds, followed by a 10 ml saline flush over 15 seconds. Contrast injection will begin simultaneously with the start of data acquisition. Imaging will be performed over a 16-18 cm field of view using a minimum matrix of 256x192 and 64 slices of thickness ≤ 2.5 mm, depending on the size of the breast. Other pulse sequence specifications will include: TR ≤ 20 ms, TE = 4.5 ms, flip angle ≤ 45°. Fat-suppression will be used. Signal averaging can be used to improve image quality. The resulting scan time will be between 4.5-5 minutes. k-space sampling will be ordered such that the lowest k-space lines are acquired halfway through the data acquisition; thus, temporal sampling of the first post-contrast scan will be between 2 min 15 sec and 2 min 30 sec. An interscan delay between
the first and second post-contrast scans will be used if needed such that temporal sampling of the second post-contrast scan is between 7 min 15 sec and 7 min 45 sec.

For the protocol extension, MR imaging requirements will be changed to allow bilateral imaging. Changes will also be made to the temporal sampling of the contrast-enhanced study. Patients will be imaged in the prone position with an intravenous catheter inserted prior to the start of imaging. The MRI exam should include a localization scan and a T2-weighted sequence, followed by the contrast-enhanced T1-weighted series. Unilateral sagittal imaging over the symptomatic breast, or bilateral axial imaging can be performed, however the same format should be maintained for both T2 and dynamic T1 imaging. For T2-weighted imaging, a fast spin echo sequence with fat-suppression should be performed using the following parameters: 2D, spin echo, field of view (FOV) 16-20 cm (unilateral) or 32-40 cm (bilateral), 3 mm slice thickness, skip 0.5 mm, 512x192 minimum matrix (unilateral or bilateral), frequency A/P, 2 NEX, no phase wrap, fat-sat, echo train length 8-16, 1 echo, effective TE 80-140 ms, TR 4000-6000 ms. For the dynamic contrast-enhanced study, high resolution (≤ 1 mm in-plane spatial resolution), three-dimensional, fat-suppressed, T1-weighted imaging should be performed, with a maximum scan time of 3 minutes. One data set should be acquired before injection of Gd-DTPA and repeated following injection for a minimum of 10 minutes. Gd-DPTA should be administered at a dose of .1 mmol/kg body weight over 15 seconds, followed by a 10 ml saline flush over 15 seconds. Contrast injection should begin simultaneously with the start of data acquisition. T1-weighted imaging should be performed using the following parameters: FOV 16-20 cm (unilateral) or 32-40 cm (bilateral), and minimum matrix of 256 x 192 (unilateral) or 512 x 384 (bilateral). A minimum of 64 slices should be acquired of thickness ≤ 2.5 mm, depending on the size of the breast(s). Other pulse sequence specifications will include: TR ≤ 35 ms, TE = 4.5 ms, flip angle ≤ 45°. Active fat-suppression should be used. Standard k-space ordering (-k through +k) should be used.

7.6 Analysis of Imaging Studies
MR image data will be centrally archived at the ACR with all patient-identifying information removed. Methods of evaluation will include both qualitative image interpretation and quantitative image analysis. MR image interpretation for all Questions/Aims will be performed by the site radiologist according to the Breast MRI Lexicon (see description below under Image Interpretation). Pathologic assessments (as defined in Table 3) will be used as the gold standard. Automated quantitative methods for measuring disease extent will also be tested.

7.6.1 MR Image Interpretation
Image interpretation will be performed according to the ACR BIRADS – MRI (2003 Edition). A copy of the lexicon is included as Appendix III. The breast MRI lexicon provides a common language for describing architectural features, time course of contrast enhancement and disease extent. Initial training (see 7.5.5) will be conducted on use of the current breast MRI lexicon. Radiologic interpretation of MR images will assess lesion size, shape, extent, distribution and kinetics as well as other characteristics including breast density and T2 appearance. Morphologic pattern will be defined for every patient on baseline MRI studies according to the classifications listed in Appendix III. (Note that the
categories listed in Appendix III have been modified from those described under Preliminary Studies and listed in Table 1, based upon initial experience applying these terms to test cases.) The degree and temporal pattern of enhancement will be assessed visually according to the classifications listed in Appendix III.

Separate readers for MRI and mammography are preferable; however, if MRI and mammography are interpreted by a single reader, the reading order will be randomized.

7.6.2 **Quantitative Image Analysis**

All MRI studies will be analyzed using methods developed at UCSF for automated measurement of volume and contrast enhancement characteristics. In this method, multiple quantitative parameters are extracted for estimation of tumor volume and parameters related to contrast kinetics: initial percent enhancement, \( PE = \frac{S_1-S_0}{S_0} \), and signal enhancement ratio (SER) = \( \frac{S_1-S_0}{S_2-S_0} \), where \( S_0, S_1 \) and \( S_2 \) are the pre-contrast, first post-contrast and second-post contrast signal intensities of the three time-point data acquisition.

The primary quantitative measurement to be made by MRI is an estimate of tumor volume. The existing malignancy criteria for defining tumor volume are based on receiver operating characteristic (ROC) optimization in a retrospective group of 180 patients with histopathologic correlation who did not undergo neoadjuvant treatment. Re-optimization of malignancy criteria for post-neoadjuvant histopathology will be performed in a training set of 50 patient studies acquired at UCSF. Secondary measurements will consider enhancement characteristics of the tumor, including peak SER value, spatial distribution, and volume fractions of SER ranges. Measurements of these quantities will be followed over the course of treatment.

Image data will be made available for analysis by alternative quantitative methods and multi-reader studies. Multiple models for analyzing contrast enhancement will be tested and compared. These will include pharmacokinetic analysis using a three-compartmental model, empirical models using indices such as signal enhancement ratio (SER) or other time course indices (TCI), including slope, speed, or area under the enhancement curve, and three-phase visual assessment. Reader studies will evaluate inter-observer agreement for morphologic pattern classification and estimation of disease extent.

7.6.3 **MRI Assessment of Residual Disease**

1. Residual disease extent will be measured according to two methods:
   
   Longest diameter measured by visual assessment using the F classification according to TFQ staging criteria for breast MRI (see TFQ Staging Classification System, Appendix III.II). The F category measures the maximum diameter of suspicious MRI enhancement, including the index lesion. Maximum diameter by MRI (\( LD_{MRI} \)) will be assessed as the longest dimension of suspicious enhancement seen on either lateral-medial or cranial-caudal maximum intensity projection (MIP) images created from the first post-contrast data set.
2. Tumor volume, in cubic centimeters, measured quantitatively by automated computer analysis, as described previously. Both criteria will be used to assess amount of residual disease and change in size with treatment.

7.6.4 Retrospective Optimization for Detection of Disease Extent after Chemotherapy
A test set of 50 studies will be used to re-optimize criteria for defining disease following neoadjuvant chemotherapy. Decreased signal enhancement is often observed in treated tumors. Correlation of disease extent on MRI and pathology following neoadjuvant treatment will be used to retrospectively determine optimal enhancement thresholds for defining malignancy on post-treatment MRI. The test set will be comprised of cases already collected at UCSF.

7.6.5 MRI Interpretation Training Protocol
A 1-day MRI interpretation training workshop, led by Dr. Hylton, involving all readers will be held prior to the start of case accrual. The goal of the workshop will be to facilitate the use of uniform interpretation criteria (as described previously), and to familiarize readers with the MRI Interpretation Form. A training data set will be comprised of cases already collected at UCSF. The overall session will be coordinated by Dr. Hylton. The mammography correlation will be reviewed by Dr. Sickles, and the pathology correlation will be reviewed by Drs. Schnall, Chen, and Esserman.

A second 1-day training MRI interpretation workshop involving all readers will be held after accrual of the first 50 cases, using these cases as a training set, to refine interpretive criteria (if necessary) and to reinforce proper reader utilization of the MRI Interpretation Form.

7.6.6 MRI and MRS protocol for ACRIN 6657 Trial Extension
The objective of the protocol extension is to investigate the usefulness of [tCho] measured in breast tumors using $^1$H MRS for predicting tumor response to treatment. $^1$H MRS data will be acquired immediately following contrast-enhanced MRI. Three combined MRI/MRS exams will be performed during treatment at the following timepoints: 1) within four weeks prior to start of neoadjuvant chemotherapy, 2) within 20-28 hours of the first chemotherapy treatment OR within 48-96 hours of the first chemotherapy treatment, and 3) at the completion of chemotherapy and prior to surgery. The MRI/MRS exam will be performed on a 1.5 Tesla or 3.0 Tesla MR imaging system and will consist of the following sequences:

- Bilateral axial localizer
- Sagittal T2-weighted fast spin echo sequence of the symptomatic breast
- Contrast-enhanced study using a 3D, T1-weighted, fast gradient echo technique and active fat-suppression with the following sequence specifications: TR ≤ 24 ms, minimum TE (with fat and water in phase), single or interleaved sagittal (FOV 18-22 cm) slice acquisition, 512 x 256 or 256 x 256 imaging matrix, 32-64 slices, ≤ 2 mm section thickness.
- Single voxel MRS using TE-averaging
- Diffusion-weighted echo planar or fast spin echo sequence (Optional)

The technical specifications for performing the single voxel $^1$H MRS were developed by investigators at the University of Minnesota (Pat Bolan, Michael Garwood) and are included in the appendix. Dr. Bolan will work directly with individual sites and equipment manufacturers to implement the MRS measurement technique at each of the clinical sites. Data acquisition for the single voxel measurement will take approximately 7 minutes. Including time for scan prescription and voxel placement, the additional scan time incurred by the MRS measurement is expected to be approximately 15 minutes.

MRS data will be transferred to ACRIN Headquarters as part of the existing procedures for transferring imaging exam data following each patient study. MRS data will be subsequently transferred to University of Minnesota for processing and quantification of choline concentration.

7.7 Evaluation of Outcome

Our initial goal is the determination of the accuracy of tumor volume estimates, disease extent, and distribution by MRI. We will compare post-neoadjuvant tumor extent measured by MRI, with histopathology. The sensitivity and specificity of MRI for diagnosis of residual carcinoma post-chemotherapy will be evaluated. The training set will be used to refine malignancy criteria based on PE and SER thresholds. The accuracy of pre-neoadjuvant volume measurements can be extrapolated from our existing data on histopathologic correlation. Pre-treatment and post-treatment MRI measurements will be used to compute change in tumor volume with treatment.

Both clinical response and pathologic residual disease will be captured at the end of neoadjuvant treatment and will be used as intermediate outcomes for assessing the performance of MRI in defining residual disease and measuring response, in comparison to mammography. Clinical response will be assessed by physical exam and categorized as complete, partial, minimal, none, or progressive disease. Histopathologic diagnosis will include both standard clinical evaluation and description of disease distribution as outlined in Table 2. A secondary objective for assessing MRI methodology is to determine whether changes in enhancement behavior, as measured by peak SER and SER distribution, are meaningful measures of response, and whether they are predictive of end response and outcome when measured after the first cycle of AC. The outcome variables to be evaluated as primary and secondary endpoints of the CALGB trial will be mean number of positive axillary lymph nodes, pathologic complete response (CR) after chemotherapy, duration of disease-free survival (DFS), and overall survival (OS). Retrospective optimization of MR enhancement parameters will be made using these endpoints and their association with outcome variables will be tested statistically.

For the ACRIN 6657 Protocol Extension, separate groups of patients will be evaluated using MRS at 1.5 Tesla and 3.0 Tesla; both groups will undergo MRS at 20-28 hours following their first cycle of chemotherapy. The results in these two groups will test whether the University of Minnesota results obtained at 4T, 24 hours post-treatment, can be reproduced at 3T and at 1.5T. Since the majority of clinically available high field...
systems available clinically are at 3T, it is important to determine whether the University of Minnesota results can be obtained using 3T systems. While it is anticipated that breast MRS performance will be better at 3T than 1.5T, it is also important to test whether the result can be obtained at 1.5T.

At each field strength, separate groups of patients will be studied at 20-28 hours and at 48-96 hours following the first cycle of chemotherapy. The results in these groups will test whether the predictive value of [tCho] is dependent on post-treatment timing. Since the 24-hour post-treatment timing is difficult to meet in practice, this comparison will determine if less restrictive timing can be used for measuring [tCho].

Additional functional information (ADC, SER) will be acquired as part of the MRI/MRS exam and will be compared to [tCho] for measuring early treatment response. This study will thus allow us to test and compare several functional measurements by MRI/MRS that may yield non-invasive markers for predicting tumor response to treatment. Such a marker or combination of markers, available early in the course of treatment, could potentially be used as a surrogate endpoint for clinical trials evaluating novel therapeutic agents and dosing strategies.

7.8 Physical Examination

Physical examination will include the recording of tumor size in centimeters (measured in one dimension), as well as tumor location (distance in centimeters from the center of the nipple), and o’clock position. Clinical change in size will be recorded as the largest change in a single dimension of the tumor. Clinical response categories are defined as follows: complete response (disappearance of all lesions) partial response (at least 30% decrease in longest diameter of primary tumor) stable disease (neither partial response nor progressive disease); or progressive disease (at least 20% increase in longest diameter of primary tumor).

7.9 Mammography

7.9.1 Mammographic Technique

All patients will have mammography performed at times corresponding to the first and last MRI studies. Mammographic interpretation will be performed at each site. All sites will perform mammography in accordance with the standards set by the American College of Radiology. All mammographic studies will consist of standard craniocaudal (CC) and mediolateral oblique (MLO) views. In addition, fine-detail mammograms will be obtained of the cancer in both craniocaudal and true-lateral projections, using either spot-compression or spot-compression magnification technique (depending on the usual practice at the local site). If magnification is employed, the magnification factor will be recorded to permit accurate tumor size measurement. Care will be taken to ensure that fine-detail mammograms are not limited by motion blur.

7.9.2 Mammographic Interpretation

Mammograms will be interpreted by the site and coded according to the ACR BI-RADS™ Lexicon. Mammographic assessment will be reported on the Mammography Interpretation Form (IA). Tumor size will be measured in two ways: size of the tumor mass itself, and distance between ends of tumor
spiculations, if present. Tumor sizes will be measured in the left-right, inferior-superior, and anterior-posterior dimensions on all four mammographic images (standard CC, standard MLO, fine-detail CC, and fine-detail true-lateral). The longest dimension of tumor measured will also be recorded independently on the Mammography Interpretation Form.

7.10 Ultrasound

7.10.1 Ultrasound Technique
Ultrasound exams are considered optional but will be included if performed as part of standard care. Ultrasound exams performed at times corresponding to the first and last MRI studies will be interpreted by the site radiologist. All sites will perform ultrasound in accordance with the standards set by the American College of Radiology.

7.10.2 Ultrasound Interpretation
Standard radiologic interpretation of ultrasound exams will be performed. Tumor sizes will be measured in the left-right, inferior-superior, and anterior-posterior dimensions. The longest dimension of tumor measured will also be recorded independently on the Ultrasound Interpretation Form.

7.11 Pathology

7.11.1 Core Biopsies
Core biopsy specimens will be processed by the SPORE pathology investigators at individual sites. Standard and study-specific tissue markers will be measured and these results will be included in the companion study database. Details can be found in the CALGB 150007 Correlative Science Companion Trial.

7.11.2 Post-Treatment Surgery
MR images will be reviewed prospectively by the radiology, surgery, and pathology co-investigators at each institution. Following the final MRI exam and prior to surgery, a consultation between the surgery, pathology, and radiology co-investigators will be held to identify residual disease on MRI and coordinate surgical and pathology strategies for obtaining correlative assessments for enhancing lesions on MRI. This will be accomplished using standardized methods for specimen marking and sectioning at 1 cm spacings in the sagittal plane, from lateral to medial edges of the specimen. Pathologic assessment and survival will be categorized and reported as described in Table 2.
**TABLE 2 PATHOLOGIC ASSESSMENT AND SURVIVAL**

<table>
<thead>
<tr>
<th>Category</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absence of Invasive Cancer: 90 % Survival</strong></td>
<td></td>
</tr>
<tr>
<td>No DCIS</td>
<td></td>
</tr>
<tr>
<td>Presence of DCIS</td>
<td></td>
</tr>
<tr>
<td>Minimal (&lt; 1cm)</td>
<td></td>
</tr>
<tr>
<td>Moderate, widespread (&gt; 1cm, specify extent)</td>
<td></td>
</tr>
<tr>
<td><strong>Microscopic Residual Invasive Cancer: 70% Survival</strong></td>
<td></td>
</tr>
<tr>
<td>A. Single focus (specify size)</td>
<td></td>
</tr>
<tr>
<td>i. No associated DCIS</td>
<td></td>
</tr>
<tr>
<td>Presence of associated DCIS</td>
<td></td>
</tr>
<tr>
<td>- Minimal (&lt; 1cm)</td>
<td></td>
</tr>
<tr>
<td>- Moderate, widespread (&gt; 1cm, specify extent)</td>
<td></td>
</tr>
<tr>
<td><strong>Gross (Macroscopic) Residual Invasive Cancer: 70% Survival for A and 50% for B</strong></td>
<td></td>
</tr>
<tr>
<td>A. Less than 1 cm² (specify size)</td>
<td></td>
</tr>
<tr>
<td>i. No associated DCIS</td>
<td></td>
</tr>
<tr>
<td>Presence of associated DCIS</td>
<td></td>
</tr>
<tr>
<td>- Minimal (&lt; 1cm)</td>
<td></td>
</tr>
<tr>
<td>- Moderate, widespread (&gt; 1cm, specify extent)</td>
<td></td>
</tr>
</tbody>
</table>

8.0 **STATISTICAL CONSIDERATIONS**

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9.0 ADVERSE EVENT REPORTING

9.1 Definition of Adverse Event

An Adverse Event (AE) is any untoward 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), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

9.2 Definition of Serious Adverse Effect

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

- Results in death or
- Is life-threatening (at the time of the event), or
- Requires inpatient hospitalization or prolongation of an existing hospitalization, or
- Results in persistent or significant disability or incapacity, or
- Congenital anomaly or birth defect.

9.3 Adverse Event Grading

Grade is used to denote the severity of the adverse event.

1 – Mild
2 – Moderate
3 – Severe
4 – Life-threatening or disabling
5 – Fatal

9.4 Adverse Event Attribution

Attribution is the determination of whether an adverse event is related to a study treatment or procedure.
Attribution categories are:

**Definite** – *AE is clearly related* to the study treatment or procedure.
**Probable** – *AE is likely related* to the study treatment or procedure.
**Possible** – *AE may be related* to the study treatment or procedure.
**Unlikely** – *AE is doubtfully related* to the study treatment or procedure.
**Unrelated** – *AE is clearly NOT related* to the study treatment or procedure.

9.5 **Expected Adverse Events from MRI**
- Hemorrhage (hematoma at the injection site)
- Infection (catheter related infection) at the injection site

9.6 **Expected Adverse Events from Contrast Agent (gadolinium)**
- Nausea
- Headache
- Hives
- Temporary low blood pressure
- Allergic reaction

9.7 **Expected Adverse Events from Needle Placement**
- Minor discomfort
- Bleeding
- Infection
- Bruising

9.8 **Expected Adverse Events from Mammography**
- Bruising
- Discomfort

9.9 **Expected Adverse Events from Ultrasound**
- No expected adverse events.

9.10 **Reporting of Adverse Events**
Prompt reporting of adverse events is the responsibility of each investigator, clinical research associate, and nurse engaged in clinical research.

**Routine reporting** is defined as any adverse events that are documented in the AE CRF and submitted to ACRIN for preparation of a report for Data and Safety Monitoring Board (DSMB) review and annual reports and final study report to the appropriate federal regulatory agencies.

**Expedited reporting** is defined as any adverse events that meet the criteria of serious and severity as indicated in either the protocol or the ACRIN Adverse Event Reporting Manual and require immediate notification to NCI and ACRIN in a specified timeframe.

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. Only adverse events related to imaging should be reported according to ACRIN guidelines; biopsy-related adverse events should be reported according to the protocol for CALGB 150007.

9.11 When to Report
The reporting of AEs in this protocol will conform to the following:

9.11.1 Grade 3 Expected and Unexpected AEs with attribution of possible, probable, or definite will be reported by routine reporting procedures.

9.11.2 All hospitalization (or prolongation of existing hospitalization) for medical events equivalent to CTC Grade 3, 4, 5 which precipitated hospitalization must be reported within ten (10) working days of first knowledge of the event. Routine reporting procedures also apply.

9.11.3 Grade 4 Expected AEs with attribution of possible, probable, or definite will be reported by routine reporting procedures.

9.11.4 Grade 4 Unexpected AEs with attribution of possible, probable, or definite will be reported within ten (10) days of first knowledge of the event by Expedited Written Report. These reports should be sent to ACRIN, NCI’s Cancer Imaging Program (CIP), and the local Institutional Review Board (IRB). Routine reporting procedures also apply.

9.11.5 Grade 5 AEs, or Deaths with attribution of possible, probable, or definite will be reported within 24 hours of first knowledge of the event by Telephone Report to ACRIN and NCI-CIP and followed by Expedited Written Report within ten (10) days of first knowledge of the event, regardless of whether the event was expected or unexpected. These reports should be sent to ACRIN, NCI’s Cancer Imaging Program (CIP), and the local Institutional Review Board (IRB). Routine reporting procedures also apply.

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

9.11.7 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/CIP and to ACRIN within 24 hours of first knowledge of the event.

9.12 How to Report

Investigators participating in the imaging 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.

9.12.2 Completed expedited reports should be sent to:

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

To make a 24-hour telephone report, contact NCI/CIP at (301) 496-0737, available 24- hours a day (recorder after hours from 4:30 PM to 8:30 AM ET). A copy of all expedited adverse event reports should be faxed to NCI/CIP by fax at (301) 480-3507.

9.12.3 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 first knowledge of the event. To make a telephone report to ACRIN, call (215) 717-2763, available 24 hours a day (recorder after hour from 4:30 PM to 8 AM ET).

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

10.0 INSTITUTIONAL AUDITS

10.1 Institutional on-site audits will be completed within 18 months of a site’s enrolling its first ACRIN participant. Subsequent audits will be scheduled per the outcome of the initial audit. Auditors will follow procedures established by the Biomedical Imaging Program (BIP) 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 also will be reviewed at the audit. More information about ACRIN auditing procedures can be found in the ACRIN Auditing Manual, available on the ACRIN web site (www.acrin.org).

10.2 To help sites prepare for audits and assure that clinical RAs maintain records appropriately, the BDMC 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.
10.3 **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 10.5 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.

10.4 **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).

10.5 **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
- 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.

### 10.6 Audit Source Documentation

<table>
<thead>
<tr>
<th>Form</th>
<th>Data Collection</th>
<th>Source Documentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A0 Registration</td>
<td>At time of registration via the ACRIN web site.</td>
<td>Completed, signed (research associate), and dated AO form. Consent form, signed by participant and site personnel (as defined by local IRB).</td>
</tr>
</tbody>
</table>
| IA Mammography Interpretation Form | Mammography protocol specific time-points: 1- within 3 months before or 2 weeks after entry MRI but before start of treatment. 2-after the final chemotherapy treatment and before surgery.  
Data Due: Within 2 weeks of each study mammogram via the ACRIN web site. If using prior mammogram at study entry, the IA is due before the start of treatment. | Completed, signed (reader), and dated IA forms. Mammography reports, if generated. |
| M3 MRI Form: Pre-Treatment | MRI protocol specific time-point: 1-within 4 weeks before start of neoadjuvant treatment.  
Data Due: Within 2 weeks of the study entry MRI-1 exam via the ACRIN web site. | Completed, signed (reader), and dated M3 form. MRI report, if generated. |
| IB* Ultrasound Interpretation Form | Ultrasound protocol specific time-points: 1-corresponds with MRI-1. 2-corresponds with MRI-4.  
Data Due: Within 2 weeks of the study diagnostic ultrasound, if performed, via the ACRIN web site. | Completed, signed (reader), and dated IB forms. Ultrasound reports. |
| M4 MRI Form: Treatment and Post-Treatment | MRI protocol specific time-points: 2-at least 2 weeks after the first cycle and before the second cycle. 3-between AC and paclitaxel regimens, if patient continues to paclitaxel. 4-within 3 or 4 weeks after final chemotherapy treatment and before surgery.  
Data Due: Within 2 weeks of each study specific MRI-2, 3, 4 exams via the ACRIN web site. | Completed, signed (reader), and dated M4 forms. MRI reports, if generated. |
| MS MRS Form Pre-Treatment, Treatment and Post-Treatment | MRI/MRS protocol specific time-points: MRI/MRS 1-within 4 weeks before start of neoadjuvant treatment. MRI/MRS 2-at least 2 weeks after the first cycle and before the second cycle. MRI 4-within 3 or 4 weeks after final chemotherapy treatment and before surgery.  
Data: Completed by Research Associate. Submitted by site within 2 weeks of each study specific MRI/MRS-1, 2, 4 exams via the ACRIN web site. |
| S1 | Surgical Pathology Form | **Data Due:** Within 2 weeks of surgery via the ACRIN website. | Completed, signed (research associate), and dated S1 form. Surgical pathology report, surgical report. |
REFERENCES


APPENDIX I
ACRIN 6657 & CALGB 150007

SAMPLE CONSENT FOR RESEARCH STUDY

Contrast-Enhanced Breast MRI and MRS Correlative Science Studies to Characterize Tumor Response in Patients Undergoing Neoadjuvant Treatment for Locally Advanced Breast Cancer

A clinical trial is a research study that carefully tests new ways to prevent, diagnose, or treat diseases such as breast cancer. Clinical trials include only patients who choose to take part in them. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, “Taking Part in Clinical Trials: What Cancer Patients Need To Know,” is available from your doctor.

You have been asked to take part in this study because you and your doctor have decided to treat your breast cancer with standard chemotherapy that includes an anthracycline (this will be referred to as Type 1 chemotherapy) followed by treatment with a taxane chemotherapy drug (this will be referred to as Type 2 chemotherapy) before surgery.

In an effort to better understand how different women respond to chemotherapy, you have been asked to participate in an MRI/MRS imaging study and a tissue and blood biomarker study. These studies will not change your treatment, but will allow us to learn about how your tumor responds to chemotherapy treatment. These studies are being carried out together and all participants must be enrolled on both studies. We have thus created one consent form for both trials and will refer to these studies as one trial with two parts.

WHY IS THIS STUDY BEING DONE?
The main goals of this study are to:

1. Determine whether we can predict how women will respond to certain chemotherapy treatments on the bases of:
   1. the particular markers on their breast cancer cells and blood samples, and
   2. the arrangement of cancer cells in their breast, as shown by MRI (magnetic resonance imaging detects breast lesions) and MRS (magnetic resonance spectroscopy obtains information about the chemical content of the breast lesions) scans.
   3. the properties of breast cancers measured using MRS (magnetic resonance spectroscopy)
2. Accurately measure how the tumors shrink using MRI scans.

Information about tumor markers will be obtained by examining core biopsies performed before treatment and during treatment (these core biopsies are optional) and a tissue sample collected during your surgery.

MRI/MRS scans will be performed before and during treatment to determine the effectiveness of drugs in shrinking tumors and changing the arrangement of cancer cells in the breast while patients are undergoing chemotherapy. The information we get from MRI scans will be compared to the information found on mammograms.
Ultimately, this research is being done to determine whether MRI/MRS scans can be routinely used in women receiving chemotherapy to monitor shrinkage of breast tumors prior to breast surgery, and to predict (early in the course of treatment) which treatments will be most effective for women with cancer.

At the present time, almost all women receive chemotherapy because it is not known who benefits most from such treatment. We hope that this study will show which women will respond best to chemotherapy and other types of treatment.

**HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?**

About 384 women at 11 participating institutions will take part in this study.

**WHAT IS INVOLVED IN THE STUDY?**

As stated earlier, this study is a combination of two studies. The components of these two studies are:

1) An MRI/MRS component

2) Biopsies (tissue from your breast) that will be done to look for specific molecular tissue markers.

To complete the two components of this study, you will also have 2 mammograms. If your doctor feels that it is necessary you will also have 2 ultrasounds. A small amount (about two tablespoons) of blood will also be drawn.

Any tissue or blood that is taken from you in the course of these studies will be used only for this trial. No part of your tissue or blood will be used for any other study unless you agree.

If you take part in this study, you will have the following tests and procedures:

**MRI (Magnetic Resonance Imaging) and MRS (Magnetic Resonance Spectroscopy) Scans:**

You will have four MRI/MRS scans.

- the first MRI/MRS scan will be before you begin chemotherapy.
- the second MRI/MRS scan will be done after you begin the first cycle of Type 1 chemotherapy.
- the third MRI/MRS scan will be after the completion of all of your chemotherapy and before you have surgery.
- There are two additional MRI/MRS scans that are optional. Thirty patients will be asked to have an additional scan before beginning Type 1 chemotherapy. All patients will be asked to have an additional scan after completing Type 1 chemotherapy.

I agree to have the additional MRI/MRS scan before beginning Type 1 chemotherapy.

Yes____  No____
I agree to have the additional MRI/MRS after completing Type 1 chemotherapy.

Yes____ No____

The MRI procedure will not require hospitalization, withholding or delay of treatments, blood tests or special preparation. You will be placed in the center of the MRI machine, which is a large cylindrical magnet. The MRI machine produces a strong magnetic field that passes through your body. Pulses of radio frequency energy will be transmitted into your body. A computer attached to the MRI machine will process these signals from your breast into a picture. At some point during the examination, an MRI contrast agent (a dye like liquid called gadolinium) will be injected into a vein in your arm through a small catheter. This agent is routinely used during MRI examinations. The contrast agent improves the images of your breast by highlighting certain tissues. The entire procedure will take about an hour. You will have to lie still on your stomach during that time. A padded table will be provided for comfort.

Patients with some types of metallic surgical implants will not be able to participate in the study. Most of these implants are compatible with MRI, but a small number are not. Please notify your physicians if you have any metallic surgical implants (for example heart valves, aneurysm clips, orthopedic prosthesis) prior to enrolling in the study. Other situations, which might exclude you from the imaging study, include metal fragments in your eye(s) or other parts of your body, having a pacemaker, or not being able to lie still or on your stomach.

**Mammogram:** You will have 2 mammograms.
- the first mammogram will be before you start chemotherapy
- the second mammogram will be after you complete the chemotherapy and before you have surgery.

**Blood samples**
You will have blood collected at two time points for research purposes to learn more about how patients respond to different chemotherapy treatments and the possibility of predicting whether treatment for breast cancer will be effective. You will have about 1 tablespoon of blood drawn before you begin and after you have completed Type 1 chemotherapy.

**Biopsy (core needle) and Tissue Sample**
You will have a core needle biopsy(ies) done before you start Type 1 chemotherapy, a second optional biopsy(ies) at the beginning of Type 2 chemotherapy, and a small amount of tissue will be taken at the time of surgery in order for us to follow molecular (cell) changes during your therapy. This is the “marker” portion of the study looking at changes that occur in the cancer cells themselves.

I agree to have the optional biopsy(ies) at the beginning of Type 2 chemotherapy.

Yes____ No____

I agree to have the optional biopsy(ies) after completing Type 1 chemotherapy.

Yes____ No____
A core needle biopsy is a procedure whereby your doctor will insert a needle into your breast to extract a piece of tissue about the size of pencil lead. Your doctor will anesthetize (numb) the area to be biopsied prior to inserting the needle to minimize discomfort. You may have bruising and some minor discomfort after this procedure, but it should be no more than the discomfort experienced after a blood draw.

**Ultrasound**

If indicated by your physician, you will have 2 ultrasounds. The first ultrasound will be before you start chemotherapy and the second ultrasound will be after you complete chemotherapy and before you have surgery.

A schema (or study plan) showing when these MRI/MRS scans, biopsies, tissue sample will be done is shown:

<table>
<thead>
<tr>
<th>Before Chemotherapy</th>
<th>Weeks 1-12</th>
<th>Weeks 13-25</th>
<th>Week 27</th>
<th>Treatment after Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI/MRS scan</td>
<td></td>
<td></td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Blood sample</td>
<td></td>
<td></td>
<td></td>
<td>U</td>
</tr>
<tr>
<td>Biopsy</td>
<td></td>
<td></td>
<td></td>
<td>R</td>
</tr>
<tr>
<td>Mammogram</td>
<td>30 patients will have an optional MRI/MRS scan</td>
<td>All patients will be asked to have an Optional MRI/MRS scan before beginning cycle 1</td>
<td>Optional biopsy before the start of Type 2 chemotherapy</td>
<td>G</td>
</tr>
<tr>
<td>Ultrasound (if indicated by your doctor)</td>
<td>MRI/MRS scan before beginning cycle 1</td>
<td>MRI/MRS scan, Blood sample,</td>
<td>Mammogram Ultrasound (if indicated by your doctor)</td>
<td>E, R, Y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tissue sample</td>
</tr>
</tbody>
</table>

**HOW LONG WILL I BE IN THE STUDY?**

You will be in the study during the entire time of your treatment, and we will check with your doctor to see how you are doing every 6 months for approximately 10 years.

The researcher may decide to take you off this study if it is in your medical best interest, funding is stopped, your condition worsens, or new information becomes available.

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

**WHAT ARE MY TREATMENT OPTIONS?**

If you agree to take part in this study, you and your doctor have decided to treat your breast cancer with chemotherapy before your surgery. You will receive standard chemotherapy that includes an anthracycline chemotherapy drug (Type 1 chemotherapy) followed by a taxane chemotherapy drug (Type 2 chemotherapy).
During the initial breast cancer work up, your doctor may have done a test to determine whether your breast cancer is over-expressing (producing more that the normal amount) a gene called HER-2/Neu. Your doctor may use this information to help determine additional treatment options and understand more about your cancer’s characteristics.

If your doctor determines that your breast cancer is over-expressing HER-2/neu, you may be offered treatment with Herceptin as part of your standard care.

**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. There also may be other side effects that we cannot predict. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen the side effects. Many side effects go away shortly after the MRI/MRS and gadolinium contrast is stopped. However, in some cases side effects can be serious or long lasting.

**Risks Associated with MRI (Magnetic Resonance Imaging) and MRS (Magnetic Resonance Spectroscopy)**

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

**Risks Associated with Gadolinium**

*Less likely*
- Headaches and nausea.

*Less likely, but Serious*
- Allergic reaction

*Very Rare, but Serious*
- Nephrogenic sclerosing fibrosis (NSF) is a condition associated with the injection gadolinium contrast and has been seen in patients with severe kidney disease. Symptoms of NSF are tightening or scarring of the skin and organ failure. In some cases it can be life-threatening.

**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

Reproductive risks: You should not be or become pregnant while on this study. A pregnancy test is recommended prior to entering on this study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with breast cancer by allowing patients receiving chemotherapy before surgery to be evaluated by MRI/MRS in the future. This study may show that MRI/MRS can consistently and accurately find out who will respond to chemotherapy, even very early on in the treatment. Women who are not responding could then stop chemotherapy and move to another form of treatment.

WHAT OTHER OPTIONS ARE THERE?
You may choose to not participate in these studies. Your option to participate in this study will not affect the care you receive for your breast cancer in any way.
Your choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study

Please talk to your doctor about your choices before deciding if you will take part in this study.

WHAT ABOUT CONFIDENTIALITY?
Every effort will be made to keep your personal information confidential, although we cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN) in Philadelphia and at the Center for Statistical Sciences at Brown University in Providence, Rhode Island and at the CALGB Statistical Center at Duke University in North Carolina. Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Cancer and Leukemia Group B (CALGB, Food and Drug Administration (FDA), and the National Cancer Institute (NCI).

WHAT ARE THE COSTS?
You will receive no payment for taking part in this study. However, if you agree have the additional MRI/MRS scan before you begin Type 1 chemotherapy you will be compensated up to the amount of $100.

Taking part in this study may lead to added costs to you or your insurance carrier. If your insurance company does not pay for the MRI/MRS imaging, the American College of Radiology
Imaging Network (ACRIN) will reimburse the cost of the MRI/MRS exams, except for the first (baseline) scan and the scan done before surgery, as these scans are standard care for all patients before having chemotherapy or before surgery or the tissue taken at the time of surgery.

There will be no charge to you for the cost of the research biopsies done before beginning Type 1 chemotherapy, nor the optional biopsies before beginning Type 2 chemotherapy.

There will be no charge to you or your insurance carrier for the research studies that will be done using your blood, biopsy samples or tissue taken at surgery.

Please ask about specific details regarding reimbursement, any expected 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.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

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

As part of this study, you will have tissue and blood taken over the course of this study. The researchers think that they will completely use all of blood and tissue for their studies. However, if these studies do not use all of the tissue and blood, the researchers will not use your tissue or blood for any studies not related to this trial without your permission. If your permission cannot be obtained for any future studies, your tissue and blood will be discarded.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For information about your disease and research-related injury, you may contact:

_________________________  _______________________
Name                             Telephone Number

For information about this study, you may contact:

_________________________  _______________________
Name                             Telephone Number

For information about your rights as a research subject, you may contact:

(OPRR suggests that this person not be the investigator or anyone else directly involved with the research)

_________________________  _______________________
Name                             Telephone Number

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USE OF SPECIMENS

About Using Tissue and Blood for Research
You are going to have a biopsy (or surgery) to see if you have cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care. You will also have tissue taken and blood drawn specifically for the research studies described above.

Your tissue and blood may be helpful for research. The research that may be done with your tissue and blood probably will not help you. It might help people who have cancer and other diseases in the future.

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

Things to Think About
The choice to let us keep the left over tissue and blood for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue and blood can be kept for research, you can change your mind at any time. Just contact your study doctor and let him or her know that you do not want us to use your tissue. Then the tissue will no longer be used for research.

Sometimes tissue and blood are used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue and blood will be used only for research and will not be sold. You will not be paid for allowing your leftover tissue and blood to be used in research even though the research done with your tissue may help to develop new products in the future.

OPTIONAL
It is possible that at some time in the future, that as part of deciding on what therapy to give you, a new test might be available that could be done on some of the tissue or blood that is now thought of as leftover. This situation is unusual, but it could happen. In order to see that not all this leftover tissue is used up, the CALGB will take care to see that some of your cancer tissue is stored for 10 years so that it is available should it be needed by you or your doctors. Depending on the amount of leftover tissue that is submitted for this study, however, there may not be any left over tissue to store.

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

Risks
There are very few risks to you. The greatest risk is the release of information from your health records. The CALGB will protect your records so that your name, address, and phone number will be kept private. The chance that this information will be given to someone else is very small.
1. My tissue and blood may be kept for use in research to learn about, prevent, treat, or cure cancer.
   Yes ____ No____

2. My tissue and blood may be kept for research about other health problems (for example: causes of diabetes, Alzheimer’s disease, and heart disease).
   Yes ____ No____

3. My doctor (or someone from the XYZ Group) may contact me in the future to ask me to take part in more research.
   Yes ____ No____

WHERE CAN I GET MORE INFORMATION?

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

You may also visit the NCI’s Web site at http://cancer.gov/
• For NCI’s clinical trials information, go to: http://cancer.gov/clinicaltrials/
• For NCI’s general information about cancer, go to http://cancer.gov/cancerinfo/

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

SIGNATURE

I have been given a copy of all _____ [insert total number of pages] pages of this form. I have read it or it has been read to me. I understand the information and had have had my questions answered. I agree to take part in this study.

Participant _____________________

Date __________________________

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APPENDIX II

ACRIN 6657
Institution # ______
Case # ___________

ELIGIBILITY CHECK (page 1 of 2)

The following questions will be asked at study registration:

______________ (Y) 1. Name of institutional person registering this case (initials only)

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

______________ (Y) 3. Is the participant eligible for this study?

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

______________ 5. Participant Initials

______________ 6. Verifying Physician (site PI)

______________ 7. Participant’s ID Number 
(do not utilize a medical record number or radiology assigned number)

______________ 8. Date of Birth (mm-yyyy)

______________ 9. Ethnic Category
1 Hispanic or Latino
2 Not Hispanic or Latino
3 Unknown

______________ 10. Race
1 American Indian or Alaskan Native
2 Asian
3 Black or African American
4 Native Hawaiian or other Pacific Islander
5 White
6 More than one race
7 Unknown

______________ 11. Gender

______________ 12. Participant’s Country of Residence

______________ 13. Zip Code
14. Participant’s Insurance Status

APPENDIX II

ACRIN 6657
Institution # ______
Case # ___________

ELIGIBILITY CHECKLIST (page 2 of 2)

15. Will any component of the participant’s care be given at a military or VA facility?

16. Calendar Base Date (mm-dd-yyyy)

17. Registration Date (mm-dd-yyyy)

18. Treatment Start Date (mm-dd-yyyy)

19. Date of Pre-Treatment MRI (mm-dd-yyyy)

20. Name of Medical Oncologist

21. Is the participant enrolled in CALGB 150007 or CALGB Limited Access Trial? *

   CALGB Protocol # ________

   CALGB Case # ____________

22. Is the patient receiving neoadjuvant chemotherapy consisting of an anthracycline based regimen alone or followed by a taxane? *

   * Either Q21 or Q22 must be Yes

23. Is the patient pregnant?

24. Are there any contraindications to the MRI procedure?
   (Ferromagnetic protheses, claustrophobia, etc?)

Completed by ________________________ Date ________________
**APPENDIX III**  
*Breast MRI Lexicon*

I. **Morphologic Categories and Terms**

<table>
<thead>
<tr>
<th>Lesion type</th>
<th>Subtype</th>
<th>Internal Enhancement</th>
<th>Shape/Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focus/Foci</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Mass</td>
<td>n/a</td>
<td>homogeneous</td>
<td>smooth round</td>
</tr>
<tr>
<td></td>
<td></td>
<td>heterogeneous</td>
<td>lobulated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rim enhancement</td>
<td>irregular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dark septations</td>
<td>spiculated</td>
</tr>
</tbody>
</table>

Non-masslike enhancement

<table>
<thead>
<tr>
<th></th>
<th>subtype</th>
<th>Internal Enhancement</th>
<th>Shape/Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal</td>
<td>n/a</td>
<td>stippled</td>
<td>smooth</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>irregular</td>
</tr>
<tr>
<td>Segmental</td>
<td></td>
<td>heterogeneous</td>
<td>n/a</td>
</tr>
<tr>
<td>Regional</td>
<td></td>
<td>clumped</td>
<td>n/a</td>
</tr>
<tr>
<td>Patchy</td>
<td></td>
<td>homogeneous</td>
<td>n/a</td>
</tr>
</tbody>
</table>

**Definitions for lesion types**

<table>
<thead>
<tr>
<th>Lesion types</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foci</td>
<td>Focal enhancement smaller than 5 mm</td>
</tr>
<tr>
<td>Mass</td>
<td>Space occupying lesion greater than 5 mm</td>
</tr>
<tr>
<td>Non-mass-like enhancement</td>
<td></td>
</tr>
<tr>
<td>Ductal</td>
<td>Enhancement in a duct that may or may not branch</td>
</tr>
<tr>
<td>Segmental</td>
<td>Enhancement in a triangular shape <em>(towards nipple)</em></td>
</tr>
<tr>
<td>Regional</td>
<td>Enhancement not confined to a single duct</td>
</tr>
<tr>
<td>Patchy</td>
<td>Multiple regions of enhancement</td>
</tr>
<tr>
<td>Diffuse</td>
<td>Widely disseminated enhancement</td>
</tr>
</tbody>
</table>

**Definitions for internal enhancement terms**

| stippled | non-confluent  less than 2mm dots of enhancement, like sand |
| heterogeneous | confluent and non-confluent, mixed enhancement |
| clumped    | confluent regions of enhancement, like cobblestones |
| homogeneous | confluent, diffuse enhancement |

**Associated findings**

<table>
<thead>
<tr>
<th>Nipple Retraction</th>
<th>Nipple invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin thickening <em>(focal)</em></td>
<td>Skin thickening <em>(diffuse)</em></td>
</tr>
<tr>
<td>Edema</td>
<td>Lymph adenopathy</td>
</tr>
<tr>
<td>Fluid filled ducts</td>
<td>Abnormal signal void</td>
</tr>
<tr>
<td>Cysts</td>
<td>Architectural distortion</td>
</tr>
</tbody>
</table>

Chest wall invasion  
Skin invasion  
Hematoma/blood  
Pre-contrast high duct signal  

**Recommendations of the OWH Working Group on Breast MRI**

ACRIN 6657  
Version 05/29/2007
### Breast MRI Lexicon

#### II. TFQ Staging Classification System**

<table>
<thead>
<tr>
<th>T</th>
<th>F</th>
<th>Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No primary</td>
<td>F0 no other area of suspicious enhancement</td>
</tr>
<tr>
<td>Tis</td>
<td>in situ</td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>&lt; 0.5 cm</td>
<td>F1 &lt;= 10 cm</td>
</tr>
<tr>
<td>T1b</td>
<td>0.5-0.9 cm</td>
<td>F2 11-20 mm</td>
</tr>
<tr>
<td>T1c</td>
<td>1.0-2.0 cm</td>
<td>F3 21-30 mm</td>
</tr>
<tr>
<td>T2</td>
<td>2.1-5.0 cm</td>
<td>F4 31-40 mm</td>
</tr>
<tr>
<td>T3</td>
<td>&gt; 5.0 cm</td>
<td>F5 41-50 mm</td>
</tr>
<tr>
<td>T4a</td>
<td>chest wall</td>
<td>F6 51-60 mm</td>
</tr>
<tr>
<td>T4b</td>
<td>skin</td>
<td>F7 61-70 mm</td>
</tr>
<tr>
<td>T4c</td>
<td>chest wall and skin</td>
<td>F8 71-80 mm</td>
</tr>
<tr>
<td>T4d</td>
<td>inflammatory</td>
<td>F9 81-90 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F10 91-100 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FX &gt; 100 mm</td>
</tr>
</tbody>
</table>

*T=classification of index lesion  
F=maximum diameter of suspicious MRI enhancement, including the index lesion  
Q=number of theoretical quadrants occupying 25% of the breast in adjacent regions

**Recommendations of the OWH Working Group on Breast MRI\(^9\)
Breast MRI Lexicon

III. Morphologic Pattern Classifications

| Pattern 1: | Single uni-centric mass with well-defined margin |
| Pattern 2: | Multi-lobulated mass with well-defined margin |
| Pattern 3: | Area enhancement with irregular margins – with nodularity |
| Pattern 4: | Area enhancement with irregular margins – without nodularity |
| Pattern 5: | Septal spreading; streaming |
Breast MRI Lexicon

IV. Enhancement Classifications

**Enhancement Degree**

Signal intensity increase between $S_0$ and $S_1$ will be classified in order of increasing grade, according to the following:

- **Minimal**
- **Moderate**
- **Marked**

**Enhancement Pattern**

The temporal pattern of contrast enhancement will be classified in order of increasing grade, according to the following:

- **Gradual**: Signal intensity increases between $S_0$ and $S_1$ and continues to increase between $S_1$ and $S_2$
- **Sustained**: Signal intensity increases between $S_0$ and $S_1$ and remains constant between $S_1$ and $S_2$
- **Washout**: Signal intensity increases between $S_0$ and $S_1$ and decreases between $S_1$ and $S_2$

Where

- $S_0 =$ pre-contrast signal intensity
- $S_1 =$ first post-contrast signal intensity
- $S_2 =$ second post-contrast signal intensity

All tumors will be classified by the area of highest enhancement grade.
In general, the MRS acquisitions will use a single-voxel, spin-echo sequence, with water suppression and TE averaging. Quantification will be performed using water as an internal reference. An externally-referenced calibration will also be performed when feasible as a control. The specific MRS pulse sequence used may vary between the different MR manufacturers and software versions. The procedure for acquiring an in vivo spectrum is shown by the flowchart in Figure 1.

At least one voxel must be acquired per patient and followed throughout the chemotherapy cycle. If time permits, additional voxels may be acquired to sample sub-regions of a tumor, or other tumor foci. In this case, one voxel will be considered the primary voxel and labeled “voxel A”. Other voxels are considered secondary, and should be labeled alphabetically (B, C, D, ...). In follow-up studies, the primary voxel should be acquired before acquiring any secondary voxels.

**Figure 1 - Procedure for in vivo MRS acquisitions**

**Voxel Planning**
Voxels will be planned on either the MR scanner’s console or an attached workstation. In the baseline (MR11) study, the voxel should be sized and positioned to cover the maximum extent of the lesion while minimizing inclusion of adipose tissue and non-enhancing tissues. The high-resolution 3D images post-contrast and subtraction images should be used for this purpose. Using a multiplanar reformatting of the 3D images is highly recommended to ensure that the voxel is placed correctly in sagittal, axial, and coronal views. For all MRS studies other than the baseline (MRI1), the baseline images with voxel location should be available, either
electronically or as hardcopy, to help plan the new voxel. The voxel should be positioned to *cover the same region* as in the baseline scan. This may require adjustment of the voxel size as the lesion responds to treatment.

Immediately after planning the voxel, a sagittal, 2D gradient echo low-resolution scout image should be acquired in the center of the voxel. This will be used to validate the voxel position, and as a reference to verify that no motion occurs during the MRS acquisition. Typical parameters are TE=4.5ms, TR=20ms, FOV 16-18cm, matrix 128x128, slice thickness 2cm, flip angle 30°.

**Prescan**

After planning the voxel, the manufacturer’s automatic prescan (power calibration, shim, and frequency correction) should be performed. A single-shot, non-suppressed spectrum should then be acquired (TE=50ms) and processed on the console. This spectrum should be evaluated for both lipid content and shim quality. The lipid content can be determined by the relative sizes of the water and lipid (1.3ppm) resonances. If the ratio of the water-to-fat peak amplitudes is low, then the lipid content is too high and may bias the subsequent tCho measurement. If W:F is less than 2, the voxel dimensions and/or position should be readjusted, and the procedure restarted. It is sufficient to evaluate the W:F ratio by simple visual inspection; no fitting is required.

The shim quality should be evaluated by measuring the linewidth of the water peak at its half maximum (FWHM). This can be done by fitting the peak to a Lorentzian model, or by direct measurement. If the FWHM is greater than 0.25 ppm, it will be necessary to readjust the shimming by repeating the auto-shim, or by manually adjusting the linear shims.

After an acceptable shim is found, the water suppression (and optional lipid suppression) should be adjusted (manually or automatically) and verified with a single scan. The suppression should be adjusted so that the spectrum meets the following requirements:

1. there is at least one reference peak (water or lipid) with signal-to-noise of 100 or greater
2. the water peak is not inverted
3. the 3-3.5ppm region of the spectrum is flat, without artifacts or a large slope

If these criteria are not met, the water suppression should be adjusted and re-evaluated.

**Acquisition**

Once fully calibrated, an unsuppressed water reference spectrum should be acquired to measure $M_0$ and $T_2$ of water. With water (and optional lipid) suppression turned off, five different echo times (TE=40, 50, 75, 100, 125 ms) should be measured with a repetition time of 6s. This scan will be saved as the water reference.

[Optional] If a spectrum can be acquired using the body coil as both a transmitter and receiver, then the scan can be compared to a phantom study to perform a externally-referenced absolute quantification that is corrected for coil loading. While not an optimal quantification, this can be used as a control for the standard internally-referenced quantification, to determine if water concentrations are changing. This requires that the system be able to switch between using the breast coil and body coil as the receiver, and requires that the transmit voltage (or power) be recorded. If the system is capable, a single-shot power reference scan should be collected after the water reference and prior to the TE-averaged scan. This acquisition is identical to the water reference scan, but only acquired at one echo time (TE=50ms) and using the body coil as the receiver.
After all calibrations, the TE-averaged scan will be acquired using the parameters in Table 1. After MRS acquisition, the 2D scout image acquired before the voxel acquisition should be reacquired without altering the parameters or position.

Table 1 - MRS Acquisition Specifications

<table>
<thead>
<tr>
<th>Localization</th>
<th>PRESS or LASER. OVS is optional.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voxel Size</td>
<td>Sized to cover lesion and exclude adipose and normal glandular tissue. The preferred size is 20x20x20mm or larger; no single dimension smaller than 10mm. Voxel need not be isotropic.</td>
</tr>
<tr>
<td>Water suppression</td>
<td>Frequency-selective excitation and crushing of the water resonance (CHESS, VAPOR, or variant). The suppression bandwidth should be 0.5-1ppm, centered at 4.7ppm.</td>
</tr>
<tr>
<td>Fat suppression</td>
<td>Not required. Frequency-selective inversion recovery or suppression may optionally be used, but may not affect (&lt;1%) the 2-4ppm region.</td>
</tr>
<tr>
<td>TE Averaging</td>
<td>TE will be varied between 50 and 200ms in at least 64 increments. 1-4 averages may be acquired at each TE value, for a total of 64-256 FIDs.</td>
</tr>
<tr>
<td>Phase cycling</td>
<td>Optional. May be applied for a fixed TE (i.e., up to 4-step)</td>
</tr>
<tr>
<td>Repetition time (TR)</td>
<td>3 s</td>
</tr>
<tr>
<td>Sampling</td>
<td>3T: 1024 complex points acquired over 512ms (2kHz) 1.5T: 512 complex points acquired over 512 ms (1kHz)</td>
</tr>
</tbody>
</table>

For each voxel acquired in each study, the following data must be transmitted to ACRIN:

1) Water reference scan
2) power reference scan and transmit power calibration [optional]
3) TE-averaged scan
4) Parameters verifying all of the required data (TE, voxel size & position, etc.)
5) Pre- and post- MRS scout images

If multiple voxels are acquired in a study, the files must clearly be labeled to indicate which voxel they are associated with. Each of the files must include raw, complex data: not processed or averaged. Digital oversampling and downsampling to the required matrix size is acceptable.

Analysis

All data from both patient scans and QC scans will be transferred to ACRIN for centralized processing and analysis. Data can be transferred in the native file format for each scanner, provided all the required information is available. The software and source code developed for reading and analyzing the data will also be made available for individual sites for their internal use.

The MRS processing will be similar to the procedures described in Bolan et al., MRM 2003. All spectra, including the water reference and the TE-averaged data, will be DC corrected and automatically phase adjusted. For the water reference spectra, each spectrum will be modeled by
a single water and a single lipid resonance, using a Voigt lineshape model (combined Lorentz and Gauss). The fitting will be performed by minimizing the residuals in the frequency domain. The time-domain amplitude of each peak will be measured for each TE value, and fit with a monoexponential decay to estimate both $T_2$ and the zero-TE amplitude for both water and lipid.

The TE-averaged data will be frequency corrected using cross-correlation between sequential acquisitions to measure and correct respiration-induced frequency variations (Bolan et al. MRM 2004; Katz-Brull et al. MRM 2003). After correction, all spectra will be averaged together to make a single TE-averaged spectrum. The tCho resonance will be modeled with a Voigt lineshape, and fit over the 3-3.4ppm region of the spectrum. The time-domain amplitudes of the tCho and water resonances will be used to calculate the internally-referenced tCho concentration [tCho]. Error estimates will be generated using the standard Cramer-Rao minimum variance bounds. If a power reference scan is available, the externally-referenced tCho, water, and fat concentrations will be estimated using the QC scans for calibration.

All the above procedures will be implemented in software to allow fully-automatic processing. After processing, these spectra and associated data will be reviewed by a physicist to evaluate spectral quality. The physicist will evaluate spectral linewidth, quality of fit, presence of subject motion (from the frequency variation and scout images), presence of sidebands or other spurious RF signals, and uniformity of the spectral baseline. If the spectral data is determined to be good quality, the water and tCho concentrations, along with the water $T_2$ measurement, will be used for further statistical analysis.

**Quality Control**

A standard phantom measurement will be used for quality control (QC). These scans will be used to compare the performance between sites, to monitor consistency at each site, and as a external reference for quantification. Prior to scanning subjects, each site that will perform MRS measurements must complete and submit a series of 4 QC measurements performed on different days. A scan should be repeated whenever a major system change takes place (new coil, software/ hardware upgrade, etc). A similar but shorter QC scan (~15 minutes) should be performed at least once per week in any week an patient is scanned. For this shorter scan, only one spectrum should be acquired in the normal phantom.

The QC scan is designed to evaluate localization quality, artifact suppression, sensitivity, and stability. The performance will depend on the MR scanner, coil, and pulse sequence. The scan itself is intended to emulate an MRS voxel acquired from a lesion in a non-dense breast (predominantly adipose tissue). This phantom will consist of a 40 mm plastic sphere (i.e., a ping-pong ball) containing 1mM phosphocholine chloride, 0.1 mM Gd-DTPA (to reduce T1), and 10 mM DSS (dimethyl silapentane sulfonate; a frequency/lineshape reference). This sphere will be positioned in the center of a 2000 mL plastic bottle containing vegetable (canola) oil, with the center of the sphere located 5 cm above the bottom of the bottle. A second control phantom, identical in all ways except with no phosphocholine, will also be used for control studies. All phantoms will be produced in a single batch at one location (UMN) to insure consistency.

To perform the QC measurement, both normal and control phantoms should be placed in the breast coil. The bottles should be positioned so that the spheres are approximately in the “center” of the coil, so that each sphere is positioned similarly to a breast lesion. Foam pads and other positioning aids should be used to ensure that the bottle is consistently positioned in the same
location within the coil. Additionally, saline bags or manufacturer-supplied phantoms should be placed on top of the coil to emulate the load of a body. The placement of these loading phantoms must also be done consistently as they can affect the coil sensitivity. By default, the normal phantom should be placed in the right breast position, and the control phantom (no PCho) should be placed in the left breast position. The full QC will be performed in both configurations to test all coil elements.

After positioning, the phantoms should be imaged using the same high-resolution T1-weighted protocol and parameters used for the human DCE-MRI studies at that site, but with a 16 cm FOV, and with reduced image matrix (128x128). Using these images, a 20x20x20 mm (full-width half-max) voxel should be placed inside the sphere. Note that the various manufacturers have different conventions for defining voxel sizes, so the nominal voxel dimension should be adjusted to produce a FWHM of 20mm. A spectrum should then be acquired using the standard sequence and procedure described for human scans, including manual adjustment of shimming and water suppression if needed, and the power reference scan if feasible. TE should be varied from 50-200 ms in 64 increments, with no averaging at each step. The water reference and TE-averaged scans must be saved for analysis. The same acquisition should be performed in both the normal and control phantoms. After completion of the protocol, the bottles should be switched and the scan repeated. This full QC scan will result in 4 voxels acquired: right and left breasts, normal and control phantoms. For the weekly QC scan, only one voxel need be acquired from the normal phantom in either the right or left breast.

The analysis of the QC scans will be similar to the in vivo analysis described above. The metrics evaluated will include:

- The signal-to-noise of the water resonance (based on the Voigt fit)
- The signal-to-noise of the tCho resonance (based on the Voigt fit)
- The flatness of the tCho region in the control spectrum
- The internally-referenced tCho concentration, [tCho]
- The linewidth of the tCho resonance
- The variance of phase and frequency over the TE-averaged scan

Additionally, these spectra will be reviewed by a physicist for artifacts, sidebands, and other spectral abnormalities.
APPENDIX V

American College of Radiology Imaging Network
General Qualifying Application

PARTICIPANT INSITUTION

Name of Institution  
_______________________________________________________________________________

Street Address  
_______________________________________________________________________________

Street Address  
_______________________________________________________________________________

City, State, Zip code  
_______________________________________________________________________________

This application is for (check as many as apply):

☐ One hospital

☐ One hospital with free-standing, non-hospital facilities (clinics, imaging centers, etc.)

☐ A multi-hospital system

☐ A multi-hospital system with free-standing, non-hospital facilities (clinics, imaging centers, etc.)

☐ One free-standing, non-hospital facility (clinic, imaging center, etc.)

☐ More than one free-standing, non-hospital facilities (clinics, imaging centers, etc.)

☐ Other (specify):  
_______________________________________________________________________________

If more than one site is covered by this application, please list other sites:

_________________________________________________________________________________

_________________________________________________________________________________

_________________________________________________________________________________

_________________________________________________________________________________

_________________________________________________________________________________

_________________________________________________________________________________

_________________________________________________________________________________

_________________________________________________________________________________
STAFF

ACRIN Site Investigator (Include CV) ________________________________________________________

Telephone Number ________________________
Fax Number ________________________
E-mail Address ________________________

Number of Diagnostic Radiologists: __________ % ABR Certified ____________
Comments (optional)
________________________________________________________________________________________
________________________________________________________________________________________
________________________________________________________________________________________

Number of Physicists: __________ % ABR Certified ____________
Comments (optional)
________________________________________________________________________________________
________________________________________________________________________________________
________________________________________________________________________________________

Number of Data Managers/Research Assistants: __________
Comments (optional)
________________________________________________________________________________________
________________________________________________________________________________________
________________________________________________________________________________________

Other staff who will directly support ACRIN activities (do not list regular clinical technologists, nurses, etc.)
________________________________________________________________________________________
________________________________________________________________________________________
________________________________________________________________________________________
I.S. INFRASTRUCTURE

Do you have the I.S. capability to: (Please check)

1. Register and enter data forms over the internet  Yes ☐  No ☐
2. Browser: Internet Explorer 4.0 or Netscape 4.0 higher  Yes ☐  No ☐
3. View PDF documents  Yes ☐  No ☐

IMAGING EQUIPMENT (Available for use in protocols)

<table>
<thead>
<tr>
<th>Type</th>
<th>Number of Machines</th>
<th>Last Inspected certified by:_____ (agency)</th>
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</thead>
<tbody>
<tr>
<td>X-ray</td>
<td></td>
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<tr>
<td>MRI</td>
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<td>CT Scan</td>
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<tr>
<td>Ultrasound</td>
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<tr>
<td>PET Scan</td>
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<tr>
<td>SPEC/Other Nuclear Medicine</td>
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<tr>
<td>Mammography</td>
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<tr>
<td>Fluoroscopy/Angio/Intervention</td>
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ACCREDITATION

1. Is your hospital accredited by JCAHO? (Please check one)  Yes ☐  No ☐

   Attach a copy of your most recent survey/accreditation report (or executive summary if applicable).
   Non-hospital sites should provide a narrative summary regarding their medical record keeping program and facilities.

2. Facility inspection/certification by city/state agencies. Attach a copy of your most recent survey/accreditation report (or executive summary if applicable).

<table>
<thead>
<tr>
<th>Agency</th>
<th>Frequency of Inspection</th>
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</table>
3. Radiology-specific accreditation

**MQSA Compliance**
Please check your accrediting body. Attach a copy of your certificate.

- [ ] ACR
- [ ] State Accreditation

**ACR Accreditation**
Please check all modalities that are accredited by the ACR. If applicable, attach a copy of your certificate.

- [ ] Mammography
- [ ] Stereotactic Breast Biopsy
- [ ] Ultrasound Guided Breast Biopsy
- [ ] MRI
- [ ] Ultrasound

**AIUM Accreditation**
Please check all modalities that are accredited by the AIUM. If applicable, attach a copy of your certificate.

- [ ] General US
- [ ] Ante-Partum US
- [ ] Non-Invasive Vascular US
- [ ] Breast US

**ICAVL Accreditation**
Please check all modalities that are accredited by the ICAVL. If applicable, attach a copy of your certificate.

- [ ] Vascular
- [ ] Echo
- [ ] Nuclear Medicine

**Other Accreditation**
Please document any additional accreditation. If applicable, attach a copy of your certificate.

- [ ] If no ACR MRI Accreditation, please submit a brief narrative summary sufficient to demonstrate an acceptable level of quality. This summary might include details of technologist staffing and certification, radiologist staffing and certification, QA program and publications from the MRI unit.
If no ACR or AIUM US Accreditation, please submit a brief narrative summary sufficient to demonstrate an acceptable level of quality. This summary might include details of technologist staffing and certification, radiologist staffing and certification, QA program and publications from the US unit.

<table>
<thead>
<tr>
<th>Modality Accredited</th>
<th>Accrediting Body</th>
<th>Date</th>
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**CLINICAL MATERIAL**

1. Average number of new cancer patients seen in the hospital/institution/healthcare system *(please circle one)* per year. During the last calendar year, please indicate the following:

   Number of new patients seen
   
   Number of cancer-related hospital admissions / year

List approximate number of new patients per year in the following anatomical locations *(primary tumors only - do not include metastasis to these sites)*. Or, you may attach a print out from your tumor registry.

- CNS (eg brain, spine, etc)
- ENT (eg oral, larynx, nasopharynx, etc.)
- Skin
- Bronchus, Lung
- Upper GI (eg esophagus, stomach)
- Lower GI (eg colon/rectum)
- Hepatobiliary / pancreatic
- Peritoneum and Retroperitoneum
- Breast
- Ovary
- Cervix Uteri, Invasive
ACRIN 6657  Version 05/29/2007

Uterus
Kidney, Ureter, Bladder
Testis
Prostate
Hodgkin’s Disease
Other Lymphomas
Primary Bone and Joint
Connective and Soft Tissue Sarcomas
Other sites not specified above
Benign

GENERAL

List participation in other National Cooperative Groups:

<table>
<thead>
<tr>
<th>Group</th>
<th>Average No. Patients Entered Per Year</th>
<th>No. Patients Entered Into Studies in Previous Year</th>
<th>Of Those in Previous Year, Percent Evaluable</th>
<th>No. Active Protocols</th>
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Does your institution have a Tumor Registry? (Please check one)  Yes ☐  No ☐

Does your institution have an Institutional Review Board? (Please check one)  Yes ☐  No ☐

If no, please provide the name and address of an affiliate institution’s or Commercial’s IRB that will provide this service for you?

Name ____________________________
Address ____________________________

Does your institution have an assurance document for human subjects that has been approved by the Office for Protection from Research Risks (OPRR), National Institutes of Health? (Please check one)
If yes, please indicate the type of assurance (multiple project or cooperative project) and the assurance number.

Type

Number

Does your department have a Residency Training Program in Radiology? (Please check one)
Yes ☐  No ☐

If Yes, Total # Residents

List any unique features of your program of potential value to ACRIN

Signature of ACRIN Site Investigator

Date

Signature of Radiology Department Chair

Date

Please review checklist prior to forwarding entire application to:

ACRIN Administrator, Attn. GQA
American College of Radiology
American College of Radiology Imaging Network
1818 Market Street, Suite 1600
Philadelphia, PA 19103
Fax: 215-717-0936