

**AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK**

**ACRIN 6657**

**CONTRAST-ENHANCED BREAST MRI and MRS FOR EVALUATION  
OF PATIENTS UNDERGOING NEOADJUVANT TREATMENT  
FOR LOCALLY ADVANCED BREAST CANCER**

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FOR A COMPLETE PROTOCOL***

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**Version Date: March 8, 2010  
Activation Date: December 21, 2001  
Amendments 1 - 6**

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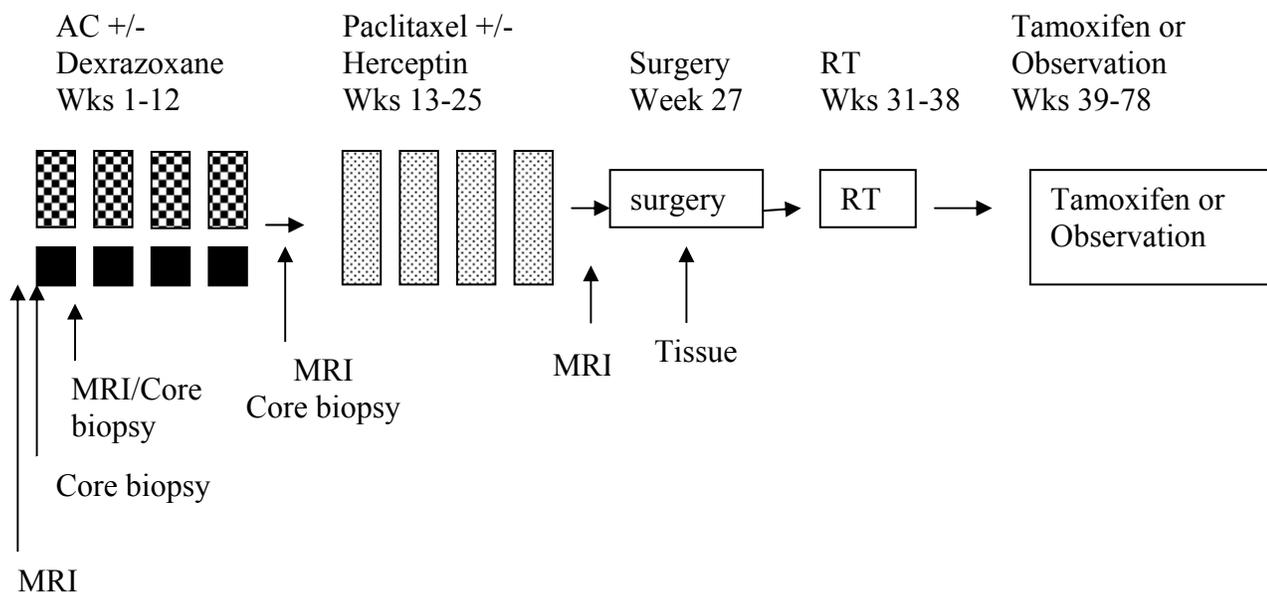
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**Eligibility (see Section 5.0 for details) ORIGINAL**

- Patients receiving neoadjuvant chemotherapy consisting of an anthracycline-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 prosthesis.

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

**ACRIN 6657/CALGB 150007 SCHEMA (original)**

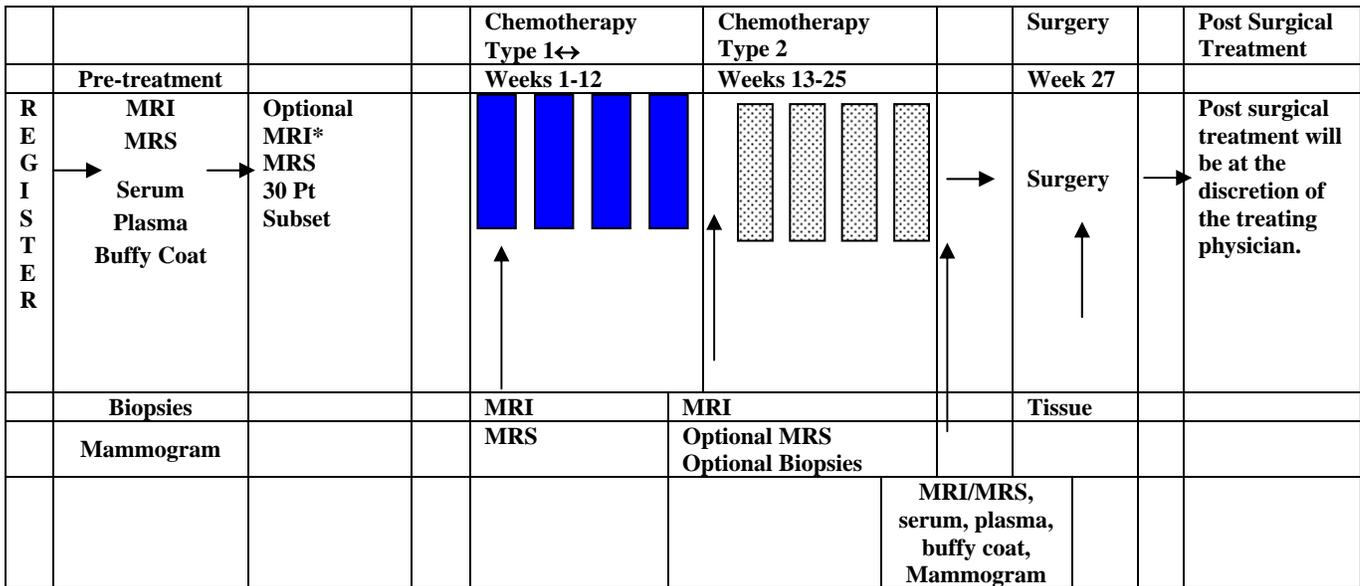


**SEE PAGE 5 FOR ELIGIBILITY AND SCHEMA REVISIONS.**

**Eligibility Revision (See Section 5.0 for Details) AMENDMENT 5 (10/14/08)**

- Patients receiving neoadjuvant chemotherapy consisting of a taxane-based regimen only (chemotherapy Type 1) or followed by an anthracycline (chemotherapy Type 2) and enrolled in CALGB Correlative Science trial 150007.

**ACRIN 6657/CALGB 150007 SCHEMA (Amendment 5 of Protocol Extension)(XX/XX/XX)**



MRI <sub>1</sub>	MRI <sub>1,1</sub>	MRI <sub>2</sub> **	MRI <sub>3</sub> *,**	MRI <sub>4</sub>	
<i>(within 4 wks prior to cycle 1 of Type 1)</i>	<i>(30 patient subset after baseline scan, but prior to cycle 1 of Type 1)</i>	<i>(at least 2 weeks after the first cycle of Type 1 and prior to the second cycle of Type 1)</i>	<i>(between Type 1 and Type 2)</i>	<i>(after Type 2 and before surgery)</i>	
MRS	MRS 1.1 <i>(accompanying MRI<sub>1,1</sub> in 30 patients)</i>	MRS	MRS <i>(optional)</i>	MRS	
Core Biopsy Serum Sample		Core Biopsy** <i>(24-96 hours after start of Type 1)</i>	(Core Biopsy)* <i>(optional)</i>	Serum Sample	Surgical Tissue <i>(at Surgery)</i>
Mammo				Mammo	
Ultrasound <i>(optional)</i>				Ultrasound <i>(optional)</i>	

\*MRI<sub>3</sub> and Core Biopsy: between Type 1, taxane-based chemotherapy and Type 2, anthracycline-based therapy, if the patient continues to anthracycline therapy

\*\*The following changes will apply to the schema for ACRIN 6657 Protocol Extension: MRS will be performed in combination with each MRI exam; MRI<sub>2</sub> will be performed either 1) 20-28 hours or 2) 48-96 hours, after the first cycle of Type 1; the second core biopsy (24-96 hours after start of Type 1) will not be performed; MRI<sub>3</sub> is no longer optional, but is mandatory.

## **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.<sup>1-8</sup> 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.<sup>2, 4-6, 9-17</sup>

MRI has shown promise as a staging tool and can accurately represent the extent of cancer when compared to pathology specimens.<sup>18</sup> 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.<sup>19</sup>

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.

In the original protocol, women receiving neoadjuvant chemotherapy consisting of a taxane-based regimen only or followed by an anthracycline will be eligible to enroll in both the Correlative Science trial (CALGB 150007) and the MR imaging protocol (ACRIN 6657). The order of chemotherapy regimen is reversed in the protocol extension. Type 1 chemotherapy refers to the taxane-based treatment only; Type 2 chemotherapy refers to the taxane followed by an anthracycline-based treatment.

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.<sup>20-22</sup> 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.<sup>20</sup> 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 IIIc breast cancer is strongly predictive of an excellent long-term survival.<sup>23-27</sup> 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.<sup>23</sup>

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.<sup>24-27</sup> 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 standard-of-care 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 Type 2 chemotherapy based on response to Type 1 chemotherapy. 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 <sup>1</sup>H MR Spectroscopy of Breast Tumors**

A number of studies have shown that total choline concentration [tCho] measured by <sup>1</sup>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.<sup>36</sup> 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 <sup>1</sup>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 <sup>1</sup>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**

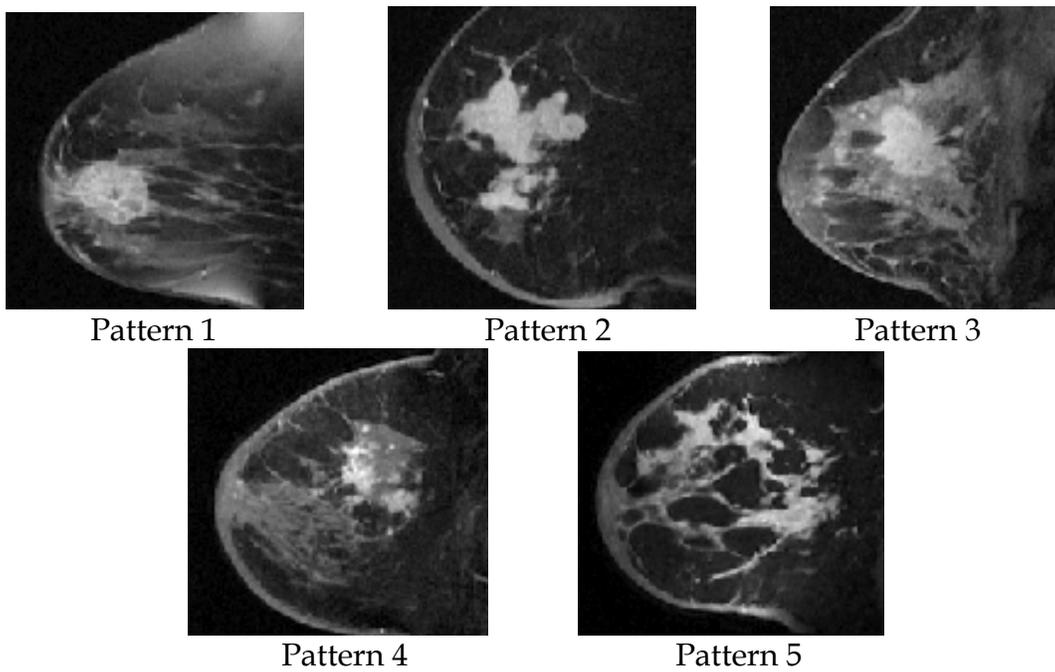
A group of 42 patients with stage III/IV breast cancer underwent MRI before and following a complete course (4 cycles) of adriamycin/cytosin (AC) chemotherapy. Thirty-four of these patients have completed treatment and undergone surgery. Eighteen of the 34 patients also had one MRI exam following their 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**

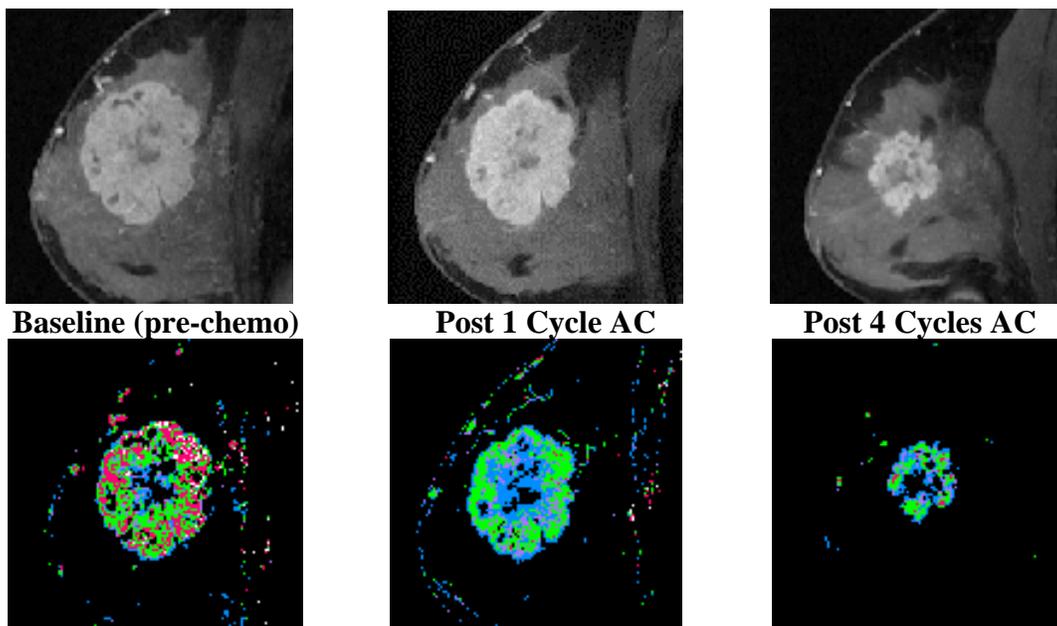
Tumor classification by MRI pattern appears to correlate with clinical response and nodal status. Several distinct spatial patterns have been identified on MRI in the group of stage III and stage IV patients. We have classified these morphologically different patterns by which tumor enhancement is distributed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

TABLE 1	
Morphologic Pattern:	
1	Single uni-centric mass with well-defined margin
2	Multi-lobulated mass with well-defined margin
3	Area enhancement with irregular margins –with nodularity
4	Area enhancement with irregular margins-without nodularity
5	Septal spread; streaming

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.



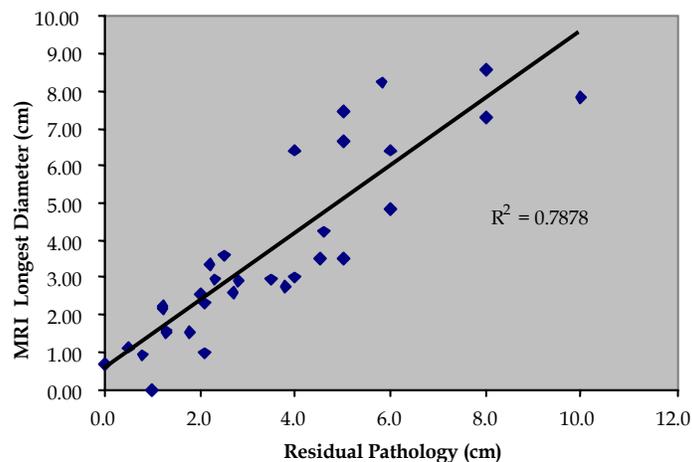
<i>Baseline (pre-chemo):</i>	<i>Post 1-cycle AC:</i>	<i>Post 4-cycles AC:</i>
<i>peak SER</i> = 2.1	<i>peak SER</i> = 1.5	<i>peak SER</i> = 1.6
<i>Volume</i> = 65 cm <sup>3</sup>	<i>Volume</i> = 42 cm <sup>3</sup>	<i>Volume</i> = 4 cm <sup>3</sup>
<i>%Red+White</i> = 41%	<i>%Red+White</i> = 3%	<i>%Red+White</i> = 16%

**Figure 2** 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

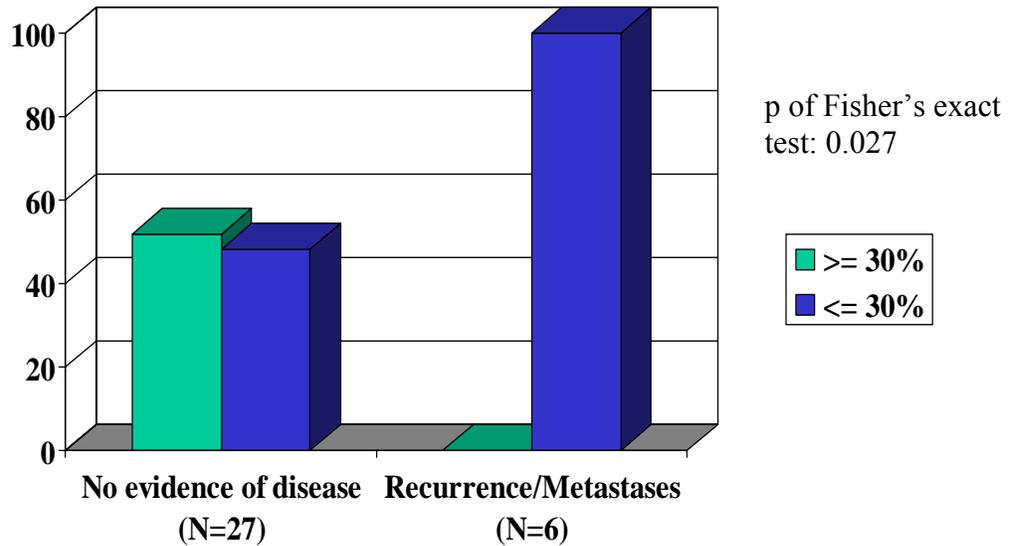
For preliminary analysis, we have used the size of residual disease on pathology and number of positive axillary nodes as intermediate endpoints. Both of these measurements have been shown to predict patient outcome following neoadjuvant chemotherapy and surgery.<sup>26-27</sup> MRI was found to accurately 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).<sup>32</sup>

Figure 3: Size of Residual Disease: Pathology vs. MRI



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).<sup>33-34</sup>

Figure 4: MR Change in Longest Diameter



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).<sup>35</sup> 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 5: Mean Change in Longest Diameter by Imaging Pattern

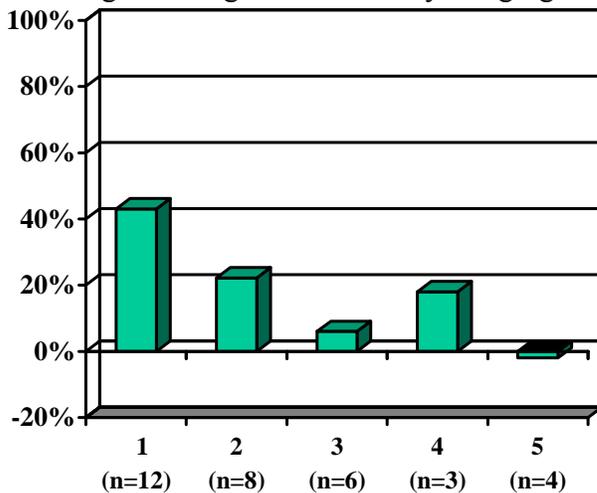


Figure 6: % Recurrence by Imaging Pattern

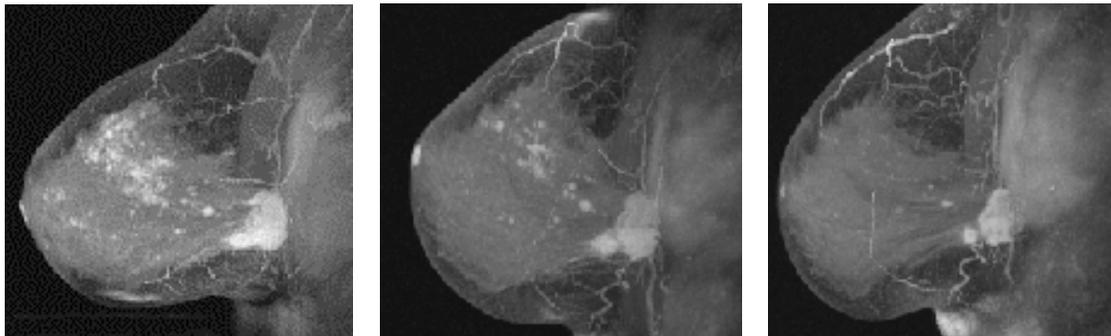
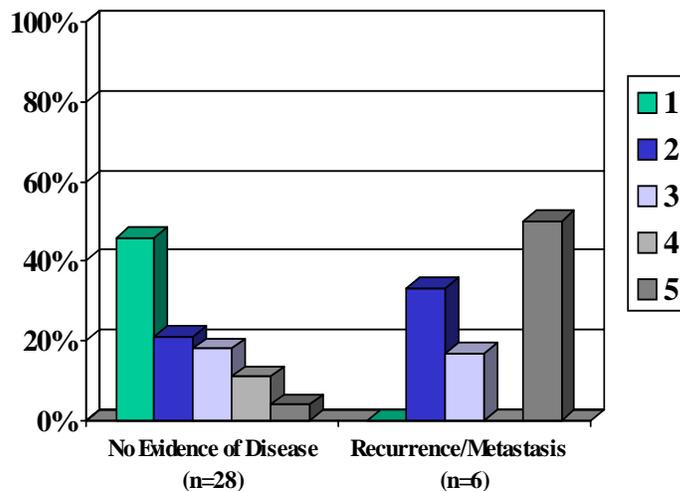


Figure 7. Multifocal disease shows two distinct patterns of distribution with different rates and degree of shrinkage with neoadjuvant treatment

## 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 <sup>1</sup>H 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 [tCho] measured early in treatment can add information beyond contrast-enhanced MRI. The ACRIN 6657 trial extension will obtain

pilot data using  $^1\text{H}$  MRS to determine if similar results to the Meisamy study at 4 Tesla can be obtained at 3 Tesla and 1.5 Tesla, 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 [tCho] 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 and Secondary Endpoints**

### **4.2.1 Primary Endpoint**

**4.2.1.1** Primary endpoint is disease-free three-year survival.

### **4.2.2 Secondary Endpoints**

**4.2.2.1** Extent of residual disease;

**4.2.2.2** Change in the maximum dimension of the tumor over time;

**4.2.2.3** Change in the tumor volume over time.

### **4.2.3 The following measurements will be used as surrogates for the secondary endpoints:**

**4.2.3.1** Maximum dimension of tumor size measured by MRI, mammography and pathology;

**4.2.3.2** MRI volume;

**4.2.3.3** MRI peak signal enhancement ratio (SER);

**4.2.3.4** SER Distribution (% of tumor in Highest SER category);

**4.2.3.5** Morphological pattern;

**4.2.3.6** Change in tumor size by clinical exam.

## **4.3 Primary Aims of ACRIN 6657**

Four MRI exams will be performed as part of the MRI companion study: pre-neoadjuvant therapy (MRI<sub>1</sub>), after 1 cycle of Type 1 therapy (MRI<sub>2</sub>), between Type 1 and Type 2 (MRI<sub>3</sub>), and after completion of neoadjuvant treatment and prior to surgery (MRI<sub>4</sub>). MRI<sub>1</sub> will serve as a baseline to characterize the pre-treatment breast. The purpose of MRI<sub>2</sub> is to evaluate whether MRI changes early in treatment can predict overall response. MRI<sub>3</sub> 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<sub>4</sub>, 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):

**4.3.1** 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.**

- 4.3.2** 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.**

#### **4.4 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):

- 4.4.1** 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.**

- 4.4.2** 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.**

- 4.4.3** What is the conditional probability of response to Type 2 chemotherapy based on MR response to Type 1 chemotherapy?

**Aim 5: Estimate the conditional probability of response to Type 2 based on MRI measured response to Type 1.**

## **4.5 Aims of the ACRIN 6657 Protocol Extension**

**4.5.1** The objective of the ACRIN 6657 protocol extension is to investigate the usefulness of total choline concentration [tCho] measured by <sup>1</sup>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. Two changes to the imaging protocol will be made: 1) addition of a single voxel <sup>1</sup>H MRS acquisition (and optional diffusion-weighted MRI acquisition) to the MRI exam, and 2) change of the timing of the post 1<sup>st</sup> cycle MRI/MRS exam.

**4.5.2** 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 <sup>1</sup>H MRS technique at 3 Tesla (or 1.5 Tesla), is predictive of pathologic response and final change in tumor volume by MR imaging.**

**4.5.3** 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 apparent diffusion coefficient (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**

ACRIN 6657 eligibility criteria match that of CALGB Correlative Science trial 150007. Patients with histologically-documented tumors per CALGB criteria that are at least 3 cm who choose to undergo neoadjuvant chemotherapy will be eligible to participate in the Correlative Science and Imaging companion trials (CALGB 150007/ACRIN 6657). The therapeutic regimen will consist of AC followed by a taxane for patients enrolled under the original trial protocol, and will consist of a taxane alone (Type 1) or taxane followed by AC (Type 1 followed by Type 2) for patients enrolled as part of the protocol extension. See Section 3.0 of the CALGB 150007 protocol for the complete eligibility description.

### **5.1 Inclusion Criteria Specific to the ACRIN 6657 MRI Study**

**5.1.1** IRB approval/Signed informed consent

**5.1.2** Patients must have a calculated creatinine clearance of > 30 mL/min (modified Cockcroft and Gault formula) based on a serum creatinine level obtained within 28 days of registration in order to participate.

Creatinine Clearance for Males:  $([140 - \text{age (years)}] \times \text{weight (kg)}) / (\text{serum creatinine} \times 72)$

Creatinine Clearance for Females: Creatinine Clearance (male)  $\times 0.85$

### **5.2 Exclusion Criteria Specific to the ACRIN 6657 MRI Study**

**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](http://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 web site.

- 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 are out of range, and data that are 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 pass these logic checks. Forms that are not completed in one sitting can still be submitted and completed at a later date. The data are 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 are transferred into the clinical database. No further direct revision of the submitted data are allowed after this point. An e-mail is generated and sent to the site listing all of the data completed and just submitted. Should a problem occur during transmission, this automated response supplies an explanation and instructions for resubmitting the data.
- 6.2.5** If a temporary problem prevents access to the Internet, investigators should wait until access is restored to submit data. Investigators should notify the DMC of the problem and the DMC will give an estimated time when access is expected to be restored. If access will be unavailable for an extended period, sites must seek another Internet Service Provider (ISP). On a short-term basis, the ACR can serve as an ISP.

### **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 are then entered into the database. A variable in the new record is set to "Unreviewed" until the data are 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 DMC 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 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 for resolution.

- 6.4.2** If the program detects missing or problematic data, the DMC will send a Request for Information (query letter) to the investigator specifying the problem and requesting clarification. The DMC 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 via email for timely submission of data through the use of a Forms Due Report. 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

<b>Forms</b>	<b><u>Data Submission</u></b>
<b>Registration Form</b>	Completed by site research associate (RA) and submitted at the time of registration via ACRIN web site.
<b>Mammography Interpretation Forms</b>	<p><b>Mammography protocol specific time-points:</b>  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.</p> <p><b>Data:</b> 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 Baseline form is due before the start of treatment.</p>
<b>Mammography Images/Films</b>	Mammo 1-corresponds with MRI-1 and must be submitted by site within 4 weeks of registration. Mammo 2-corresponds with MRI-4 and must be submitted by site within 2 weeks of mammogram.
<b>Mammography Reports</b>	Mammo 1-corresponds with MRI-1 and must be submitted by site within 4 weeks of registration via mail or fax. Mammo 2-corresponds with MRI-4 and must be submitted by site within 2 weeks of mammogram via mail or fax.
<b>Ultrasound Interpretation Forms</b> *optional imaging	<p><b>Ultrasound protocol specific time-points:</b>  US 1-corresponds with MRI-1.  US 2-corresponds with MRI-4.</p> <p><b>Data:</b> Completed by radiologist. Submitted by site within 2 weeks of the study diagnostic ultrasound, if performed, via the ACRIN web site.</p>
<b>Ultrasound Reports</b>	Ultrasound 1-corresponds with MRI-1 and must be submitted by site within 4 weeks of registration via mail or fax. Ultrasound 2-corresponds with MRI-4 and must be submitted by site within 2 weeks of ultrasound via mail or fax.
<b>MRI Forms</b>	<p><b>MRI protocol specific time-points:</b>  MRI 1-within 4 weeks before start of neoadjuvant treatment.  MRI 1.1-within 72 hours post Baseline (for 30 consented patients only).  MRI 2-within 20-28 or 48-96 hours post Baseline.  MRI 3-after Type 1 Chemotherapy.  MRI 4-within 3 or 4 weeks after final chemotherapy treatment and before surgery.</p> <p><b>Data:</b> Completed by radiologist. Submitted by site within 2 weeks of the study specific MRI-1, 1.1, 2, 3, 4 exams via the ACRIN web site.</p>

<b>MRS Forms</b>	<p><b>MRS protocol specific time-points:</b>  MRS 1-within 4 weeks before start of neoadjuvant treatment  MRS 1.1-within 72 hours post Baseline (for 30 consented patients only).  MRS 2-within 20-28 or 48-96 hours post Baseline.  MRS 4-within 3 or 4 weeks after final chemotherapy treatment and before surgery.</p> <p><b>Data:</b> Completed by RA. Submitted by site within 2 weeks of the study specific MRI-1, 1.1, 2, 4 exams via the ACRIN web site.</p>
<b>Supplemental MRI Forms</b>	<p><b>MRI/MRS protocol specific time-points:</b>  This form is submitted <b>only</b> if additional lesion(s) are seen that were not seen on MRI 1. Use this form for continued reporting of lesions not seen on MRI.</p> <p><b>Data:</b> Completed by radiologist. Submitted by site within 2 weeks of each study specific MRI/MRS-1.1, 2, 3, 4 exams via the ACRIN web site.</p>
<b>MRI Reports</b>	<p>MRI 1-Submitted by site within 4 weeks of registration via mail or fax.  MRI 1.1, 2, 3, 4-Submitted by site within 2 weeks of MRI exams via mail or fax.</p>
<b>MRI Images</b>	<p>MRI 1-Submitted by site within 4 weeks of registration.  MRI 1.1, 2, 3, 4-Submitted by site within 2 weeks of MRI exams.</p>
<b>Surgical Pathology Forms</b>	<p><b>Data:</b> Completed by site RA based on CALGB pathology form and pathology report; submitted within 2 weeks after surgery via ACRIN web site.</p>

## **6.8 Image Submission**

Digitally generated images can be transmitted to the ACRIN Imaging Management Center (IMC) via FTP directly to the image archive. An Imaging Transmittal Worksheet (ITW) will be used to verify a complete transfer of the images to the ACRIN. The ITW is available via the ACRIN web site ([www.acrin.org/6657\\_protocol.aspx](http://www.acrin.org/6657_protocol.aspx)). The completed ITW will be faxed to the ACRIN Image Management Center (IMC) at (215) 923-1737 when the images are being transmitted to ACRIN HQ.

All images are requested to be in digital format; film submissions will not be accepted. ACRIN has developed software that allows for electronic transmission of images to the IMC that have been scrubbed of all participant identifiers. ACRIN will contact each site individually to determine their readiness and ability to utilize this system. For any questions, contact ACRIN IMC via email at [imagearchive@phila.acr.org](mailto:imagearchive@phila.acr.org); indicate in the subject line ACRIN 6657 image submission questions. Once technical capabilities have been established, imaging personnel from ACRIN will coordinate the image transmission process and options and train all operating research staff.

Images on CD, DVD, or MOD should be addressed and sent to:

ACRIN Image Archive  
ACRIN Protocol 6657 Images  
American College of Radiology  
1818 Market Street, Suite 1600  
Philadelphia, PA 19103  
Attn: ACRIN 6657 Imaging Specialist

**6.8.1** If required and part of the protocol, images maintained at ACRIN Headquarters Image Archive may be distributed to other participating sites, using FTP, MOD, or CD-ROM where appropriate, for purposes of secondary review. The header recorded on DICOM formatted image data often contains information identifying the participant by name. These identifiers **must** be scrubbed before the images are transferred.

This involves **replacing** the following:

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

This process can be completed by utilizing the software program available at the institution, or the software program provided by ACRIN.

**6.8.2** In the event that the site does not have DICOM capability or is unable to transfer images with scrubbed headers, the images may be sent on a CD or other electronic medium to ACRIN IMC for digitization/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: ACRIN Imaging Core Lab

**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, Dartmouth Medical School, and Mayo Clinic–Rochester have been added as sites for the protocol extension. Additional sites may continue to be added, depending on expertise, patient accrual projections, interest, and resources. The original ACRIN 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, reflecting the changes made in Amendment 5 (version dated 10/14/08).

### **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 web site. 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](http://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 ACRIN web registration site is not accessible, participating sites may still register a patient by faxing the completed eligibility checklist to the DMC at ACRIN (215-717-0936, ATTN: PATIENT REGISTRATION). ACRIN 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 Type 1 chemotherapy and prior to the second cycle of Type 1 chemotherapy

MRI<sub>3</sub>: between Type 1 and Type 2 chemotherapy regimens, if the patient continues to Type 2

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 ACRIN 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 changing the timing of MRI<sub>2</sub>. The MRI's for the protocol extension will be the following:

**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>:** In 1 of 2 time windows following the first cycle of Type 1 chemotherapy: 20-28 hours or 48-96 hours.

**MRI<sub>3</sub>:** MRI<sub>3</sub> is mandatory and should be completed between the conclusion of the final cycle of Type 1 chemotherapy and the first cycle of Type 2.

**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.

One additional MRI exam (MRI<sub>1.1</sub>) may be performed 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 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.

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<sub>2</sub>. 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.

#### **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 MRI<sub>1</sub> 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 Type 1

chemotherapy. For the original protocol, the baseline core biopsy should be performed *after* the baseline MRI to avoid biopsy-related image artifacts. (This scheduling may not always be possible.) For the protocol extension, the baseline core biopsy should be performed *before* the baseline MRI. This change is necessary to avoid having the biopsy occur between the baseline MRI and post-first cycle MRI, which occurs earlier than in the original protocol. One additional study-specific core biopsy may be performed as part of the Correlative Science trial at the end of Type 1 chemotherapy and prior to start of Type 2. 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**

For the original protocol, 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 ( $\leq 1$  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-DTPA 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  $\leq 2.5$  mm, depending on the size of the breast. Other pulse sequence specifications will include: TR  $\leq 20$  ms, TE = 4.5 ms, flip angle  $\leq 45^\circ$ . 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 or bilateral imaging in the sagittal or axial planes 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) 16-22 cm (sagittal) or 32-40 cm (axial), 3 mm slice thickness, skip 0.5 mm, 512x192 minimum 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. For the dynamic contrast-enhanced study, high resolution ( $\leq 1$  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-DTPA 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 16-22 cm (sagittal) or 32-40 cm (axial), and minimum matrix of 256 x 192 (sagittal) or 512 x 384 (axial). A minimum of 64 slices should be acquired of thickness  $\leq 2.5$  mm, depending on the size of the breast(s). Other pulse sequence specifications will include: TR  $\leq 24$  ms, minimum TE (with fat and water in phase), flip angle  $\leq 45^\circ$ . 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 ACRIN 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,  $PE = (S_1 - S_0) / S_0$ , and signal enhancement ratio (SER)  $= (S_1 - S_0) / (S_2 - S_0)$ , 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.<sup>27</sup>

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).<sup>19</sup> 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 <sup>1</sup>H MRS for predicting tumor response to treatment. <sup>1</sup>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 Type 1 chemotherapy treatment OR within 48-96 hours of Type 1 chemotherapy treatment, and 3) at the completion of chemotherapy and prior to surgery. An additional MRI (with MRS optional) is required between chemotherapy Type 1 and Type 2 regimens. 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), FOV 16-22 cm (sagittal) or 32-

- 40 cm (axial), and minimum matrix of 256 x 192 (sagittal) or 512 x 384 (axial), minimum of 64 slices,  $\leq 2.5$  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  $^1\text{H}$  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 Type 1 chemotherapy. 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 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<sup>TM</sup> 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**

**Absence of Invasive Cancer: 90 % Survival**

No DCIS

Presence of DCIS

- Minimal (< 1cm)
- Moderate, widespread (> 1cm, specify extent)

**Microscopic Residual Invasive Cancer: 70% Survival**

- Single focus (specify size)
- No associated DCIS

Presence of associated DCIS

- Minimal (< 1cm)
- Moderate, widespread (> 1cm, specify extent)

Multifocal (specify size of largest focus)

- No associated DCIS

Presence of associated DCIS

- Minimal (< 1cm)
- Moderate, widespread (> 1cm, specify extent)

**Gross (Macroscopic) Residual Invasive Cancer: 70% Survival for A and 50 % for B**

- Less than 1 cm<sup>2</sup> (specify size)
- No associated DCIS

Presence of associated DCIS

- Minimal (< 1cm)
- Moderate, widespread (> 1cm, specify extent)

Greater than 1 cm<sup>2</sup> (specify size)

- No associated DCIS

Presence of associated DCIS

- Minimal (< 1cm)
- Moderate, widespread (> 1cm, specify extent)

**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
- Causes congenital anomaly or birth defect.

### **9.3 Adverse Event Grading**

Grade is used to denote the severity of the adverse event, based on guidance from the CTEP Active version of the Common Terminology Criteria for Adverse Events (CTCAE).

- 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**

- Claustrophobia
- Discomfort

#### **9.6 Expected Adverse Events from Contrast Agent (gadolinium)**

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

Nephrogenic Systemic Fibrosis (NSF) or Nephrogenic Fibrosing Dermopathy (NFD), kidney disorders, may occur in patients with moderate to end-stage kidney disease (glomerular filtration rate <30mL/min/1.73m<sup>2</sup>) and in patients with renal dysfunction due to the hepatorenal syndrome or in the perioperative liver transplantation period after they have had a MRI scan with gadolinium-based MR contrast agents (GBMCA).

NSF causes fibrosis of the skin and connective tissues throughout the body. Patients develop skin thickening that may prevent bending and extending joints, resulting in decreased mobility of joints. NSF usually starts in the lower extremities. Fibrosis can also develop in the diaphragm, muscles in the thigh and lower abdomen, and lung vessels. [Reference: FDA/Center for Drug Evaluation and Research. May 23, 2007 http://www.fda.gov/cder/drug/infopage/gcca/qa\\_200705.htm](http://www.fda.gov/cder/drug/infopage/gcca/qa_200705.htm)

- Nausea
- Headache
- Hives
- Temporary low blood pressure
- Allergic reaction

#### **9.7 Expected Adverse Events from IV Needle Placement**

- Hemorrhage (hematoma at the injection site)
- Infection (catheter related infection) at the injection site
- 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 seriousness 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 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 CTCAEv3.0 Grade 3, 4, or 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 adverse events of Grades 1 through 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 above-mentioned 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**

- 9.12.1** An expedited adverse event report requires submission to the NCI/CIP and ACRIN using the paper template "Adverse Event Expedited Report—Single Agent" available on the CTEP home page, <http://ctep.info.nih.gov>. Protocols involving only imaging procedures must be submitted using a paper version.

Protocols involving only imaging procedures must be submitted using a paper version. Investigators following those protocols should omit the Course Information section and the Protocol Agent section, even though the template indicates those as mandatory. (Do not try to send the form via the web site; it will not accept a form without those fields filled in.)

General questions regarding completion of the AdEERS report or submission can be sent to [CIPSAEReporting@tech-res.com](mailto:CIPSAEReporting@tech-res.com). AdEERSMD helpline is available for any questions via phone at 301-897-7497.

- 9.12.2** To make an expedited telephone reports to NCI/CIP, contact TRI staff at (301) 897-1704, available 24 hours a day (recorder after hours from 7:30 PM to 7:30 AM Eastern Time).
- 9.12.3** An expedited adverse event report must be sent within the appropriate timeframe specified in Section 9.11 to NCI/CIP by fax at (301) 897-7402. All fatal adverse events should be reported by telephone within 24-hours of the event.
- 9.12.4** A copy of all expedited adverse event reports should be sent to ACRIN by fax at (215) 717-0936. All fatal adverse events should be reported by telephone within 24 hours of first knowledge of the event. To make a telephone report to ACRIN, call (215) 717-2763, available 24 hours a day (recorder after hours from 4:30 PM to 8:30 AM ET).
- 9.12.5** A copy of all expedited adverse event reports should be sent to ACRIN by fax at (215) 717-0936. The original signed and dated report must be sent to ACRIN at:

Attn: ACRIN 6657 AE Coordinator  
1818 Market Street, 16<sup>th</sup> Floor  
Philadelphia, PA 19103

**9.12.6** 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/pdrc.aspx](http://www.acrin.org/pdrc.aspx)).

**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 submit to ACRIN's quality assurance monitor 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). Copies of these documents must be kept on file for the trial for regulatory compliance.

## **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

Form	Data Collection	Source Documentation
Registration	At time of registration via the ACRIN web site.	Completed, signed (research associate), and dated form. Informed consent form, signed by participant and site personnel (as defined by local IRB).
Mammography Interpretation Forms	<p><b>Mammography protocol specific time-points:</b>            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.</p> <p><b>Data Due:</b> Within 2 weeks of each study mammogram via the ACRIN web site. If using prior mammogram at study entry, the IA form is due before the start of treatment.</p>	Completed, signed (reader), and dated forms. Mammography reports, if generated.
Ultrasound Interpretation Forms  <i>*optional</i>	<p><b>Ultrasound protocol specific time-points:</b>            1-corresponds with MRI-1.            2-corresponds with MRI-4.</p> <p><b>Data Due:</b> Within 2 weeks of the study diagnostic ultrasound, if performed, via the ACRIN web site.</p>	Completed, signed (reader), and dated forms. Ultrasound reports.
<b>MRI Forms:</b> <b>Baseline/Pretreatment</b> <b>Baseline/Reproducibility</b>  <b>Treatment</b> <b>Optional Treatment</b>  <b>Post-Treatment</b>	<p><b>MRI protocol specific time-points:</b>            1- within 4 weeks before start of neoadjuvant treatment.            1.1- within 72 hours post Baseline (Patient must consent to this MRI).            2- within 20-28 or 48-96 hours post Baseline.            3- after Type 1 chemotherapy but before initiation of Type 2 chemotherapy. <b><i>*This MRI is mandatory as of Amendment 5 to the ACRIN 6657 protocol.</i></b>            4- within 3 or 4 weeks after final chemotherapy treatment and before surgery.</p> <p><b>Data Due:</b> Within 2 weeks of each study specific MRI-1, 1.1, 2, 3, 4 exams via the ACRIN web site.</p>	Completed, signed (reader), and dated forms. MRI reports, if generated.
<b>MRS Forms:</b> <b>Baseline/Pretreatment</b>  <b>Baseline/Reproducibility</b>  <b>Treatment</b> <b>Post-Treatment</b>	<p><b>MRS protocol specific time-points:</b>            1- within 4 weeks before start of neoadjuvant treatment.            1.1- within 72 hours post Baseline (Patient must consent to this treatment).            2- within 20-28 or 48-96 hours post Baseline.            3- after Type 1 chemotherapy but before initiation of Type 2 chemotherapy. <b><i>*This MRS is optional for this stage of the trial, but MRI is mandatory.</i></b>            4- within 3 or 4 weeks after final chemotherapy treatment and before surgery.</p>	<b>Data:</b> Completed by research associate. Submitted by site within 2 weeks of each study specific MRI/MRS-1, 1.1, 2, (3 optional), 4 exams via the ACRIN web site.
Surgical Pathology Form	<b>Data Due:</b> Within 2 weeks of surgery via the ACRIN web site.	Completed, signed (research associate), and dated form. Surgical pathology report, surgical report.

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## APPENDIX I

### ACRIN 6657 & CALGB 150007

#### SAMPLE CONSENT FOR RESEARCH STUDY

##### **Contrast-Enhanced Breast MRI/MRS and 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 Cancer Treatment Research Studies," 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 a taxane chemotherapy drug (this will be referred to as Type 1 chemotherapy) that may be followed by treatment with an anthracycline 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 basis of:
  - the particular markers on their breast cancer cells and blood samples, and
  - 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.
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 12 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) MRI/MRS scans before and during your treatment.
- 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 scan will be done after completing Type 1 chemotherapy. The MRS portion of the third scan is optional.
- the fourth MRI/MRS scan will be after the completion of all of your chemotherapy and before you have surgery.

There is one additional MRI/MRS scan that is 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 optional MRS scan added to the MRI scan after completing Type 1 chemotherapy.

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

Yes \_\_\_\_\_ No \_\_\_\_\_

I agree to have the additional optional MRS after completing Type 1 chemotherapy.

Yes \_\_\_\_\_ No \_\_\_\_\_

The MRI/MRS procedures 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, not being able to lie still or on your stomach, or having severe kidney disease.

### **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 but 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 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.

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.

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

Yes \_\_\_\_\_ No \_\_\_\_\_

**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:

Before Chemotherapy	→	Weeks 1-12	→	Weeks 13-25	→	Week 27	→ Treatment after Surgery
Biopsy Blood sample MRI/MRS scan  Mammogram  Ultrasound (if indicated by your doctor)	30 patients  will have an optional MRI/MRS scan	Type 1 Chemotherapy  MRI/MRS scan either 20-28 hrs or 48-96 hrs after the start of Type 1 chemotherapy	MRI scan required; all participants will be asked to have an optional MRS scan	Type 2 Chemotherapy  Optional biopsy before the start of Type 2 chemotherapy	MRI/MRS scan, blood sample  Mammogram  Ultrasound (if indicated by your doctor)	S U R G E R Y  Tissue sample	Treatment after surgery will be at the discretion of your doctor.

**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 a taxane chemotherapy drug (Type 1 chemotherapy) followed by an anthracycline 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 than 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 these side effects. You should discuss these 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 associated with MRI/MRS 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

In rare cases, some patients who have a severe kidney disease, develop symptoms of tightening or scarring of the skin and organ failure called nephrogenic systemic fibrosis (NSF) and nephrogenic fibrosing dermopathy (NFD) after they have had a MRI scan with gadolinium-based contrast agent.

NSF and NDF have not been seen in patients with normal working kidneys or mild problems in kidney function. NSF and NDF cause fibrosis (thickening) of the skin and connective tissues throughout the body. Patients develop skin thickening that may prevent bending and extending joints, resulting in decreased mobility of joints. NSF and NDF usually start in the legs and feet. It can also develop in the diaphragm (muscle and connective tissue that separates the chest from the abdomen), muscles in the thigh and lower abdomen, and areas of the lungs. In very rare cases, they can lead to death. Prior to study entry, we will determine, by a routine blood test, if your kidneys are working properly in order to make sure the gadolinium contrast agent is safe for you.

Reference: FDA/Center for Drug Evaluation and Research. May 23, 2007, [http://www.fda.gov/cder/drug/infopage/gcca/qa\\_200705.htm](http://www.fda.gov/cder/drug/infopage/gcca/qa_200705.htm).

## **Risks Associated with Intravenous Catheter (IV) 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 Cancer and Leukemia Group B (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 CALGB, ACRIN, 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 to 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. Standard MRI scans are usually covered by most insurance companies, but this is not guaranteed. The study will reimburse the cost of up to three MRI/MRS exams and one additional MRI scan as needed to supplement the imaging exams that insurance covers as standard of care. Please ask your doctor about any expected additional costs or insurance problems.

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:

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Name

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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)*

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Name

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Telephone Number

## **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.

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**1. My tissue and blood may be kept for use in research to learn about, prevent, treat, or cure cancer.**

Yes \_\_\_\_ No \_\_\_\_

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**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 \_\_\_\_

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**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 have had my questions answered. I agree to take part in this study.**

**Participant**\_\_\_\_\_

**Date**\_\_\_\_\_

*<Insert other signature and date lines as appropriate per local IRB policies and procedures>*

## **APPENDIX II**

### **ACRIN 6657 Eligibility Checklist**

The ACRIN 6657 Eligibility Checklist is available on the ACRIN web site at ACRIN 6657 Protocol web page ([www.acrin.org/6657\\_protocol.aspx](http://www.acrin.org/6657_protocol.aspx)). For more detailed information, contact the ACRIN 6657 Data Manager at ACRIN. The contact information can also be found on the above-mentioned web page.

## **APPENDIX III**

### **Breast MRI Lexicon**

#### **I. Morphologic Categories and Terms**

For specific MRI morphologic categories and terms, see the American College of Radiology (ACR) BI-RADS® MRI Lexicon Classification Form (2003) online at:

[www.acr.org/SecondaryMainMenuCategories/quality\\_safety/BIRADSAtlas/BIRADSAtlasexcerptedtext/BIRADSMRIFirstEdition/ACRBIRADSMRILexiconClassificationFormDoc1.aspx](http://www.acr.org/SecondaryMainMenuCategories/quality_safety/BIRADSAtlas/BIRADSAtlasexcerptedtext/BIRADSMRIFirstEdition/ACRBIRADSMRILexiconClassificationFormDoc1.aspx).

For excerpted text from the ACR BI-RADS® Atlas\* criteria, visit:

[www.acr.org/SecondaryMainMenuCategories/quality\\_safety/BIRADSAtlas/BIRADSAtlasexcerptedtext.aspx](http://www.acr.org/SecondaryMainMenuCategories/quality_safety/BIRADSAtlas/BIRADSAtlasexcerptedtext.aspx).

\* American College of Radiology (ACR) Breast Imaging Reporting and Data System Atlas (BI-RADS® Atlas). Reston, Va: © American College of Radiology; 2003. All rights reserved.”

## Breast MRI Lexicon

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

<b><u>T</u></b>		<b><u>F</u></b>		<b><u>Q</u></b>	
T0	No primary	F0	no other area of	Q0	no quadrants of
Tis	<i>in situ</i>		suspicious enhancement		suspicious enhancement
T1a	< 0.5 cm	F1	< = 10 cm	Q1	one quadrant of
T1b	0.5-0.9 cm	F2	11-20 mm		suspicious enhancement
T1c	1.0-2.0 cm	F3	21-30 mm	Q2	two quadrants of
T2	2.1-5.0 cm	F4	31-40 mm		suspicious enhancement
T3	> 5.0 cm	F5	41-50 mm	Q3	three quadrants of
T4a	chest wall	F6	51-60 mm		suspicious enhancement
T4b	skin	F7	61-70 mm	Q4	four quadrants of
T4c	chest wall and skin	F8	71-80 mm		suspicious enhancement
T4d	inflammatory	F9	81-90 mm		
		F10	91-100 mm		
		FX	> 100 mm		

*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<sup>19</sup>

## 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.

## **APPENDIX IV**

### **BREAST MRS TECHNICAL SPECIFICATION AND PROCEDURES**

This version of the appendix (introduced in Amendment 5 of the protocol dated October 14, 2008) has been modified to simplify the protocol and documentation, and adapt the prescribed acquisitions to the capabilities of the various scanners.

#### **Overview**

This trial will use single-voxel spectroscopy (SVS) to measure total-choline-containing compounds (tCho) in patients undergoing neoadjuvant chemotherapy. The actual concentration of tCho ([tCho]) will be estimated using the water signal from the same voxel as an internal reference. Regular quality-control (QC) scans will be performed at each site using a standardized phantom to evaluate consistent MRS performance. All magnetic resonance spectroscopy (MRS) data analysis will be performed at the University of Minnesota (UMN) site. The spectra from both QC and patient scans must meet specific quality criteria (e.g., linewidth, artifacts, SNR) for acceptance.

The general acquisition procedure will be as follows:

- Complete MRI protocol with contrast agent
- Voxel placement
- Pre-scan calibrations (shim, water suppression, power adjustment, etc.)
- Water-reference acquisition
- Water-suppressed acquisition
- Post-MRS reference image

As each manufacturer provides different tools for MRS, the sequences and procedures will vary somewhat between sites. This variability is undesirable because it leads to inconsistent MRS performance between sites. Three aspects of the protocol design control for this variation:

- 1) The use of water as an internal reference automatically corrects for variations in signal reception sensitivity, flip angle adjustment, voxel size, and adipose tissue partial volume.
- 2) Regular QC scanning with quantitative analysis will be used to evaluate site consistency and compare performance between sites. Any site that shows inconsistent or poor performance will be notified and consulted to resolve the problem.
- 3) Centralized data analysis will ensure that quantitative analyses and QC metrics are applied uniformly across all platforms.

This document will describe the general protocol for all scanners. Specific instructions and guidelines describing how to implement this protocol on each of the three scanner brands (GE, Philips, Siemens) will be developed and distributed in the initial phases of the trial.

#### **Quality Control Scans**

Each site will receive two phantoms, labeled “A” and “B” for performing QC scans. Each phantom consists of a 2 liter leak-proof Nalgene bottle containing mostly vegetable oil. Approximately 2” above the bottom of the bottle there is a 1” diameter plastic sphere mounted on a post. The sphere contains 1 mM phosphocholine, a small amount of Gd-DTPA, 10 mM deuterated TSP as a reference (0 ppm), and

0.1% sodium azide (a toxic preservative). The “B” phantom is identical except without any phosphocholine, and so acts as a control. The phantoms are somewhat fragile and should be handled carefully; if dropped the ball/post can break off. This does not produce any leaks or hazards but does require a new phantom for QC scans.

A complete QC measurement, an *Entry QC scan*, needs to be performed for each MR scanner used prior to scanning subjects. The data generated by the QC scan must be sent to ACRIN (and forwarded to UMN) for analysis and validation. The complete scan must be repeated after any major upgrade of the scanner or change of breast coil. A shorter QC measurement, the *Weekly QC scan*, should be performed weekly during the patient study period or at minimum within one week of each patient scan. The data from these scans should also be submitted to the American College of Radiology Imaging Network (ACRIN) after the scans are completed. If there are artifacts or inconsistencies with either the entry or weekly QC scans, UMN will contact the site to help resolve the problem.

To perform the Entry QC scan, the “A” phantom is placed in the left breast position, and the “B” phantom placed in the right breast position of the breast coil. The bottles should be positioned so that the spheres are approximately in the “center” of the coil on its respective side, 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.

Once positioned, the operator should then acquire an axial, 3D GRE scan, comparable to the sequence used for dynamic magnetic resonance imaging (MRI) in the patient studies. Using these images as a guide, a 20x20x20 mm voxel should be placed in the sphere of the “A” phantom. Pre-scan calibration should be performed as necessary to ensure that the water suppression, transmit power adjustment, and B0 shim adjustment are acceptable (described below). Using the same shim and power settings, two acquisitions should be performed from the same voxel placed in the sphere. The first is the *water reference scan*, acquired with a long TR and an array of TE values. This will be used to measure the water signal intensity, water T2, and to evaluate spectral artifacts. The second is the *choline scan*, which uses water-suppression and averaging to detect the tCho resonance. The sequence used for the choline scan may be different for each manufacturer and is discussed further below. Finally, the choline scan should be repeated with the water-suppression turned off. This scan will be used to evaluate the size and frequency of sideband artifacts. All three QC scans should then be repeated in the “B” phantom.

These measurements described above are required for the entry QC scan. The weekly QC scan is the same, except 1) the choline scan without water suppression is not required, and 2) the measurements in the “B” phantom are not required. After all QC scans, the MRI data should be sent to ACRIN using the same DICOM file transfer used for patient studies. Additionally, the raw files from the spectroscopy acquisitions must be sent separately to ACRIN using the FTP mechanism. The raw data that needs to be transferred for each scan is summarized in Table 1.

**Table 1 – Raw data required for transmission to ACRIN for the different scan types**

<b>Scan</b>	<b>Raw Data required</b>
Entry QC scan	Water reference/T2 in A Choline scan in A Choline scan without WS in A Water reference/T2 in B Choline scan in B
Weekly QC scan	Water reference/T2 in A Choline scan in A
Patient scan	Water reference in target lesion Choline scan in target lesion

**Sequences and Parameters**

The original specification required that TE averaging would be used at sites and with all manufacturers. This was based on studies performed at UMN that showed that TE averaging was necessary to reduce lipid sideband artifacts. Initial QC scans at several sites have shown, however, that the amplitude and frequency of these sideband artifacts are quite different between different scanners. For several systems, the use of TE averaging is not necessary as there are no sideband artifacts that can impact the measurement of the tCho resonance. TE averaging is not available on all scanners, and when available can be more complex to use. We will therefore determine what sequence will be used for the choline scan based on the performance of each individual scanner. Three options are possible:

- 1) TE Averaging with water suppression. TE is varied from 50–200 ms in 64 or more steps.
- 2) Fixed TE with water and fat suppression. TE is set to 125 ms.

TE averaging is the preferred option as it reduces artifacts with little penalty. If this is unavailable or impractical for routine use for a given scanner, a fixed-TE acquisition with fat suppression may be used. Appropriate sequences for each manufacturer and software version are shown in Table 2.

**Table 2 – Sequences available for each scan and manufacturer**

	<b>TE Averaging</b>	<b>Fixed TE with WS+FS</b>	<b>Water Reference (TE arrayed)</b>
<b>Siemens VA25, VB13</b>	X	svs_se_ub (work-in-progress sequence, MEGA/BASING)	separate scans for each TE
<b>Siemens VB15</b>	X	GRACE (product sequence)	separate scans for each TE
<b>GE HDx (14)</b>	TEA-press	X	TEA-press or separate scans for each TE
<b>Philips 2.3</b>	X	Single voxel spectroscopy, with BASING	Single voxel spectroscopy, separate scans for each TE
<b>Philips 2.5</b>	Single voxel spectroscopy, with TE averaging	Single voxel spectroscopy, with BASING	Single voxel spectroscopy, separate scans for each TE

The Entry QC scan will be used to determine if the sequence performs acceptably for a given system. In addition to general MRS analysis criteria described below, the size and frequency of the sidebands from the choline scan without water suppression will be evaluated. If there are any sideband artifacts in the range of 1.2 – 2.7 ppm around the water peak that are detectable and larger than 0.002% of the water resonance, then the performance is unacceptable, and an alternate sequence will be required.

*[Rationale: a 1 mM tCho signal is ~0.01% as large as the water signal in a pure solution. If the choline scan without water suppression were to show a 0.002% sideband in the 1.2 – 2.7 ppm range around water, than an in vivo voxel with the maximum acceptable fat content (50% of the water signal) would have a 0.001% sideband in the 2.5 – 4 ppm region of the choline scan. This sideband would be 10% as large as a 1 mM tCho signal, and could interfere or bias the tCho measurement. ]*

The sequence parameters for all sequences are tabulated below in Table 3.

**Table 3 – Sequence parameters**

	<b>Water reference scan</b>	<b>Choline scan option 1 TE Averaging</b>	<b>Choline scan option 2 Fixed TE, FS</b>
Localization	PRESS, with optional OVS. Voxel size preferably 20x20x20 mm or larger. Non-isotropic and oblique voxels are acceptable. No single voxel dimension should be <10 mm.		
Water suppression	none	Frequency-selective excitation and crushing of the water resonance (CHESS, WET, VAPOR, or equivalent). The suppression bandwidth should be 0.5-2 ppm (32-126 Hz at 1.5T, 63-254 Hz at 3T).	
Fat suppression	none		Frequency-selective inversion recovery or suppression, not affecting the 2.5 – 4 ppm region.
TE	Separate acquisitions for TE = 50, 75, 100, 125, 150 ms.	TE=50–200 ms in 64 or more increments.	TE = 125 ms
TR	6 s	3s	
Averaging	1–2 for each TE value	The total # of averages (including those at different TE values) should be 64–256. Smaller voxels should be measured with 256 averages if time permits.	
Sampling	<b>1.5 T:</b> 512 or more complex points, with minimum SW = 1 kHz <b>3 T:</b> 1024 or more complex points, with minimum SW = 2 kHz		
Resonance Frequency	On water (4.7 ppm)	On 3.2 ppm (shifted -1.5 ppm from water)	

**Patient Scan**

The patient MRS scans are generally similar to the QC scans, except that the voxel placement is more challenging. For any MR exam except the baseline (MRI-1), it is critically important that the operator has access to previous images showing the location of the voxel on the MRI-1 scan and uses these to plan the voxel placement. These images can be either a hardcopy printout, or a nearby workstation that has a screen capture of the previous voxel placement in all 3 dimensions.

The standard DCE-MRI acquisition is performed first, followed by voxel placement and the MRS acquisitions. Using the early post-contrast 3D image, with reformatting to allow visualization of the voxel in coronal, axial, and sagittal planes, the voxel should be sized and positioned to cover as much of the target lesion as possible, while avoiding adipose tissue, necrotic regions, and any clip artifacts. Further discussion and examples are available from the *ACRIN 6657 Guide to MRS Acquisition Planning* provided by the UMN Lab.

Once the voxel is placed the water reference scan should be prepared and the automatic pre-scan (preparation phase) should be performed. The quality of the pre-scan should be assessed to determine if 1) the water:fat ratio is greater than two, and 2) the water linewidth (full-width at half-maximum) is smaller than the acceptable limits (see below). If the water:fat ratio is too low, the voxel positioning

should be adjusted to avoid more adipose tissue. If the linewidth is too large, it may be possible to reduce it by repeating the automatic shim, performing manual shimming, or reducing the voxel size. If it is not possible to meet either the water:fat or linewidth requirement, the study should not be aborted; the spectroscopy data should still be acquired with the best water:fat ratio and linewidth that can be achieved.

After pre-scan, the water reference scan should be acquired. The choline scan should then be prepared and acquired using the same voxel position and the same shim and power settings as used for the water reference scan. The total number of averages used, which may range from 64–256, should be adjusted based on the time available and the size of the voxel. Especially for smaller voxels or at 1.5 T, additional averages should be acquired if time allows.

After the MRS acquisition, one final 3D image should be acquired. This should have the same parameters as the sequence used for MRS localization (i.e., a DCE-MRI 3D bilateral fat-sat scan). This will be used to determine if the subject moved during the MRS acquisition. When the study is complete, the DICOM images and the raw MRS files should be sent to ACRIN for analysis.

### **Analysis**

All official MRS data analysis will be performed at the UMN site. After the scans are completed, the data will be sent to ACRIN and forwarded to UMN for analysis. The specific mechanism of data transfer is manufacturer-dependent and discussed elsewhere. 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 automatically DC corrected and phase adjusted. For the water reference spectra, each spectrum will be modeled using a Voigt lineshape (combined Lorentz and Gauss) for both the water and 1.3 ppm lipid resonances. 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 mono-exponential decay to estimate both T2 and the zero-TE amplitude ( $M_0$ ) for both water and fat.

The choline scan will also be automatically DC corrected and phase adjusted. When possible, frame-by-frame frequency and phase correction will be used to correct respiratory-induced frequency variations. The tCho resonance will be modeled with a Voigt line-shape and fit over the 3–3.4 ppm region of the spectrum. An error estimate of the fitting quality will be generated using Cramer-Rao minimum variance bounds (CRB). The CRB error is also used to specify the detection criterion: if the CRB error is  $\leq 100\%$  of the peak amplitude the tCho resonance will be considered detectable; if it is larger than 100% the tCho is considered undetectable. An undetectable tCho will be treated as a technical failure, not as a choline concentration of 0 mM. The time-domain amplitudes of the tCho and water resonances will then be used to calculate the internally-referenced tCho concentration [tCho].

All the above procedures will be implemented in software to allow fully-automatic processing. Complete processing automation was possible for the single-site data in the UMN study; however, this may not be possible with the variety of scanners included in this study. Therefore if any of the automated processing steps fail (DC correction, phase correction, frequency referencing, selecting starting parameters for spectral fitting) they will be adjusted manually.

After processing, these spectra and associated data will be reviewed by a physicist to evaluate spectral quality. The physicist will make and record qualitative evaluations of subject motion, spectral artifacts, and voxel placement using a numerical score of 1–3, where 1 is good, 2 is acceptable but flagged as potentially questionable, and 3 is unacceptable (see Table 4). These qualitative assessments will be

combined with two objective, quantitative measurements to determine if the spectra are to be considered acceptable for further analysis. If any of these five criteria are unacceptable, then the spectroscopy measurement will be considered a technical failure and not included in the final analyses.

The primary metric produced by the MRS analysis for statistical evaluation of the patient data is the internally-referenced tCho concentration, [tCho]. A summary of the MRS analysis will be provided for each data set and transmitted to ACRIN for final analysis. This summary will include [tCho], the five quality metrics described above, and several secondary metrics that should be analyzed as potential confounding factors (water T2, voxel size, water SNR per unit voxel volume, etc.).

The primary result from both the entry and weekly QC scans is that a tCho peak is detectable using the CRB detection criterion. The spectra must also meet all the quality criteria listed in Table 4 (see below), with the exception that patient motion is not relevant and therefore will be always 1. The entry QC set has two additional quality criteria. First, the sideband specification described in the *Sequences* section above (the choline scan without WS must have sidebands < 0.002% in the 1.2 – 2.7 ppm range around the water peak) must be met. Secondly, the choline scan from the B phantom must have a flat and artifact-free baseline in the 2.5-4 ppm region.

Several quantitative, objective metrics produced by both the QC scans will be recorded and tracked over time to evaluate machine stability and consistency of QC acquisition. These include the water SNR, tCho SNR, and water linewidth. If these values vary by more than 20% from their entry QC scan, the site will be alerted and consulted on how to resolve the problem.

**Table 4 – Quality criteria for Spectra**

<b>Criteria</b>	<b>Acceptance</b>
water linewidth	Evaluated on the water reference scan. The full-width half-maximum of absorption-mode spectrum < 0.25ppm (i.e., 16 Hz and 1.5 T and 32 Hz at 3 T). For magnitude-mode spectra, the limits are 26 Hz at 1.5 T and 51 Hz at 3 T).
water-to-fat ratio	In the unsuppressed water reference at TE=50ms, the ratio of water to fat is > 2 (using the peak area determined by fitting).
presence of artifacts	<p>qualitatively scored:</p> <p>1 – <b>good</b>, no detectable artifacts.</p> <p>2 – <b>fair</b>, some artifacts present, not interfering substantially with tCho resonance.</p> <p>3 – <b>poor</b>, artifacts prevent tCho measurement.</p> <p><i>examples: spurious RF signals, 60Hz AC noise, B0 sidebands, outer volume signals, baseline distortions, eddy currents</i></p>
patient motion	<p>qualitatively scored by comparing pre- and post-MRS MR images:</p> <p>1 – <b>none</b>, no detectable motion.</p> <p>2 – <b>moderate</b>, some motion present, displacements &lt; 20% of voxel dimensions.</p> <p>3 – <b>large</b>, spectra are unacceptable.</p>
voxel placement	<p>qualitatively scored by comparing images and overlain voxel geometry between current scans and previous scans:</p> <p>1 – <b>good</b></p> <p>2 – <b>fair</b></p> <p>3 – <b>poor</b></p>

## **APPENDIX V**

### **American College of Radiology Imaging Network General Qualifying Application Information**

#### **Application Process**

All participating institutions must be ACRIN-approved institutions prior to study participation and accrual. The approval process for ACRIN 6657 includes submitting an ACRIN General Qualifying Application (GQA). Detailed information is available on the ACRIN website ([www.acrin.org](http://www.acrin.org)) under list of current protocols (ACRIN 6657). The application is on the ACRIN web site at [www.acrin.org/6657\\_protocol.aspx](http://www.acrin.org/6657_protocol.aspx).