



**ACRIN Protocol 6657**  
**SUMMARY OF CHANGES**

October 14, 2008

Amendment # 5

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**Changes in therapeutic regimen structure, a now-mandatory MRI<sub>3</sub>, present an updated and simplified Appendix IV (Breast MRS Technical Specifications and Procedures), and additional edits for clarification and consistency are included in this amendment:**

**Cover Page**

Amendment 5 and version date October 14, 2008, have been added

**Table of Contents**

Page numbers were adjusted to match the current version

**Eligibility, Page 4**

The protocol formerly contained only the original schema for the trial, which is now labeled "ORIGINAL"

An "e" has been added to end of "anthracycline" to correct the typo

"... a ferromagnetic prostheses" has been corrected to "... a ferromagnetic prosthesis"

**Schema, Page 4**

"SEE PAGE 5 FOR ELIGIBILITY AND SCHEMA REVISIONS." has been added

This amendment contains revised Eligibility language to reflect the Type 1 and Type 2 chemotherapy revisions as well as the current schema for the ongoing trial and additional revisions to the MRI-description table as follows:

**"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)**

			Chemotherapy Type 1↔	Chemotherapy Type 2		Surgery		Post Surgical Treatment
	Pre-treatment		Weeks 1-12	Weeks 13-25		Week 27		
R E G I S T E R	MRI MRS → Serum Plasma Buffy Coat	Optional MRI* MRS 30 Pt Subset				Surgery		Post surgical treatment will be at the discretion of the treating physician.
	Biopsies		MRI	MRI		Tissue		
	Mammogram		MRS	Optional MRS Optional Biopsies				
					MRI/MRS, serum, plasma, buffy coat, Mammogram			

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

\*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."

**1.1 Introduction, Page 6**

4<sup>th</sup> paragraph, 1<sup>st</sup> sentence: "In the original protocol, ..." has been added; "an anthracyclin" has been replaced with "a taxane" and "a taxane" has been replaced with "an anthracycline"

In the same paragraph, "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." has been added

### **2.1 Association of Pathologic Response to Clinical Outcome in Stage III Patients Undergoing Neoadjuvant Therapy, Page 7**

1<sup>st</sup> paragraph, 5<sup>th</sup> sentence: The period has been moved from outside of the citation callout to the end of the sentence

Page 8, 2<sup>nd</sup> paragraph, 3<sup>rd</sup> sentence: “AC” has been changed to “standard-of-care”

2<sup>nd</sup> paragraph, 5<sup>th</sup> sentence: “Taxol” has been replaced with “Type 2 chemotherapy” and “AC” has been replaced with “Type 1 chemotherapy”

### **2.3 <sup>1</sup>H MR Spectroscopy of Breast Tumors, Page 8**

1<sup>st</sup> paragraph, 2<sup>nd</sup> sentence: The period has been moved from outside of the citation callout to the end of the sentence

### **3.2 Results of Preliminary Analysis, Pages 11 and 12**

2<sup>nd</sup> paragraph, under Figure 3, 1<sup>st</sup> sentence: “<=” has been replaced with “≤”

3<sup>rd</sup> paragraph, under Figure 4, 3<sup>rd</sup> sentence: The period has been moved from outside of the citation callout to the end of the sentence

### **4.1 Overall Scientific Objectives of the ACRIN 6657/CALGB 150007 Companion Trials, Page 14**

2<sup>nd</sup> paragraph, 2<sup>nd</sup> sentence: “3Tesla” and “1.5Tesla” are now “3 Tesla” and “1.5 Tesla” with spaces added for consistency

#### **4.2.2.3 Primary and Secondary Endpoints, Page 14**

“SER” is now defined as “signal enhancement ratio” at first mention

#### **4.3 Primary Aims of ACRIN 6657, Page 14**

1<sup>st</sup> paragraph, 1<sup>st</sup> sentence: “AC” has been replaced with “Type 1” and “paclitaxel” has been replaced with “Type 2”

2<sup>nd</sup> paragraph: “Section” is now capitalized for consistency

#### **4.4 Secondary Aims of ACRIN 6657, Page 15**

1<sup>st</sup> paragraph: “Section” is now capitalized for consistency

Section 4.4.3, 1<sup>st</sup> question: “paclitaxel” is now “Type 2 chemotherapy” and “AC” is now “Type 1 chemotherapy”

Similarly, in “Aim 5” of Section 4.4.3: “paclitaxel” is “Type 2” and “AC” is “Type 1”

#### **4.5 Aims of the ACRIN 6657 Protocol Extension, Page 16**

Section 4.5.1, 1<sup>st</sup> paragraph, 3<sup>rd</sup> sentence:

- “Three” is now “Two”
- parentheses have been added around “(and optional diffusion-weighted MRI acquisition)”
- the original second item “2) reduction of the number of (6657 study-related) imaging exams from 4 to 3 during the course of treatment,” has been deleted
- the original third item has been renumbered as “2)”

Section 4.5.2, 1<sup>st</sup> paragraph: “*in vivo*” is now italicized

Section 4.5.2, 2<sup>nd</sup> paragraph, Aim 6: “3 T” and “1.5 T” have been spelled out to “3 Tesla” and “1.5 Tesla” for consistency

Section 4.5.3, 5<sup>th</sup> paragraph, below Aim 8: “ADC” is spelled out at first mention as “apparent diffusion coefficient”

#### **5.0 Eligibility Criteria, Page 17**

1<sup>st</sup> paragraph, 1<sup>st</sup> sentence: “an anthracyclin based regimen alone” is now “Type 1 only”

Same paragraph, same sentence: “Type 1” was added and “a taxane” was changed to “Type 2” to read “Type 1 followed by Type 2” per the new treatment protocol

### **5.1 Inclusion Criteria Specific to the ACRIN 6657 MRI Study, Page 17**

1<sup>st</sup> paragraph, 1<sup>st</sup> sentence: “T3” is now “T2 or T3” to accurately reflect staging criteria and “that are at least 3 cm who choose to undergo neoadjuvant chemotherapy” was moved up in the sentence for clarity

Same paragraph, same sentence: “ACRIN 6657/CALGB 15007” is now “CALGB 150007/ACRIN 6657”

1<sup>st</sup> paragraph, 2<sup>nd</sup> sentence: has been revised to read “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 followed by AC for patients enrolled as part of the protocol extension”

Section 5.1.2 added: The following criterion was moved from the Exclusion Criteria into Inclusion Criteria: “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:  $\text{Creatinine Clearance (male)} \times 0.85$*

Section 5.2.3 has been deleted

### **6.1.1 General, Page 17**

The hyperlink for “[www.acrin.org](http://www.acrin.org)” has been embedded

### **6.2 Clinical Data Submission, Page 18**

Section 6.2.1, 1<sup>st</sup> paragraph, last sentence: “website” is now “web site” for consistency

Section 6.2.3: the verbs associated with “data” have been corrected in 4 places ... “data is” is now “data are” in 3 locations; “data ... passes” is now “data ... pass”

Section 6.2.4: “data is” has been corrected to “data are” in the first 2 sentences

### **6.4 Electronic Data Management, Page 18**

Section 6.4.1, 1<sup>st</sup> paragraph, 1<sup>st</sup> and 2<sup>nd</sup> sentences: “data is” has been corrected to “data are”

Section 6.4.1, 1<sup>st</sup> paragraph, 7<sup>th</sup> sentence: “research associate” is now “DMC”

Section 6.4.1, 1<sup>st</sup> paragraph, 8<sup>th</sup> sentence: “research associate at the DMC” has been deleted

Section 6.4.1, 1<sup>st</sup> paragraph, 11<sup>th</sup> sentence: “RA” has been deleted

Section 6.4.1, 1<sup>st</sup> paragraph, 1<sup>st</sup> and 2<sup>nd</sup> sentences: “RA” has been deleted

Section 6.5, 1<sup>st</sup> paragraph, 1<sup>st</sup> sentence: “via email” has been added

Section 6.5, 1<sup>st</sup> paragraph, 2<sup>nd</sup> sentence: “Distributed at intervals via the U.S. mail system directly to both the RA and the investigator at each site, ...” has been deleted, and “The” has been capitalized

### **6.7 Data Collection Table, Page 20**

2<sup>nd</sup> row, Registration Form: “RA” is spelled out as “research associate (RA)” at first mention

8<sup>th</sup> row, MRI Forms: the apostrophe in “patient’s” has been deleted; “\*This MRI is optional and will be performed only if physician orders the MRI per standard clinical care.” has been deleted

Page 21, 1<sup>st</sup> row, MRS Forms: the apostrophe in “patient’s” has been deleted; “Research Associate” is now “RA”

2<sup>nd</sup> row, Supplemental MRI Forms: a comma has been added between “1.1, 2” in the sentence beginning “Data:”

### **6.8 Image Submission, Page 21**

2<sup>nd</sup> paragraph, 3<sup>rd</sup> sentence: the email address “[imagearchive@phila.acr.org](mailto:imagearchive@phila.acr.org)” has a mailto: hyperlink embedded

### **7.0 Study Design, Pages 23–31**

Section 7.1, 2<sup>nd</sup> sentence: 2 additional sites have been included in the study extension; the sentence now reads “..., Dartmouth Medical School, and Mayo Clinic–Rochester have been added as sites ...”

Section 7.1, 4<sup>th</sup> sentence: “ACRIN” has been added before “6657”

Section 7.1, final sentence: “..., reflecting the changes made in Amendment 5 (version dated 10/14/08)” has been added to highlight the new schema for this amendment

Section 7.2, 4<sup>th</sup> sentence: “website” is now “web site”

Page 24, Section 7.3.2: “ACR” has been replaced with “ACRIN” in 3 locations and “the” has been deleted before the second instance of what is now “ACRIN”

Section 7.4.1, 4<sup>th</sup> paragraph, MRI<sub>2</sub> and 5<sup>th</sup> paragraph, MRI<sub>3</sub>: “AC” and “paclitaxel” have been replaced with Type 1- and Type 2-therapy language to read

*“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”*

Section 7.4.1, final paragraph of page 24: “ACRIN” has been added in the 1<sup>st</sup> sentence in front of “6657” and the following text has been deleted from the 2<sup>nd</sup> sentence “1) making the MRI exam between treatment regimens optional (MRI<sub>3</sub> above), and 2)”

Page 25, Section 7.4.1, 2<sup>nd</sup> paragraph, related to MRI<sub>2</sub>: “treatment” has been deleted and “AC” has been replaced with “Type 1 chemotherapy”

Page 25, Section 7.4.1, 3<sup>rd</sup> paragraph, related to MRI<sub>3</sub>: revised from “will be optional” to specify that this MRI is now mandatory “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.”

Section 7.4.1, 5<sup>th</sup> paragraph, 1<sup>st</sup> sentence: “(MRI<sub>1,1</sub>)” has been added

Section 7.4.1, 5<sup>th</sup> paragraph, 2<sup>nd</sup> sentence: “each” has been deleted

Page 26, Section 7.4.3, 1<sup>st</sup> paragraph, 2<sup>nd</sup> sentence: “AC” has been replaced with “Type 1 chemotherapy”

Section 7.4.3, 1<sup>st</sup> paragraph, 3<sup>rd</sup> sentence: “For the original protocol ...” replaces “If possible ...”

Section 7.4.3, 1<sup>st</sup> paragraph, 3 sentences have been added: “*(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.*”

Section 7.4.3, 1<sup>st</sup> paragraph, 7<sup>th</sup> sentence following the additional text above: now reads “*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.*” to reflect the changes in treatment

Section 7.5, 1<sup>st</sup> sentence: “For the original protocol, ...” has been added

Page 27, Section 7.5, 1<sup>st</sup> full paragraph, 1<sup>st</sup> sentence: “For the protocol extension, ...” has been underlined

Section 7.5, 1<sup>st</sup> full paragraph, 5<sup>th</sup> sentence: “sagittal imaging over the symptomatic breast,” has been deleted, “axial” has been deleted, and “in the sagittal or axial planes” has been added

Section 7.5, 1<sup>st</sup> full paragraph, 6<sup>th</sup> sentence: “20” is now “22” cm, “unilateral” is now “sagittal,” “bilateral” is now “axial,” and an extra space has been deleted at the end of the sentence

Section 7.5, 1<sup>st</sup> full paragraph, 10<sup>th</sup> sentence: “20” is now “22” cm, “unilateral” is now “sagittal” in 2 parenthetical locations, and “bilateral” is now “axial” in 2 parenthetical locations

Section 7.5, 1<sup>st</sup> full paragraph, 12<sup>th</sup> sentence: “35” ms is now “24” ms, “minimum” has been added, “= 4.5 ms” has been replaced with “(with fat and water in phase)”

Section 7.6, 1<sup>st</sup> paragraph, 1<sup>st</sup> sentence: “ACR” is now “ACRIN”

Page 28, Section 7.6.2, 1<sup>st</sup> paragraph, final sentence: The period has been moved from outside of the citation callout to the end of the sentence

Section 7.6.3, under #1, 1<sup>st</sup> sentence: The period has been moved from outside of the citation callout to the end of the sentence

Page 29, Section 7.6.6, header: “P” in “Protocol” has been capitalized

Section 7.6.6, 1<sup>st</sup> paragraph, 3<sup>rd</sup> sentence: “the first” has been replaced with “Type 1” in 2 locations

Section 7.6.6, 1<sup>st</sup> paragraph, 4<sup>th</sup> sentence: “An additional MRI (with MRS optional) is required between chemotherapy Type 1 and Type 2 regimens.” has been added

Page 30, Section 7.6.6, 3<sup>rd</sup> bullet point in sequence, 1<sup>st</sup> on page: “... 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, ≤ 2.5 mm section thickness.” replaces “... single or interleaved sagittal (FOV 18-22 cm) slice acquisition, 512 x 256 or 256 x 256 imaging matrix, 32-64 slices, ≤ 2 mm section thickness.”

Section 7.7, 2<sup>nd</sup> paragraph, 4<sup>th</sup> sentence: “AC” has been changed to “Type 1 chemotherapy”

Page 31, Section 7.7, 2<sup>nd</sup> paragraph on page, 3<sup>rd</sup> sentence: “clinically available” has been deleted to reduce repetition

### **8.1 and 8.2 Overview and Study Design, Page 33**

Section 8.1, 2<sup>nd</sup> sentence: “... consisting of an anthracyclin based regimen only or followed by a taxane ...” has been changed to “... consisting of a taxane-based regimen only (Type 1) or followed by an anthracycline-based regimen (Type 2) ...”

Section 8.1, 6<sup>th</sup> sentence: “CALGB” has been added

Page 34, Section 8.2, 2<sup>nd</sup> sentence: “AC alone” has been changed to “Type 1 chemotherapy alone”; “Taxol” is now “Type 2 chemotherapy”

Section 8.2, 3<sup>rd</sup> sentence: “AC and Taxol” is now “Type 1 and Type 2 chemotherapies”

### **8.4 Specific Aims and Corresponding Analysis, Page 37**

Section 8.4.2, Aim 3, 2<sup>nd</sup> paragraph, final sentence: “A” has been added to the beginning of the sentence

Section 8.4.2, Aim 5: “paclitaxel” has been changed to “Type 1” in 2 locations and “AC” has been changed to “Type 2” in 2 locations

### **8.5 Aims of the ACRIN 6657 Protocol Extension, Page 38**

Section 8.5.1, 2<sup>nd</sup> sentence: “ACRIN” has been added

Section 8.5.2, Aim 6: text has been bolded for consistency

Section 8.5.2, Aim 6, 2<sup>nd</sup> paragraph, 1<sup>st</sup> and 2<sup>nd</sup> sentences: “CI” is now “confidence interval”

Page 39, Section 8.5.2, Aim 6, 3<sup>rd</sup> paragraph, 1<sup>st</sup> sentence: “Aims” has been capitalized

Section 8.5.3, header: underline has been added

Section 8.5.3, Aim 7, 1<sup>st</sup> line: a tab has been added for formatting consistency

Section 8.5.3, Aim 7 and Aim 8: have been formatted to align beneath “Aim 7” for consistency

Section 8.5.3, Aim 7 and Aim 8, 2<sup>nd</sup> paragraph for each, 2<sup>nd</sup> sentence for each: “CI” is now “confidence interval” and “differences” at the end of the sentence was been made plural

Page 40, Section 8.5.3, Aim 9, 2<sup>nd</sup> paragraph, 1<sup>st</sup> sentence: “-“ is now “and”

### **8.6 Targeted Sample Size, Pages 40-44**

1<sup>st</sup> paragraph, 2<sup>nd</sup> sentence: “#” has been deleted

Pages 41 and 42, Tables 3 and 4: table titles have been formatted

Page 42, 1<sup>st</sup> paragraph below Table 4: “three” is “3” and “four” is “4” in two series of locations; “Table” has been capitalized twice; a period has been deleted from the parenthetical in the last sentence

Page 43, Section 8.6.3, 2<sup>nd</sup> paragraph:

- 2<sup>nd</sup> sentence, “CI” has been changed to “confidence interval”
- next-to-last sentence, “proportions” is plural, “then” is “than”
- final sentence, “The table five” is now “Table 5”

Tables 5: table title has been formatted for consistency

Page 44, Section 8.6.3, 1<sup>st</sup> paragraph below Table 5, 4<sup>th</sup> sentence: “CI” is “confidence interval”

Section 8.6.3, 2<sup>nd</sup> paragraph below Table 5, 1<sup>st</sup> sentence: “-“ is now “and”

### **8.7 Accrual Rates, Page 44**

1<sup>st</sup> paragraph, 1<sup>st</sup> sentence: “original” has been added

1<sup>st</sup> paragraph: the final sentence “*Additional sites will be added as part of the protocol extension.*” has been added

### **8.9.3 Early Termination of Participant Accrual in the Protocol Amendment, Page 45**

1<sup>st</sup> paragraph, 2<sup>nd</sup> and 3<sup>rd</sup> sentences: “CIs” is “confidence intervals”

1<sup>st</sup> sentence, 5<sup>th</sup> sentence: “CI” is “confidence interval”

### **9.0 Adverse Event Reporting, Page 46**

Section 9.2, 5<sup>th</sup> bullet: “Congenital” has been revised to “Causes congenital”

Section 9.3, 1<sup>st</sup> line: “..., based on guidance from the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0” has been added

Page 47, Section 9.6, 1<sup>st</sup> paragraph, 2<sup>nd</sup> sentence: “Gd” has been changed to “gadolinium”

Page 48, Section 9.10, Expedited reporting, 3<sup>rd</sup> paragraph, 1<sup>st</sup> sentence: “serious” is now “seriousness”; a hyperlink has been embedded for “[ACRIN Adverse Event Reporting Manual](#)”

Section 9.10, 4<sup>th</sup> paragraph, 1<sup>st</sup> sentence: a hyperlink has been embedded for "[ACRIN Adverse Event Reporting Manual](#)"

Section 9.10, 4<sup>th</sup> paragraph, 3<sup>rd</sup> sentence: "to be" has been deleted

Section 9.11.3, 1<sup>st</sup> sentence: "CTC" is now "CTCAEv3.0" and "or" was added

Page 49, Section 9.11.5, 1<sup>st</sup> sentence: "Expected" and "Unexpected" are now capitalized

Section 9.11.6, 1<sup>st</sup> sentence: "Expected" is capitalized, "adverse" is added, "Grades" is capitalized, "-" has been changed to "through," and "Unexpected" is capitalized

Section 9.12.3, 1<sup>st</sup> sentence: "report" is singular, "with" is now "within," "appropriate" has been added, and "specified in Section 9.11" has been added

Section 9.12.4, 2<sup>nd</sup> sentence: "of" has been added

Section 9.12.4, 3<sup>rd</sup> sentence: "hours" is plural

Page 50, Section 9.12.5, 1<sup>st</sup> sentence: has now been split into 2 sentences (a period and capital "T" have been added) and "at:" has been added to the end of the now-2<sup>nd</sup> sentence

### **10.0 Institutional Audits, Page 50**

Section 10.1, final sentence: a hyperlink was embedded in "[ACRIN Auditing Manual](#)" and the URL for regulatory documents was updated to "[www.acrin.org/pdrc.aspx](http://www.acrin.org/pdrc.aspx)"

Page 51, Section 10.4, 1<sup>st</sup> sentence: "Sites must have on hand ..." has been revised to "Sites must submit to ACRIN's quality assurance monitor ..."

Section 10.4, final sentence: "*Copies of these documents must be kept on file for the trial for regulatory compliance.*" has been added

Page 52, Section 10.6, Audit Source Documentation table, 2<sup>nd</sup> row, 3<sup>rd</sup> column, 2<sup>nd</sup> sentence: "Informed consent" was added before "form"

Section 10.6, Audit Source Documentation table, 3<sup>rd</sup> row, 2<sup>nd</sup> column, 2<sup>nd</sup> paragraph (Data Due), 2<sup>nd</sup> sentence: "form" has been added

Section 10.6, Audit Source Documentation table, 5<sup>th</sup> row, 2<sup>nd</sup> column, 5<sup>th</sup> line (for MRI3): has been revised to read "**3-** after Type 1 chemotherapy but before initiation of Type 2 chemotherapy. ***\*This MRI is mandatory as of Amendment 5 to the ACRIN 6657 protocol.***"

Section 10.6, Audit Source Documentation table, 6<sup>th</sup> row, 2<sup>nd</sup> column, 5<sup>th</sup> line: "MRI/MRS 3-after Type 1 chemotherapy but before initiation of Type 2 chemotherapy. ***\*This MRS is optional for this stage of the trial, but MRI is mandatory.***" has been added

Section 10.6, Audit Source Documentation table, 6<sup>th</sup> row, 3<sup>rd</sup> column: "(3 optional)," has been added

### **Appendix I Sample Informed Consent for Research Study, Pages 56-64**

Title: has been revised to "**Contrast-Enhanced Breast MRI/MRS and ...**" from "**Contrast-Enhanced Breast MRI and MRS ...**"

2<sup>nd</sup> paragraph, 1<sup>st</sup> sentence: "an anthracycline" has been replaced with "a taxane chemotherapy drug"; "that may be" has been added; and "taxane" has been replaced with "an anthracycline"

Under "WHY IS THIS STUDY BEING DONE?" 1<sup>st</sup> paragraph: goals have been reformatted/combined under #1 to read as follows:

- "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.”

Under “WHY IS THIS STUDY BEING DONE?” 3<sup>rd</sup> paragraph: “the” has been deleted from the 1<sup>st</sup> and the 2<sup>nd</sup> sentences

Page 57, under “How Many People Will Take Part in the Study?”: the number of sites has been updated to “12”

Under “What Is Involved in the Study?” 1<sup>st</sup> paragraph, item #1: has been revised to read “MRI/MRS scans before and during your treatment.” instead of “An MRI/MRS component”

Under “What Is Involved in the Study?” 3<sup>rd</sup> paragraph: “If you take part in this study, you will have the following tests and procedures:” has been made bold

Under “**MRI (Magnetic Resonance Imaging) and MRS (Magnetic Resonance Spectroscopy) Scans:**” extensive revisions have been made, including increasing the number of scans detailed to “four” and altering/simplifying the descriptions for each scan:

“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.”*

Page 58, under “**MRI (Magnetic Resonance Imaging) and MRS (Magnetic Resonance Spectroscopy) Scans:**”:

- 1<sup>st</sup> consent line item, “optional” has been added
- 2<sup>nd</sup> consent line item, “optional MRS” has replaced “MRI” and “and before beginning Type 2 chemotherapy” has been deleted
- 1<sup>st</sup> paragraph, 1<sup>st</sup> sentence, “/MRS” has been added and “procedures” is now plural

Under “**Biopsy (core needle) and Tissue Sample**” 2<sup>nd</sup> paragraph: “A core needle biopsy is a procedure ...” has been added, moved up from below the consent signature language; it has been deleted from immediately after the consent line on page 59

Page 59, under “**Ultrasound**” in the schema table: “MRI scan required; all participants will be asked to have an optional MRS scan” has been added

Under “What Are My Treatment Options?” 1<sup>st</sup> paragraph: “a taxane” replaces “an anthracycline” and “an anthracycline” replaces “a taxane”

Page 60, under “What Are the Risks of the Study?” 1<sup>st</sup> paragraph, 1<sup>st</sup> sentence: “these” has been added before “side effects”

Under “What Are the Risks of the Study?” 1<sup>st</sup> paragraph, 2<sup>nd</sup> sentence: “possible side effects” has been revised to “these”

Under “What Are the Risks of the Study?” 1<sup>st</sup> paragraph, 6<sup>th</sup> sentence: “associated with MRI/MRS” has

been added

Under “Likely” risks associated with the MRI/MRS, 1<sup>st</sup> bullet: “Minor discomfort due to noise” has been revised to “The MRI unit is noisy”

Under “Likely” risks associated with the MRI/MRS, 2<sup>nd</sup> bullet: “machine” is now “magnet”

Under “Less likely” risks associated with gadolinium, 1<sup>st</sup> bullet: content has been reduced to a single bullet point combining “Headaches and nausea”

Under “Very rare, but Serious” risks associated with the gadolinium, 2<sup>nd</sup> paragraph has been extensively revised to read:

*“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.”*

Page 61, under “What About Confidentiality?” 1<sup>st</sup> paragraph: “CALGB” has been written out as “Cancer and Leukemia Group B” at first mention and parentheses have been placed around “(CALGB)”

Page 62, under “What About Confidentiality?” 2<sup>nd</sup> paragraph: the “CALGB” acronym is used and “Cancer and Leukemia Group B” is deleted along with parentheses around “(CALGB)” and “ACRIN” has been added

Under “What Are the Costs?” 2<sup>nd</sup> paragraph has been rewritten to read:

*“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.”*

Page 64, under “Signature” 1<sup>st</sup> paragraph, 1<sup>st</sup> sentence: “... all \_\_\_[insert total number of pages] pages of ...” has been added

### **Appendix III Breast MRI Lexicon, Page 67**

Section I. Morphologic Categories and Terms has been updated to provide a link to the American College of Radiology’s 2003 BI-RADS® criteria, available online, and now reads:

“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).”

Also, the following footnote has been added: “\* 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.”

### **Appendix IV Breast MRS Technical Specification and Procedures, Pages 71-78**

Appendix IV has been completely replaced with text developed to simplify and correct the explanation for breast MRS technical specifications 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>
<i>Localization</i>	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.		
<i>Water suppression</i>	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).	
<i>Fat suppression</i>	none		Frequency-selective inversion recovery or suppression, not affecting the 2.5 – 4 ppm region.
<i>TE</i>	Separate acquisitions for TE = 50, 75, 100, 125, 150 ms.	TE=50–200 ms in 64 or more increments.	TE = 125 ms
<i>TR</i>	6 s	3s	
<i>Averaging</i>	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.	
<i>Sampling</i>	1.5 T: 512 or more complex points, with minimum SW = 1 kHz 3 T: 1024 or more complex points, with minimum SW = 2 kHz		
<i>Resonance Frequency</i>	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>
<i>water linewidth</i>	<i>Evaluated on the water reference scan. The full-width half-maximum of absorption-mode spectrum &lt; 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).</i>
<i>water-to-fat ratio</i>	<i>In the unsuppressed water reference at TE=50ms, the ratio of water to fat is &gt; 2 (using the peak area determined by fitting).</i>
<i>presence of artifacts</i>	<p><i>qualitatively scored:</i></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>
<i>patient motion</i>	<p><i>qualitatively scored by comparing pre- and post-MRS MR images:</i></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>
<i>voxel placement</i>	<p><i>qualitatively scored by comparing images and overlain voxel geometry between current scans and previous scans:</i></p> <p>1 – <b>good</b></p> <p>2 – <b>fair</b></p> <p>3 – <b>poor</b></p>